Doppler, Cardiotocography, and Biophysical Profile Changes in Growth-Restricted Fetuses

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OBJECTIVE: To assess from diagnosis to delivery the Doppler studies of the umbilical artery, middle cerebral artery, umbilical vein, ductus venosus, and amniotic fluid index of fetuses with idiopathic growth restriction.

METHODS: A total of 145 singleton growth-restricted fetuses with abnormal umbilical artery pulsatility indexes were studied. Cesarean delivery was performed because of abnormal biophysical profile or nonreassuring fetal heart rate pattern.

RESULTS: There were 4 fetal and 50 neonatal deaths. Two growth-restricted groups were identified: Group A (n = 44) included fetuses in whom all measures became abnormal preceding an abnormal biophysical profile or nonreassuring nonstress test. Group B (n = 101) included fetuses in whom 1 or more measures were normal at the time of cesarean delivery. There was no statistically significant difference in perinatal morbidity and mortality between the 2 groups. Neonatal death was increased in fetuses with umbilical artery reversed flow (odds ratio 2.34, 95% confidence interval 1.16–4.73; $P < .05$) and ductus venosus reversed flow (odds ratio 4.18, 95% confidence interval 2.01–8.69; $P < .05$). A significant correlation was also found between low birth weight and adverse perinatal outcome.

CONCLUSION: In fetuses with idiopathic growth restriction, 1) low birth weight, 2) umbilical artery reversed flow, and 3) ductus venosus absent or reversed flow are associated with an increased perinatal morbidity and mortality.

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LEVEL OF EVIDENCE: II-2

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The American College of Obstetricians and Gynecologists has chosen to define intrauterine growth restriction as a fetus with an estimated weight below the 10th percentile for gestational age[1] because perinatal mortality and morbidity increases when the birth-weight is below that percentile.[2–6] Previous studies have suggested that, in growth-restricted fetuses, serial Doppler measures could provide more information than a single random measurement.[7–11] However, previous studies have reported either a small number of growth-restricted fetuses or have not differentiated fetuses with idiopathic growth restriction from those in which maternal diseases might have played a causal role in their development. To further assess the changes that occur in growth-restricted fetuses from time of diagnosis to delivery, we serially determined with Doppler ultrasonography the changes that occur in flow velocity waveforms in the umbilical artery, middle cerebral artery, ductus venosus, and umbilical vein of growth-restricted fetuses in pregnancies with no other complications. In these fetuses we also determined the changes that occur in fetal heart rate, amniotic fluid, and biophysical profile. These fetuses were initially diagnosed as having an abnormal umbilical artery and were delivered before 32 weeks of gestation because of abnormal cardiotocography or abnormal biophysical profile. We selected 32 weeks of gestation because after this gestational age the management differs in the centers involved in this study.

MATERIALS AND METHODS

The study population consisted of singleton fetuses studied prospectively over a 4-year period, between 2001 and 2004. The patients were recruited in the hospitals of the University of Padua, Italy; University of Rome "La Sapienza," Italy; and University of Sassari, Italy. The study was approved by the institutional review boards of the institutions in which the

patients were enrolled, and the patients gave informed consent to participation in this study.

Among fetuses with an estimated weight below the 10th percentile and abnormal umbilical artery pulsatility index (> 2 standard deviations from the mean for gestational age), we selected those that fulfilled the following criteria: 1) Gestational age established before 20 weeks by ultrasound or known last menstrual period; 2) Normal fetal anatomy; 3) Absence of maternal pathology; 4) Delivery before 32 weeks of gestation; 5) Forward umbilical artery diastole; 6) Normal amniotic fluid index (≥ 5 cm); 7) Absence of pulsation in the umbilical vein; 8) Forward ductus venosus diastolic flow; 9) At least 3 consecutive Doppler measurements before delivery; 10) Last Doppler measurement obtained within 24 hours from delivery.

