Predictors of Neonatal Outcome in Early-Onset Placental Dysfunction

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OBJECTIVE: To identify specific estimates and predictors of neonatal morbidity and mortality in early onset fetal growth restriction due to placental dysfunction.

METHODS: Prospective multicenter study of prenataly diagnosed growth-restricted liveborn neonates of less than 33 weeks of gestational age. Relationships between perinatal variables (arterial and venous Dopplers, gestational age, birth weight, acid-base status, and Apgar scores) and major neonatal complications, neonatal death, and intact survival were analyzed by logistic regression. Predictive cutoffs were determined by receiver operating characteristic curves.

RESULTS: Major morbidity occurred in 35.9% of 604 neonates: bronchopulmonary dysplasia in 23.2% (n=140), intraventricular hemorrhage in 15.2% (n=92), and necrotizing enterocolitis in 12.4% (n=75). Total mortality was 21.5 % (n=130), and 58.3% survived without complication (n=352). From 24 to 32 weeks, major morbidity declined (56.6% to 10.5%), coinciding with survival that exceeded 50% after 26 weeks. Gestational age was the most significant determinant ($P<.005$) of total survival until $26^{6/7}$ weeks ($r^2=0.27$), and intact survival until $29^{2/7}$ weeks ($r^2=0.42$). Beyond these gestational-age cutoffs, and above birth weight of 600 g, ductus venosus Doppler and cord artery pH predicted neonatal mortality ($P<.001$, $r^2=0.38$), and ductus venosus Doppler alone predicted intact survival ($P<.001$, $r^2=0.34$).

CONCLUSION: This study provides neonatal outcomes specific for early-onset placenta-based fetal growth restriction quantifying the impact of gestational age, birth weight, and fetal cardiovascular parameters. Early gestational age and birth weight are the primary quantifying parameters. Beyond these thresholds, ductus venosus Doppler parameters emerge as the primary cardiovascular factor in predicting neonatal outcome.

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Prematurity is a leading cause of neonatal mortality and morbidity and an important antecedent to poor neurodevelopment and childhood and adult disease.[1] Among preterm neonates, birth weight below the 10th percentile is an independent risk factor for these adverse outcomes.[2,3] However, such neonates are a heterogeneous group that includes small, but appropriately grown, neonates who usually do well and others for whom small size is a manifestation of intrauterine growth restriction. The second group accounts for most of the morbidity and mortality among small neonates. Underlying etiologies for intrauterine growth restriction include aneuploidy,

nonaneuploid syndromes, viral infections, and associated fetal anomalies where outcomes are not altered by intervention. In contrast, placental dysfunction causes growth restriction in otherwise normal fetuses. These fetuses are then at risk for progressive metabolic deterioration, with manifestations in almost any organ system, leading to adverse fetal and neonatal outcomes.[4,5] Although intervention for fetal indications has the potential to improve outcome, it can also produce significant complications from iatrogenic preterm delivery.[6,7] Because the risk of complication in these otherwise normal fetuses after delivery reflects both the liabilities of intrauterine compromise and the penalties of prematurity, the balance of these determines whether intervention (principally delivery) will improve outcome. The recent Growth Restriction Intervention Trial suggests that this balance is especially important before 33 weeks of gestation.[8]

Prenatal identification of isolated placental dysfunction as a cause of fetal growth restriction is critical. Ultrasound biometry documenting small fetal size implies placental dysfunction, while Doppler ultrasonography directly demonstrates placental vascular abnormality. Specifically, as the villous vascular tree becomes compromised, elevated umbilical artery Doppler blood flow resistance rises progressively, reflecting the structural abnormality.[9] The combination of a small fetal abdominal circumference with elevated umbilical artery Doppler blood flow resistance provides the most specific diagnosis of placenta-based fetal growth restriction.[10] Doppler evaluation of fetal cerebral and venous circulations has amplified our understanding of placental dysfunction, providing evidence that placenta-based fetal growth restriction manifests progressive cardiovascular signs heralding fetal acidemia and stillbirth.[4,5,11,12]

Prenatal techniques assessing fetal risk have evolved significantly in the past decade as we understand the process of fetal growth restriction with increasing specificity. At the same time, relating fetal findings to complication rates specific to preterm growth-restricted neonates has not yet been realized in clinical practice. This study aimed to ascertain gestational age–specific neonatal survival and complication rates for liveborn growth-restricted neonates with early onset placental dysfunction.

PARTICIPANTS AND METHODS

A prospective international multicenter study was conducted from January 2000 to March 2006 at 12 academic perinatal centers with tertiary neonatal intensive care. Patients carrying a fetus with suspected fetal growth restriction were included if they had accurate assignment of gestational age by menstrual dating and corroborating sonogram at less than 20 weeks of gestation and met the following criteria: 1) singleton fetus with normal anatomy on high-resolution sonography, 2) fetal abdominal circumference less than the 5th percentile for gestation, 3) placental vascular dysfunction documented by elevated umbilical artery pulsatility index by local reference ranges, 4) liveborn delivery at 24–$32^{6/7}$ weeks of gestation, 5) normal fetal/neonatal karyotype, and 6) intact membranes without evidence of chorioamnionitis and/or perinatal infection.