Patients were recruited between 24 and 30.4 weeks of gestation. After entrance into the study the patients were managed with the following protocol. Biometry was assessed every 2 weeks. If there was a cerebroplacental ratio ≥ 1.0,[12] Doppler studies and biophysical profile were performed every 4 days. The patient was admitted to the hospital in presence of a cerebroplacental ratio less than 1.0. After admission of the patients to the hospital, Doppler studies, biophysical profile, and cardiotocography were performed every day until delivery. Delivery was indicated in presence of either an abnormal biophysical profile (≤ 4/10) or by the presence of variable decelerations characterized by a decrease in heart rate from the baseline of at least 30 beats per minute (at least 6 in 60 minutes) or late decelerations (at least 5 repetitive decelerations). For biophysical profile scores we used the deepest pocket of amniotic fluid. The Doppler data were not used for timing the delivery. The clinicians managing the cases were aware of the Doppler results.

Pulsed wave Doppler ultrasound studies were performed with the following pulsed color Doppler systems: 128 Xp and Elegra (Siemens Medical Solutions, Mountain View, CA), HDI 5000 (Philips Medical Systems, Bothell, WA), and Voluson 530 Expert (GE Medical Systems, Milwaukee, WI). We used 3.5- or 5-MHz probes with spatial peak temporal average intensities less than 100 mW/cm^2 in both imaging and Doppler modes. All recordings were obtained in the absence of fetal breathing and fetal movements. An average of 3 consecutive Doppler velocity waveforms for each vessel was used for statistical analysis. The umbilical artery different patterns (abnormal umbilical artery pulsatility index; absent umbilical artery end-diastolic velocity, and reversed umbilical artery diastole) were considered independently, as 3 different patterns of progressive severity. The middle cerebral artery was studied as previously reported.[13] The ductus venosus was studied at its origin from the umbilical vein, and the waveforms were considered abnormal if there was either absent or reversed flow at late diastole. Umbilical vein waveforms were obtained before the entrance of the vein into the abdomen and the presence of pulsation was considered abnormal.

Amniotic fluid was considered abnormal in presence of an amniotic fluid index less than 5 cm. Perinatal outcome endpoints included the perinatal mortality and the composite perinatal morbidity. Neonatal morbidity included any complication from birth to 28 days of life.[14]

In the study group, the last antenatal testing was performed at least 24 hours before delivery. All patients received only 1 course of steroids (betamethasone 12 mg intramuscularly every 24 hours twice) after admission to the hospital.

Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, IL). Continuous variables were tested for normality (Kolmogorov-Smirnov test). Initially, we determined the cumulative onset time of each continuous variable up to the time of delivery. A stepwise multiple regression was used to assess whether the abnormality of 1 vessel may affect the distance from time 0 (day of delivery because of nonreassuring fetal testing). Next, we applied the Kaplan-Meier analysis for the fetuses in whom all the variables were abnormal by the time cesarean delivery was performed. The Breslow's test was used to assess the difference between curves obtained by the Kaplan-Meier analysis.[15,16]

Categorical variables were analyzed with χ^2 or Fisher exact test when appropriate. We obtained the odds ratio to assess whether a correlation among the variables and the perinatal outcome existed. For continuous variables such as birth weight, we used analysis of variance to assess whether a difference existed among the mean values of each variable. $P < .05$ was considered to indicate statistical significance.

RESULTS

One hundred forty-five patients fulfilled all the criteria for inclusion in this study. There were 2 groups of growth-restricted fetuses: in one group (n = 44) all Doppler measures became abnormal and preceded an abnormal biophysical profile or abnormal cardiotocography. A second group (n = 101) included growth-restricted fetuses in whom 1 or more measures were not altered in the presence of abnormal biophysical profile or abnormal fetal heart rate testing.