In patients meeting inclusion criteria, consistent Doppler ultrasound examinations were conducted serially. Doppler waveforms were obtained according to standards established by the originating institution. These techniques ensure highest reproducibility of measurements from each vessel.[4] In the umbilical artery, end-diastolic velocity was classified as either present or absent/reversed. In the middle cerebral artery, a pulsatility index more than two standard deviations below gestational age mean was defined as brain-sparing, indicating abnormally reduced cerebral blood flow resistance. The ductus venosus Doppler index was considered abnormally elevated when more than two standard deviations above the gestational mean. Ductus venosus velocity during atrial systole was characterized as forward or absent/reversed. For purpose of analysis the last complete Doppler assessment was used to assign the degree of testing abnormality.

Indication for, gestational age at and route of delivery, birth weight, cord artery birth pH, and Apgar scores at 1 and 5 minutes were recorded. All pregnancies were managed with the intention to intervene for nonreassuring fetal status. Fetal acidemia was defined by a cord artery pH below 7.20, while severe metabolic compromise was defined by a pH of 7.00 or less or a base deficit below −12.0 or both.[13] A five-minute Apgar below 7 assigned by the attending neonatologist was evidence of difficult resuscitation.

Bronchopulmonary dysplasia was diagnosed by typical radiographic criteria.[3] Intraventricular hemorrhage was classified by Papile's criteria,[14] grade 3 hemorrhage being associated with ventricular dilatation and grade 4 with parenchymal extension. The diagnosis of necrotizing enterocolitis required the presence of more than one clinical sign, such as bilious gastric aspirate or emesis, abdominal distention, occult or gross fecal blood, more than one radiographic finding such as pneumatosis intestinalis, and hepatobiliary gas or pneumoperitoneum.[3] Neonates with any of these complications were consid-

ered to have suffered major morbidity. Neonatal death during the first 28 days was ascertained. Gross intact survival was defined by the absence of these morbidities until discharge.

Standardized information on prenatal Doppler findings, delivery circumstances, cord artery pH, Apgar scores, and neonatal course were submitted to the coordinating study center at the University of Maryland, Baltimore. Approval for the study protocol by the local institutional review board was obtained by each participating center. Statistical analysis was performed in consultation with the Division of Biostatistics and Bioinformatics, Department for Epidemiology and Preventive Medicine of the University of Maryland School of Medicine. Results of the last Doppler study before delivery were analyzed with SPSS 13.0 (SPSS Inc, Chicago IL). Proportional distribution of categorical variables was studied by the χ^2 or Fisher exact tests. Continuous variables were compared by Mann-Whitney *U* or *t* test based on their distribution as determined by the Shapiro-Wilk test. Intercenter variation for Doppler parameters, gestational age at delivery, birth weight, and categorical outcome variables was evaluated with χ^2 and Mann-Whitney *U* tests. Subsequently, relationships between outcomes were compared between individual centers and the residual cohort. Finally, independent contribution of individual centers to mortality and morbidity was assessed by logistic regression analysis.

Stepwise forward logistic regression with analysis of colinearity was performed to identify estimates of neonatal morbidity, mortality, and intact survival. For this analysis Doppler parameters, birth weight, gestational age, umbilical artery cord artery pH, birth acidemia, and a 5-minute Apgar score less than 7 were independent variables, and individual outcomes the dependent variables. Each variable was regressed against other predictors to determine its tolerance ($1\text{-}R^2$). Variables with a variance inflation factor (1/tolerance) of greater than 10 were excluded for colinearity.[15] For continuous variables identified as significant contributors, receiver operating characteristic curves were computed. The area under the curve and 95% confidence interval of the receiver operating characteristic curve were analyzed, and predictive cutoffs were determined.[16] $P<.05$ was considered significant for all statistic tests. The required *P* value was adjusted to $<.01$ or $<.001$ according to the number of tests performed in an individual analysis.

RESULTS

Six hundred four patients met inclusion criteria. In the whole patient cohort, median maternal age was 29 years (range 14–43), and the majority of patients were nulliparous (n=380, 62.9%) and predominantly Caucasian (n=513, 84.9%). The majority had markedly abnormal umbilical artery Doppler; end-diastolic velocity was absent/reversed in 362 (59.9%), 424 (70.2%) had brain sparing, and the ductus venosus Doppler index was elevated in 283 (46.9%). In 128 fetuses (21.1%), ductus venosus atrial systolic velocities were either absent or reversed. Delivery was almost exclusively by cesarean delivery without labor (588, 97.4%), in most instances for nonreassuring fetal assessment or fetal distress. Almost all patients (530, 87.8%) received at least one course of corticosteroids, 80.5% (486) completing a course before delivery. The median birth weight was 600 g (range 390–1,510). The umbilical artery pH was less than 7.20 in 223 (36.9%), and severe metabolic compromise was present in 30 (5.0%) neonates. The 5-minute Apgar score was less than 7 in 169 neonates (28%) (Table 1).

Bronchopulmonary dysplasia was the most frequent neonatal complication (n=140, 23.2 %), followed by severe intraventricular hemorrhage (n=92, 15.2%) and necrotizing enterocolitis (n=75, 12.4%). At least one of these complications was present in 35.9% of neonates (n=217). Incidence of bronchopulmonary dysplasia and severe intraventricular hemorrhage was significantly related to gestational age, with the highest rates between 25 and 28 weeks of gestation. Although the incidence of necrotizing enterocolitis also peaked during these weeks, the proportional distribution was not significantly related to gestational age. As gestational age advanced, a drop in major morbidity from 56.6% at 24 weeks to 10.5% at 32 weeks resulted in a significant increase in neonatal survival and intact survival (Fig. 1).

Mortality within 28 days of life was 20.0% (n=121), and the overall mortality before discharge was 21.5% (n=130). The majority of all deaths (n=86) occurred after the first week of life. The intact survival rate was 58.3% (352 infants of 604 live births). Figure 1 depicts the significant increase in neonatal survival and intact survival with advancing gestational age. Median survival gained per day in utero was 2% (range 1.1–2.6) between 24 and 27 weeks and 1% (range 0–1) thereafter. Components of neonatal demise decreased sequentially. The early neonatal death rate fell sharply for births after 27 weeks, while late neonatal deaths plateaued for births after 30 weeks. Infant mortality was virtually constant across gestation (Table 2).

Of the potential predictors of perinatal outcomes, umbilical artery and ductus venosus Doppler abnormalities, severe metabolic compromise, and low

Table 1. Maternal Demographics and Doppler and Perinatal Characteristics

	Intact Survivors (n=352)	Nonintact Survivors (n=252)	*P*
Maternal age [y, median (range)]	28 (14–43)	28 (16–40)	.144
Parity			
Para 0	221 (62.9)	159 (62.8)	.938
Para 1	97 (27.4)	69 (22.3)	.962
Para 2	27 (7.6)	19 (6.7)	.952
Para 3 or greater	7 (2.0)	5 (4.1)	.997*
Maternal race			
African American	36 (10.2)	36 (14.3)	.129
Asian	7 (2.0)	7 (2.8)	.589*
Caucasian	307 (87.2)	206 (81.7)	.064
Hispanic	2 (0.6)	3 (1.2)	.654*
Umbilical artery end diastolic velocity			
Present	163 (46.3)	79 (31.3)	<.001
Absent	78 (22.2)	55 (21.8)	.923
Reversed	111 (31.5)	118 (46.8)	<.001
Brain sparing	235 (66.8)	189 (75.0)	.035
Ductus venosus			
Elevated Doppler index	133 (37.8)	150 (59.5)	<.001
Absent/reversed atrial systolic velocity	43 (12.2)	(85 33.7)	<.001
Antenatal steroids			
None	49 (13.9)	25 (9.9)	.139
Incomplete course	21 (6.0)	23 (9.1)	.140
Completed course	282 (82.7)	204 (86.4)	.225
Gestational age at delivery [median (range)]	$30^{1/7}$ ($25^{2/7}$–$32^{6/7}$)	$28^{0/7}$ ($24^{0/7}$–$32^{6/7}$)	<.001
Birth weight [g, median (range)]	958 (410–1,510)	697 (330–1,500)	<.001
Mode of delivery			
Spontaneous vaginal	10 (2.8)	6 (2.4)	.802*
Cesarean delivery	342 (97.2)	246 (97.6)	
Indication for delivery			
Nonreassuring biophysical profile score	58 (16.5)	40 (15.9)	.843
Nonreassuring Doppler parameters	109 (31.0)	79 (31.3)	.920
Nonreassuring fetal heart rate	59 (16.8)	29 (11.5)	.071
Spontaneous late decelerations	5 (1.4)	12 (4.8)	.022*
Fetal distress/bradycardia	8 (2.3)	4 (1.6)	.797*
Oligo-/anhydramnios	34 (9.7)	21 (8.3)	.577
Severe preeclampsia	39 (11.1)	40 (15.6)	.331
HELLP	19 (5.4)	24 (9.5)	.052
Eclampsia	2 (0.6)	2 (0.8)	.998*
Placental abruption	11 (3.1)	1 (0.4)	.018
Cord artery pH [median (range)]	7.26 (6.9–7.40)	7.24 (6.85–7.36)	.014
pH less than 7.20	100 (33.6)	123 (55.2)	<.001
pH 7.00 or less and/or BE –12.0 or less	13 (5.5)	17 (11.0)	.052
5-minute Apgar less than 7	56 (15.9)	113 (56)	<.001

HELLP, hemolysis, elevated liver enzymes, low platelets; BE, base excess.
Data are presented as n (%) of all patients or median (range) where indicated.
* Indicates analysis by Fisher exact test; all other categorical variables were tested by χ^2 analysis. Continuous variables were tested by Mann-Whitney *U*.