Group-specific maternal demographic characteristics are presented in Table 1. All the patients

Table 1. Group-Specific Maternal Demographic Characteristics

	Group A (n = 44)	Group B (n = 101)
Maternal age	32 (27–39)	31 (24–37)
Gestational age at recruitment	26.4 (24–30)	28 (24–30.4)
Gestational age at delivery	29.6 (26–32)	28.4 (26–32)
Number of ultrasonograms performed	4 (3–16)	3 (3–10)

Values are median (range). In Group A all Doppler measures became abnormal before delivery, whereas in Group B 1 or more vessels were normal at the time of delivery.

underwent a cesarean delivery because of abnormal testing. The perinatal outcome for the fetuses of the 2 groups is reported in Table 2.

In group A, the cumulative onset time of each continuous variable up to the time of delivery indicated that the measures became abnormal in the following order: umbilical artery pulsatility index, middle cerebral artery pulsatility index, umbilical artery absent end-diastolic velocity, amniotic fluid index, reversed flow of the umbilical artery, and ductus venosus absent or reversed flow (Fig. 1). The umbilical vein did not follow a clear pattern.

A stepwise multiple regression demonstrated that with each measure that became abnormal the distance from time 0 became shorter ($P < .05$). The information provided by an abnormal middle cerebral artery pulsatility index did not add much to the information obtained only by the umbilical artery pulsatility index, whereas the absence of end-diastolic flow and reversed flow of the umbilical artery increased the R^2. Adding abnormal amniotic fluid and or ductus venosus reversed flow did not contribute any new information (Table 3).

The Kaplan-Meyer test adopted for the first group of fetuses reported that by increasing the probability for each measure to be abnormal, the time from time 0 became shorter (Fig. 2). The Breslow's test demonstrated a difference between the curves reported by the Kaplan-Meier test (Breslow = 120.43; $P < .001$).

There was no difference in terms of perinatal morbidity and mortality in the fetuses of the 2 groups. However, when the data were analyzed all together, neonatal death was increased in fetuses with umbilical artery reversed flow (odds ratio 2.34, 95% confidence interval 1.16–4.73; χ^2 test $P < .05$) and abnormal ductus venosus reversed flow (odds ratio 4.18, 95% confidence interval 2.01–8.69; χ^2 test $P < .05$) (Tables 4 and 5).

Analysis of variance showed a significant difference between the birth weights of infants based on the perinatal morbidity and mortality (Fig. 3).

DISCUSSION

Our data show that there is a progression of cardiovascular changes in ideopathic growth-restricted fetuses that precede an abnormal biophysical profile, or the presence of variables or late decelerations. The study serially assessed flow velocity waveforms of the umbilical and middle cerebral artery, umbilical vein, and ductus venosus, biophysical profile, cardiotocography, and amniotic fluid in growth-restricted fetuses.

We detected 2 groups of ideopathic growth-restricted fetuses. The first group included growth-restricted fetuses in whom all measures became progressively abnormal; the second group included growth-restricted fetuses in whom 1 or more measures were not altered in presence of abnormal fetal heart rate or abnormal biophysical profile. However, there was no difference in terms of morbidity and mortality between the fetuses of the 2 groups. It is plausible that a type II error occurred due to the number of fetuses studied. It is also possible that group B fetuses may be proven in future studies to have a better outcome than group A fetuses.

Three studies have emphasized the appearance of a temporal sequence of Doppler and biophysical changes that precede the peripheral and central circulatory systems of the severely growth-restricted

Table 2. Outcomes of the 2 Groups

	Group A (n = 44)	Group B (n = 101)
Birth weight	515–1,180 g (median 870 g)	520–1,200 g (median 985 g)
Abnormal umbilical artery pH*	21 (47.3)	31 (30.7)
Apgar < 7 at 5 min	23 (52.3)	45 (44.5)
Normal outcome	12 (27.3)	45 (44.5)
Perinatal morbidity	13 (29.5)	21 (20.7)
Neonatal mortality	18 (40.9)	32 (31.7)
Fetal demise	1 (2.3)	3 (3)