5-minute Apgar scores varied significantly across gestational ages (Table 2). The distribution of gestational age and birth weight differed significantly between healthy and affected babies. Likelihood ratios for major neonatal morbidity, mortality, and intact survival demonstrated statistically significant relationships between almost all perinatal variables and outcomes. Only middle cerebral artery Doppler, severe metabolic compromise, gender, and delivery indication had little or no impact (Table 3).

Logistic regression identified gestational age at delivery, low 5-minute Apgar, umbilical artery absent or reversed end-diastolic umbilical artery flow velocity, and ductus venosus velocity, forward or absent/reversed, as statistically significant predictors of major morbidity ($P<.005$, Nagelkerke $r^2=0.27$). Neonatal

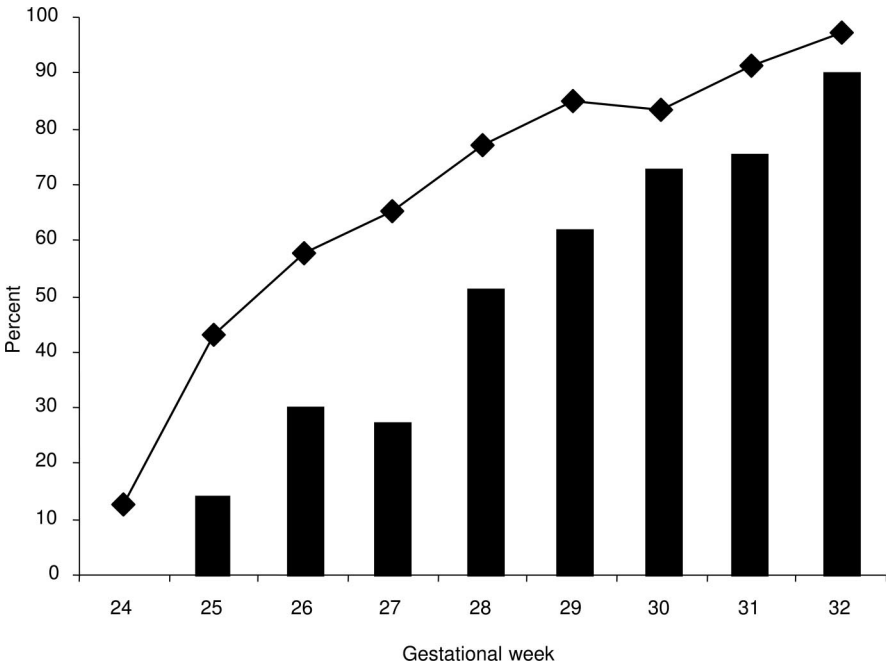


Fig. 1. Neonatal survival and intact survival rates per gestational week. This figure shows the increase in survival *(black diamonds)* and intact survival rates until discharge *(black bars)* in growth-restricted neonates with advancing gestational week.

Baschat. Neonatal Outcome in Fetal Growth Restriction. Obstet Gynecol 2007.

Table 2. Doppler and Outcome Individual Characteristics by Gestational Week

	Gestational Week									
	24	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	***P***
Infants delivered (n)	16	21	40	78	78	93	109	93	76	
Umbilical artery EDV										
Positive	6 (37.5)	6 (28.6)	5 (12.5)	14 (17.9)	27 (34.6)	38 (40.9)	45 (41.3)	45 (48.4)	56 (73.7)	
Absent	4 (25)	9 (42.9)	10 (25)	12 (15.4)	22 (28.2)	25 (26.9)	34 (31.2)	10 (10.8)	7 (9.2)	<.001
Reversed	6 (37.5)	6 (28.6)	25 (62.5)	52 (66.7)	29 (37.2)	30 (32.3)	30 (26.5)	38 (40.9)	13 (17.1)	
Brain sparing	11 (68.8)	16 (76.2)	33 (82.5)	61 (78.2)	56 (71.8)	62 (66.7)	80 (72.4)	64 (68.8)	41 (54.0)	.039
Elevated DV index	11 (68.8)	8 (38.1)	27 (67.5)	52 (66.7)	37 (47.4)	42 (45.2)	42 (38.5)	45 (48.4)	19 (25)	<.001
DV-RAV	0 (0)	5 (23.8)	12 (30)	32 (41)	19 (24.4)	18 (19.4)	13 (11.9)	20 (21.5)	9 (11.8)	<.001
Cord pH less than 7.20	5 (31.3)	9 (42.9)	17 (42.5)	37 (47.4)	31 (39.7)	39 (41.9)	36 (33.0)	28 (30.1)	21 (27.6)	.146
pH less than 7.00 and/or BE less than –12	1 (6.3)	4 (19.0)	0 (0)	11 (14.1)	1 (1.3)	3 (3.2)	5 (4.6)	1 (1.1)	4 (5.3)	.063*
5-minute Apgar less than 7	8 (50)	8 (38.1)	13 (32.5)	30 (38.5)	27 (34.6)	31 (33.3)	25 (22.9)	19 (20.4)	8 (10.5)	<.001*
BPD	4 (28.6)	9 (42.9)	19 (47.5)	37 (47.4)	20 (25.6)	25 (26.9)	13 (11.9)	11 (11.8)	2 (2.6)	<.001*
Grade III/IV IVH	9 (57.1)	6 (28.6)	9 (22.2)	21 (26.9)	14 (18)	12 (12.9)	11 (10.1)	9 (9.7)	1 (1.3)	<.001*
NEC	2 (14.3)	1 (4.8)	6 (15)	17 (21.8)	13 (16.7)	13 (14)	11 (10.1)	7 (7.5)	5 (6.6)	.085*
Early NND	8 (50.0)	9 (42.9)	8 (20)	10 (12.8)	3 (3.8)	0 (0)	5 (4.6)	1 (1.1)	0 (0)	<.001*
Late NND	4 (25)	3 (14.3)	8 (20)	15 (19.2)	14 (18)	13 (14)	12 (11.0)	7 (7.5)	1 (1.3)	<.001*
Infant death	2 (12.5)	0 (0)	1 (2.5)	2 (2.6)	1 (1.3)	1 (1.1)	1 (1)	0 (0)	1 (1.3)	.107*

EDV, end-diastolic velocity; DV, ductus venosus; DV-RAV, ductus venosus absence or reversal of atrial velocities; BE, base excess; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NND, neonatal death.

Data are presented as n (%).

* Indicates analysis by Fisher exact test; all other analyses by χ^2 test. *P* indicates overall distribution of all degrees of abnormality.

mortality was determined by gestational age at delivery, birth weight, low 5-minute Apgar score, cord artery pH less than 7.20, and ductus venosus velocity, forward or absent/reversed ($P<.001$, $r^2=0.42$). Intact survival to discharge was determined by gestational age at delivery, birth weight, low 5-minute Apgar score, umbilical artery absent or reversed end-diastolic umbilical artery flow velocity, and ductus venosus velocity, forward or absent/reversed (all $P<.001$, $r^2=0.41$).

Thresholds for the impact of gestational age were different for neonatal mortality and neonatal morbidity. In the logistic regression analysis, gestational age was the most significant determinant of neonatal survival until $26^{6/7}$ weeks and a significant contributor