Values are n (%) unless otherwise specified.
* A pH value was considered abnormal if the value was more than 2 standard deviations from the mean (normal values 7.28 ± 0.07).[21]

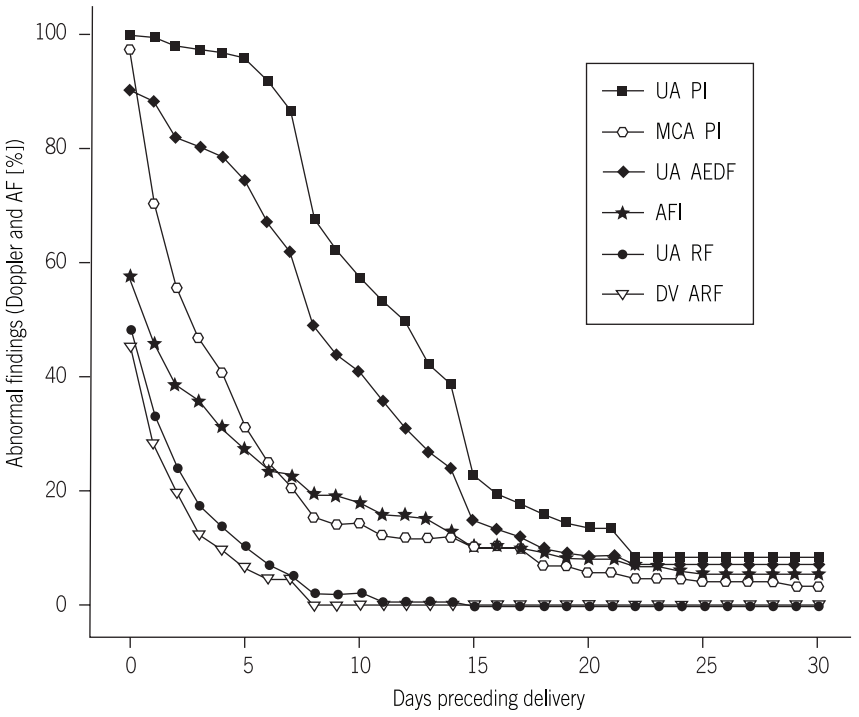

Fig. 1. Cumulative percentage for each abnormal finding has been obtained to describe the percentage of abnormal vessels in relationship to the distance from delivery (Time 0). UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; AEDF, absent end diastolic flow; AFI, amniotic fluid index; RF, reversed flow; DV, ductus venosus; ARF, absent or reversed flow.

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fetus at less than 32 weeks gestation.[9–11] The authors of these 3 studies deserve credit for providing novel insights into the disease process of the growth-restricted fetus.[17] However, although these observational studies suggest that there might be a common sequence of biophysical changes that indicate progressive fetal compromise in growth restriction, a careful review reveals some differences. For example, the involvement of the fetal brain and heart, as detected by an abnormal fetal heart rate, biophysical profile, or venous Doppler, is highly variable among the fetuses and does not follow a predictable pattern. Also, although amniotic fluid was among the first measures to become abnormal in Hecher's study,[9] it was among the last in Baschat's study.[10] Moreover, the criteria for defining an abnormal ductus venosus were different. The middle cerebral artery pulsatility index became progressively abnormal until delivery in 1 study,[9] whereas in another study 3 different patterns were described at the level of the middle cerebral artery.[10] In a previous study, Arduini et al[8] reported that in the week preceding an abnormal cardiotocography, the middle cerebral artery did not change. Moreover, 2 of the studies did not perform a biophysical profile,[9,11] whereas in another study[10] it was not clear what was the indication for delivery. Finally, when the data of 1 study were reanalyzed, it was shown that ductus venosus pulsatility index greater than 3 standard deviations from the mean for gestational age is associated with an increased risk of adverse perinatal outcome. However, the authors reported a 50% reduction in the incidence of adverse outcome for every additional week of gestation at delivery.[18]