Table 3. Perinatal Variables and Likelihood of Outcomes

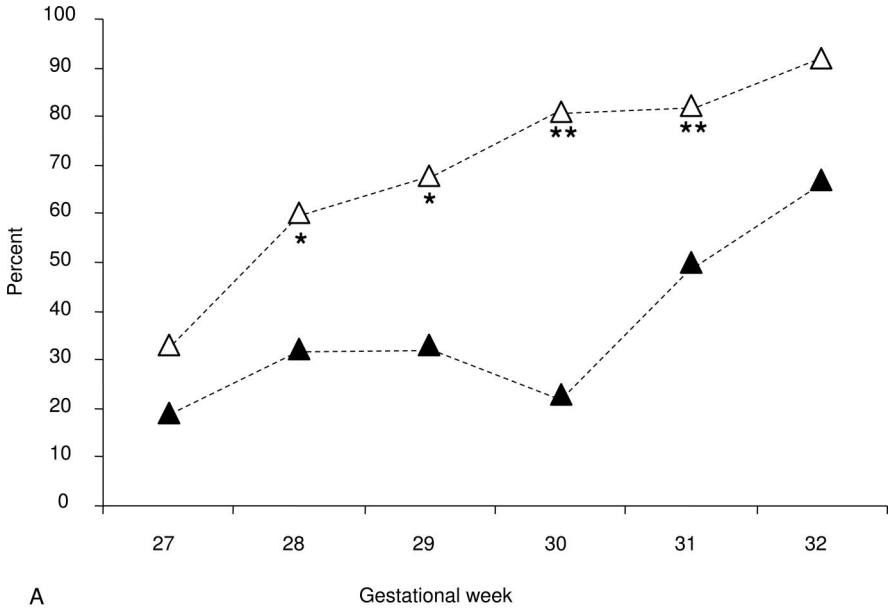
	Major Morbidity (n=217)		Neonatal Death (n=121)		Intact Survival (n=352)	
	LR (95% CI)	*P*	LR (95% CI)	*P*	LR (95% CI)	*P*
Fetal variables						
UA end-diastolic velocity						
Present (n=242)	0.65 (0.46–0.92)	.016	0.40 (0.25–0.63)	<.001	1.89 (1.35–2.65)	<.001
Absent/reversed (n=362)	1.32 (1.1–1.7)	.020	2.12 (1.44–3.12)	<.001	0.76 (0.68–0.88)	<.001
Brain sparing						
Absent (n=180)	0.72 (0.56–0.94)	.011	0.58 (0.39–0.88)	.007	1.17 (1.02–1.35)	.029
Present (n=424)	1.12 (1.1–1.33)	.012	1.12 (1.04–1.21)	.001	0.78 (0.63–0.98)	.035
Ductus venosus Doppler						
Normal (n=321)	0.58 (0.46–0.72)	<.001	0.37 (0.26–0.53)	<.001	1.45 (1.26–1.68)	<.001
Elevated index (n=283)	2.36 (1.67–3.31)	<.001	3.39 (2.21–5.22)	<.001	0.41 (0.3–0.58)	<.001
Ductus venosus a-wave						
Antegrade (n=476)	0.51 (0.42–0.62)	<.001	0.33 (0.25–0.45)	<.001	1.92 (1.5–2.49)	<.001
Absent/retrograde (n=128)	3.33 (2.25–4.98)	<.001	4.45 (2.88–6.89)	<.001	0.27 (0.18–0.41)	<.001
Delivery indication						
Maternal (n=125)	0.9 (0.70–1.51)	.097	1 (0.9–1.1)	.104	0.89 (0.66–1)	.052
Fetal (n=456)	1.07 (0.91–1.25)	.101	1 (0.68–1.47)	.204	1.2 (0.95–1.45)	.078
Neonatal variables						
Gestational age (wk)						
Less than $26^{6/7}$ (n=77)	2.72 (1.68–4.43)	<.001	5.95 (3.59–9.87)	<.001	0.14 (0.08–0.25)	<.001
More than $29^{2/7}$ (n=280)	0.38 (0.29–0.48)	<.001	0.27 (0.18–0.40)	<.001	2.12(1.79–2.5)	<.001
Birth weight (g)						
Less than 600 (n=117)	2.63 (1.75–3.98)	<.001	5.66 (3.62–8.84)	<.001	0.15 (0.09–0.24)	<.001
More than 800 (n=253)	0.47 (0.38–0.59)	<.001	0.32 (0.22–0.45)	<.001	2.1 (1.76–2.5)	<.001
Gender						
Female (n=298)	0.93 (0.83–1.05)	.270	1.01 (0.94–1.1)	.761	1.1 (0.88–1.28)	.564
Male (n=306)	1.2 (0.92–1.4)	.239	0.94 (0.69–1.3)	.730	0.96 (0.84–1.1)	.545
5-minute Apgar less than 7						
No (n=435)	0.52 (0.42–0.63)	<.001	0.25 (0.18–0.34)	<.001	2.06 (1.64–2.57)	<.001
Yes (n=169)	3.01 (2.13–4.43)	<.001	6.43 (4.19–9.88)	<.001	0.23 (0.16–0.34)	<.001
pH less than 7.20						
No (n=298)	0.59 (0.46–0.72)	<.001	0.31 (0.22–0.49)	<.001	1.42 (1.23–1.75)	<.001
Yes (n=223)	2.43 (1.7–3.51)	<.001	4.2 (2.66–6.67)	<.001	0.41 (0.29–0.59)	<.001
Severe metabolic compromise						
No (n=362)	0.63 (0.43–0.93)	.044	0.41 (0.24–0.73)	.010	1.43 (0.95–2.18)	.052
Yes (n=30)	2.16 (1.03–4.6)	.038	3.12 (1.38–7.05)	.014	0.47 (0.22–1)	.067

LR, likelihood ratio; CI, confidence interval; UA, umbilical artery.
Significances are based on χ^2 analysis of proportional distribution.

to major morbidity until $29^{2/7}$ weeks of gestation. By receiver operating characteristic curve analysis, gestational age greater than $27^{6/7}$ weeks provided the best prediction of survival (sensitivity 68.5%, specificity 68.8%, area under the curve [AUC] 0.75, 95% confidence interval [CI] 0.70–0.80, $P<.001$), and gestational age of $29^{2/7}$ weeks provided the best prediction of intact survival without major morbidity (sensitivity and specificity of 68.2%, AUC 0.77, 95% CI 0.73–0.80, $P<.001$). Similarly, birth weight loses its statistical impact on mortality and major morbidity above 600 g. When birth weight is analyzed as an individual predictor by receiver operating characteristic curve, the threshold of 800 g provides the best prediction of intact survival (sensitivity 71.9%, specificity 67.1%, AUC 0.76, 95% CI 0.72–0.79, $P<.001$).