Table 3. Stepwise Multiple Regression

Model	R^2	F	*P*
A	.896	250,200	.001
B	.900	1,028	.319
C	.930	11,558	.002
D	.938	3,387	.077
E	.972	29,71	.000
F	.974	1,69	.206

A, UA-PI; B, UA-PI, MCA-PI; C, UA-PI, MCA-PI, UA AEDF; D, UA-PI, MCA-PI, UA AEDF, AFI; E, UA-PI, MCA-PI, UA AEDF, AFI, UA RF; F, UA-PI, MCA-PI, UA AEDF, AFI, UA RF, DV-ARF (where UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; AEDF, absent end diastolic flow; AFI, amniotic fluid index; RF, reversed flow; DV, ductus venosus; ARF, absent or reversed flow).

R^2 values were obtained by adding the single vessels in the analysis. The dependent variable is the number of days from delivery, whereas the independent variables are represented by the abnormal Doppler frequencies vessel by vessel.

One of the reasons why the above studies reported conflicting results might be due to different types of growth-restricted fetuses being included in these studies and also to different tests used for timing delivery. Although our investigation shows similarities to previously reported studies, it has additional

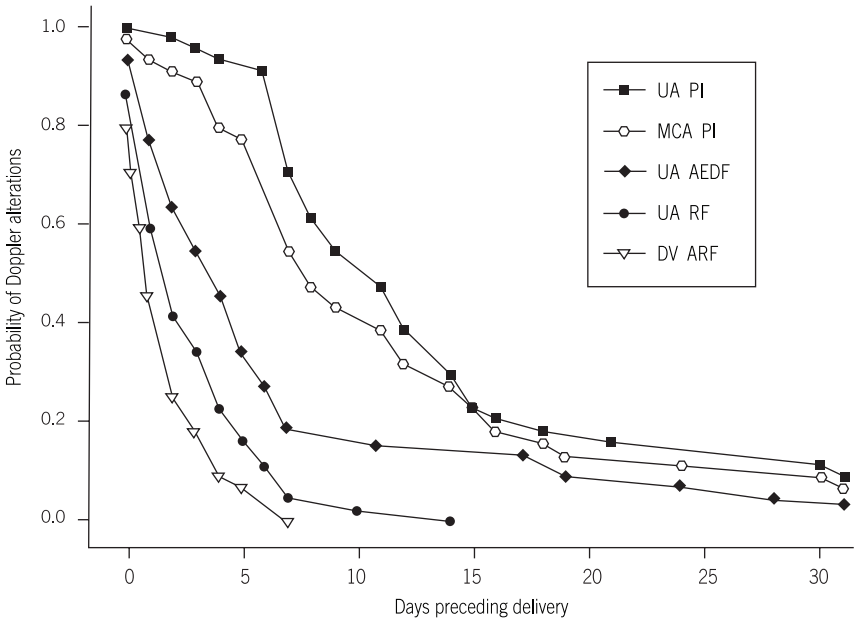

Fig. 2. Cumulative percentage for each abnormal finding has been obtained to describe the percentage of abnormal vessels in relationship to the distance from delivery (Time 0) by using Kaplan-Meyer approach. In this analysis only the cases in which all the alterations were present at time 0 were included. UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; AEDF, absent end diastolic flow; RF, reversed flow; DV, ductus venosus; ARF, absent or reversed flow.

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strengths: we were able to follow the Doppler changes that occurred in growth-restricted fetuses very early in the disease, a large number of growth-restricted fetuses were followed longitudinally, only patients who delivered before 32 weeks of gestation were included, and patients with chronic hypertension, pregnancy-induced hypertension, or other maternal pathology were excluded in such a way that only growth-restricted fetuses with abnormal Doppler, and no other reason for being growth restricted, were included in the study.

In our study, the variables that were significantly associated with perinatal outcome were umbilical artery reversed flow, ductus venosus reversed flow,

Table 4. Umbilical Artery Reversed Flow and Neonatal Deaths

	Neonatal Deaths		
	No	Yes	Total
UA-RF			
No	56 (58.9)	19 (38)	75 (51.7)
Yes	39 (41.1)	31 (62)	70 (48.3)
Total	95	50	145

UA, umbilical artery; RF, reversed flow.
Values are n (%).
Sensitivity 0.62, specificity 0.59, positive predictive value 0.44, negative predictive value 0.75.

Table 5. Ductus Venosus Absent or Reversed Flow and Neonatal Deaths

	Neonatal Deaths		
	No	Yes	Total
DV-ARF			
No	63 (66.3)	16 (32)	79 (54.5)
Yes	32 (33.7)	34 (68)	66 (45.5)
Total	95	50	145

DV, ductus venosus; ARF, absent or reversed flow.
Values are n (%).
Sensitivity 0.68, specificity 0.66, positive predictive value 0.52, negative predictive value 0.8.

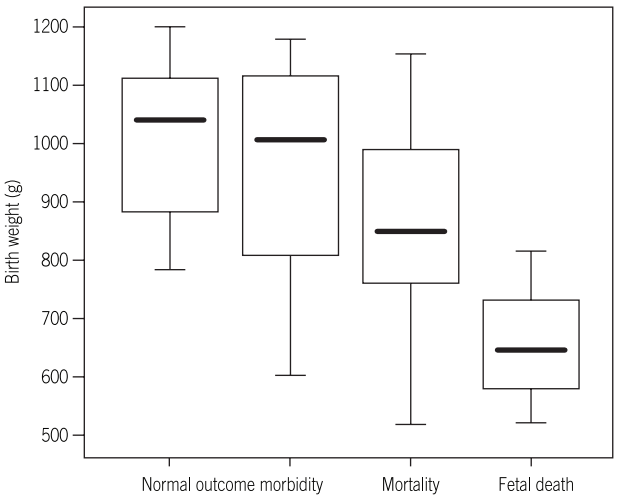

Fig. 3. Box and whisker plot of weight at delivery and perinatal outcome. In each box the dark line represents the median, and the borders represent the 25th and 75th percentiles. The whiskers represent the smallest and largest values observed.

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and birth weight. It is noteworthy that the absent or reversed flow of the ductus venosus, which is associated with a high perinatal mortality,[19] was seen 7–8 days before an abnormal biophysical profile or abnormal fetal heart rate test result. This is important because when there is umbilical artery or ductus venosus absent or reversed flow, the fetus could remain in utero for at least other 7–8 days before the appearance of a nonreassuring fetal testing. Before 32 weeks, 7–8 days can make a large difference in terms of perinatal morbidity and mortality; therefore, it is not clear whether in the presence of ductus venosus absent or reversed flow delivery should be performed. We speculate that delivering very premature growth-restricted fetuses with absent or reverse flow of the ductus venosus, despite a normal biophysical profile and reassuring fetal heart rate, is probably not a wise choice at this time. It is not clear to us why most of growth-restricted fetuses deteriorate in their biophysical profile or develop persistent variable or late decelerations and still have 1 or more normal measure. Perhaps we were too aggressive in delivering growth-restricted fetuses based on the variable decelerations. False-positive cases could have played a role in determining the delivery. In addition, the administration of steroids also could have played a role, because the steroids may affect fetal movements and breathing.[20]

We agree with others that a randomized trial based on Doppler compared with fetal heart rate monitoring is needed. However, we believe that more observational studies are required to fill the gap between the appearance of ductus venosus reversed flow and a nonreassuring fetal testing. Moreover, more observational studies are needed to elucidate the differences among idiopathic growth-restricted fetuses. For example, a first study should be observational and include other measures not included in this study to gather complete information. Following this observational study, a randomized trial could be designed.

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