Once these thresholds for birth weight and gestational age were exceeded, ductus venosus velocity, forward or absent/reversed, and a cord artery pH less than 7.20 remained the only significant predictors of neonatal mortality ($P<.001$, $r^2=0.38$). Above a 600-g birth weight and beyond $29^{2/7}$ weeks of gestation, ductus venosus velocity, forward or absent/reversed, was the only statistically significant predictor of intact survival ($P<.001$, $r^2=0.34$). The significant impact of ductus venosus velocity, forward or absent/reversed, on intact survival and neonatal mortality between 28 and 31 weeks of gestation is illustrated in Figure 2.

Intercenter comparison was limited by the small number in individual cells, but differences in mortality and total morbidity were explained by disease severity not center identity. In the logistic regression



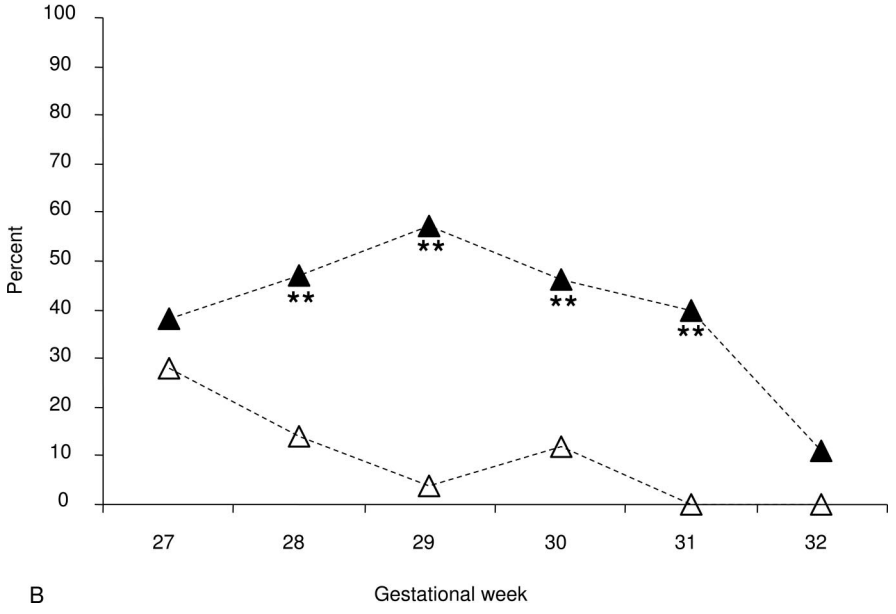


Fig. 2. Neonatal mortality and intact survival related to the ductus venosus a-wave. The figures show neonatal mortality rates for fetuses with forward flow during atrial systole in the ductus venosus (*open triangles* indicate forward flow in atrial systole) and those with absent, or reversed flow (*solid triangles* indicate absent or reversed flow in atrial systole). **A.** Intact survival. **B.** Neonatal mortality. Significant χ^2 comparisons for fetuses with positive and absent or reversed ductus venosus a-wave within each gestational week are indicated. * $P<.05$; ** $P<.005$.

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analysis, neither center of origin nor country of origin influenced the relationship between gestational age, birth weight, and Doppler parameters and neonatal morbidity (Nagelkerke $r^2=0.05$, $P=.796$), neonatal death (Nagelkerke $r^2=0.09$, $P=.534$) and intact survival (Nagelkerke $r^2=0.06$, $P=.206$).

DISCUSSION

Fetal growth restriction is a prominent contributor to perinatal mortality and morbidities extending all the way into adulthood.[1–3,17] In otherwise normal fetuses, the adverse sequelae of growth-restricted follow the interactions of deteriorating fetal status, poor transition to extrauterine life, and prematurity.[3,4,8,11,12,18] The at-risk growth-restricted fetus is now reliably identified by high resolution ultrasound evaluation of anatomy and size, combined with Doppler ultrasonography for umbilical artery flow dynamics.[10] Fetal cardiovascular responses to placental dysfunction and risks of deterioration are further assessed with arterial and precordial venous Doppler.[4,5,11,12,19] Using these ultrasound tools, we can precisely depict the fetal effects of placental failure. But because there is no effective therapy for the failing placenta, we are

left with only two management options: wait for organ maturation, accepting an increasing risk of fetal acidemia and stillbirth, or deliver and accept the risk of permanent injury from prematurity.

Avoiding unpredictable intrauterine risks and choosing management of the baby in the neonatal intensive care unit (NICU) may seem an easy option. However, in the NICU the combination of fetal growth restriction and prematurity is much worse than prematurity alone.[3,6,7] This study provides significant new guidance in that area. Because we studied a large group of prospectively identified growth-restricted fetuses with multi-vessel Doppler, we are able to quantify the impacts of fetal cardiovascular and perinatal variables on critical neonatal outcomes. Across the gestational ages with highest clinical relevance, the data provide gestational and birth weight thresholds relevant for managing clinicians and parents alike. These data apply specifically to counseling and planning management in fetal growth restriction. Neonatal survival first exceeds 50% after 26 weeks, 2 weeks later than in appropriately grown counterparts.[3,6,7] Intact survival consistently exceeds 50% only after 28 weeks. The chance to improve neonatal survival by 2% for each day in utero emphasizes efforts to maximize gestational age until at least 27 weeks and 600 g are attained.

In a general sense, the importance of gestational age in fetal growth restriction has been recognized. In the NICU, small babies contribute disproportionately to adverse outcomes.[3] This nonspecific association is reflected in the standard counseling given to prospective mothers of growth-restricted infants. Analysis of perinatal databases also demonstrated the relationship of small fetal size to poor outcome but did not recognize the specific diagnosis of placenta-based fetal growth restriction.[7] When placenta-based fetal growth restriction is quantified by prospective Doppler investigation, the effect of gestational age is so dominant that the influence of cardiovascular parameters is obscured.[4,5,11] The value of this large study is our ability to stratify neonatal outcomes by weekly increments, thereby distinguishing the effect of fetal cardiovascular status independently of gestational age. Beyond 27 weeks, ductus venosus abnormality emerges as the statistically important fetal cardiovascular predictor of neonatal complication. Before this, the impact of gestational age is so important that ductus venosus Doppler alone does not provide sufficient stratification of risk.

Absence or reversal of the ductus venosus a-wave predicts a marked decline in intact survival in our population of growth-restricted neonates. As opposed to placental or cerebral arterial abnormalities, which may be present for weeks, ductus venosus changes occur late in the progression of placenta-based fetal growth restriction.[5,12,20] The final step in progression, reversal of the ductus venosus a-wave, indicates risk for fetal cardiac, hepatic, and generalized metabolic failures,[21] which bear immediate relationship to neonatal performance. As such, ductus venosus velocity, forward or absent/reversed, is likely a reliable trigger for intervention in severe fetal growth restriction beyond 27 weeks of gestation.

To date, the lack of reliable delivery triggers across the whole spectrum of preterm gestation is highlighted by the frequency of iatrogenic prematurity in fetal growth restriction.[6,22–24] When umbilical artery Doppler is used alone to assign risk, delivery is too early. The Growth Restriction Intervention Trial study suggests that fear of fetal deterioration is a poor trigger for intervention anytime before 33 weeks. Fetal growth restriction infants randomized to early delivery did somewhat better than infants randomized to "wait for deterioration," by virtue of lower stillbirth rate. However, a 2-year follow-up study showed that survivors of early delivery paid a severe price, with a cerebral palsy rate of 10% compared with a 0% cerebral palsy rate with delayed delivery.[8,18] The Growth Restriction Intervention Trial is not a management trial; it does not identify delivery triggers.

Although ductus venosus velocity, forward or absent/reversed, may represent the best cardiovascular trigger, there may be other fetal parameters of equal importance. Short-term variation of the fetal heart rate is a biophysical parameter examined by cardiotocography that reflects central nervous system function. In severe fetal growth restriction, the ductus venosus and short-term variation become abnormal in parallel.[20] Other fetal behaviors, such as those studied in the biophysical profile score, also show late deterioration in fetal growth restriction. A pattern of cardiovascular deterioration culminates in loss of biophysical variables as placental dysfunction worsens.[25] Awaiting such a progression may allow safe extension of the pregnancy complicated by fetal growth restriction.

Safe prolongation of intrauterine time would accomplish several goals. At 24–26 weeks, safe delay would allow growth-restricted fetuses to reach a high likelihood for viability. Anytime before 34 weeks, withholding delivery allows administration of antenatal steroids which makes a critical difference in respiratory performance of the growth-restricted neonates.[3,5] The implications of delaying delivery even longer need to be evaluated in the context of long-term neurodevelopment.

The Trial of Umbilical and Fetal Flow in Europe is currently underway, investigating the ductus veno-

sus and short-term variation as delivery triggers in fetal growth restriction.[26] Additional antenatal predictors may need to be considered because the combination of fetal and neonatal factors accounted for only 40% of adverse outcomes in our study. Several nonrandomized studies suggest that, even in the face of Doppler deterioration, normal Biophysical Profile Scoring can support safely postponing delivery.[19,27–29]

This study quantifies the impact of gestational age, birth weight, and ductus venosus Doppler parameters on neonatal outcome in placenta-based fetal growth restriction. In these patients, expectations need to orient themselves along the specific outcomes provided here. Thresholds for mortality emphasize the importance of safe prolongation at very early gestational ages. Beyond these thresholds, absence or reversal of the ductus venosus a-wave emerges as the primary fetal cardiovascular parameter affecting neonatal outcome and, therefore, requires evaluation in a randomized management trial.

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