Fetal cerebral Doppler changes and outcome in late preterm fetal growth restriction: prospective cohort study

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CONTRIBUTION

What are the novel findings of this work?
In this prospective multicenter observational study of late preterm singleton pregnancies at risk of fetal growth restriction (FGR), fetal cerebral Doppler changes were found to be associated with adverse perinatal outcome.

What are the clinical implications of this work?
We confirm an association between abnormal fetal cerebral Doppler and adverse perinatal outcome in late preterm singleton pregnancies at risk of FGR. Whether cerebral flow changes are a marker of fetal compromise and whether intervention changes the risk for poor outcome can be answered only in a randomized intervention study.

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ORIGINAL PAPER

ABSTRACT

Objectives *To explore the association between fetal umbilical and middle cerebral artery (MCA) Doppler abnormalities and outcome in late preterm pregnancies at risk of fetal growth restriction.*

Methods *This was a prospective cohort study of singleton pregnancies at risk of fetal growth restriction at 32 + 0 to 36 + 6 weeks of gestation, enrolled in 33 European centers between 2017 and 2018, in which umbilical and fetal MCA Doppler velocimetry was performed. Pregnancies were considered at risk of fetal growth restriction if they had estimated fetal weight and/or abdominal circumference (AC) < 10th percentile, abnormal arterial Doppler and/or a fall in AC growth velocity of more than 40 percentile points from the 20-week scan. Composite adverse outcome comprised both immediate adverse birth outcome and major neonatal morbidity. Using a range of cut-off values, the association of MCA pulsatility index and umbilicocerebral ratio (UCR) with composite adverse outcome was explored.*

Results *The study population comprised 856 women. There were two (0.2%) intrauterine deaths. Median gestational age at delivery was 38 (interquartile range (IQR), 37–39) weeks and birth weight was 2478 (IQR, 2140–2790) g. Compared with infants with normal outcome, those with composite adverse outcome (n = 93; 11%) were delivered at an earlier gestational age (36 vs 38 weeks) and had a lower birth weight (1900 vs 2540 g). The first Doppler observation of MCA pulsatility index < 5th percentile and UCR Z-score above gestational-age-specific thresholds (1.5 at 32–33 weeks and 1.0 at 34–36 weeks) had the highest relative risks (RR) for composite adverse outcome (RR 2.2 (95% CI, 1.5–3.2) and RR 2.0 (95% CI, 1.4–3.0), respectively). After adjustment for confounders, the association between UCR Z-score and composite adverse outcome remained significant, although gestational age at delivery and birth-weight Z-score had a stronger association.*

Conclusion *In this prospective multicenter study, signs of cerebral blood flow redistribution were found to be associated with adverse outcome in late preterm singleton pregnancies at risk of fetal growth restriction. Whether cerebral redistribution is a marker describing the severity of fetal growth restriction or an independent risk factor for adverse outcome remains unclear, and whether it is useful for clinical management can be answered only in a randomized trial. © 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Poor third-trimester fetal growth is associated with adverse perinatal outcome[1,2]. The only therapeutic option is timely delivery. This poses a dilemma as delivery too early risks the baby suffering the effects of moderate–late prematurity, whereas delivery too late risks further fetal compromise increasing the risk of suboptimal outcome or stillbirth. There remains little evidence on which to base the timing of delivery of such babies in the late preterm period. The problem is twofold: first, there is no consensus on how to identify the fetus at risk for compromise and, second, an evidence-based monitoring strategy remains to be defined[3].

The association between fetal middle cerebral (MCA) and umbilical artery Doppler impedance ratios and adverse outcome has been well described, deriving mainly from retrospective studies[4–6]. The key question is whether abnormal cerebral artery Doppler is a non-injurious response to fetal compromise or is itself a marker of compromise and ongoing damage necessitating early delivery. Without this information, it cannot be known if using these Doppler parameters to decide on intervention by delivery is beneficial for infant outcome. Guidelines of the Royal College of Obstetricians and Gynaecologists on small-for-gestational-age (SGA) fetuses[7] state that 'MCA Doppler may be a more useful test in SGA fetuses detected after 32 weeks of gestation', but perhaps wisely do not define the parameters that should trigger a decision to deliver. The usefulness of MCA Doppler and cerebral blood flow redistribution in improving perinatal and/or long-term outcome can be assessed only by randomization in a prospective study, but current data are insufficient to decide how such a trial should be designed.

As part of the design process for the TRUFFLE-2 randomized trial for determining optimal timing for delivery in the context of late preterm fetal growth restriction, we undertook a prospective observational feasibility study. The objectives of this study were to quantify perinatal morbidity and mortality in contemporary clinical practice and to determine which thresholds for umbilical and MCA Doppler are most strongly associated with adverse perinatal outcome in late preterm singleton pregnancies at risk of fetal growth restriction, and which thus might be most appropriate for evaluation in a future randomized interventional study in late preterm fetal growth restriction.

METHODS

Setting

This was a prospective multicenter observational study conducted between 1 April 2017 and 1 July 2018 in 33 European perinatal centers with fetal medicine and specialized neonatal intensive care services.

Participants

Women were eligible if they had a singleton pregnancy from 32 + 0 to 36 + 6 weeks of gestation with a fetus considered at risk for growth restriction, defined as estimated fetal weight (EFW) and/or abdominal circumference (AC) < 10th percentile, abnormal fetal arterial Doppler and/or

a fall in AC growth velocity of more than 40 percentile points from the 20-week scan. The references for EFW, AC and Doppler parameters were based on local charts. In order to be eligible, the fetus had to have positive umbilical artery end-diastolic flow and a normal cardiotocogram (CTG) with short-term variation of the fetal heart rate > 3.0 ms, using Dawes–Redman CTG analysis. Gestational age was calculated from certain menstrual age and/or ultrasound assessment before 22 weeks of gestation. Women were ineligible for inclusion if there was known, planned or impending delivery based on maternal obstetric complications, uterine contractions or rupture of membranes, or if the fetus had a known or suspected structural or chromosomal abnormality.

Further monitoring

Women were monitored using fetal biometry and Doppler assessment of umbilical and fetal MCA pulsatility index (PI), with a recommended minimum interval of 1 week between assessments. Z-scores were calculated for MCA-PI and UCR using reference data from normal pregnancies in the study of Arduini and Rizzo[8], and for fetal weight using the Hadlock fetal growth charts[9]. UCR Z-scores were calculated as reported previously[10]. The study was not blinded and clinicians who were collecting the data were also involved directly in the management and delivery of those women. However, there was no guidance as to what findings should trigger delivery, which was left to local custom. Management, including maternal steroid administration and delivery, was undertaken according to local clinical protocols.

Definitions

Maternal hypertension was defined as blood pressure $\geq$ 140/90 mmHg and proteinuria was defined as > 0.3 g/L on a 24 h collection of urine or urine dipstick result of '1+' or more. Hypertensive disorders were defined as chronic if hypertension existed prior to 20 weeks' gestation or required treatment prior to pregnancy, or as gestational if the onset of hypertension occurred after 20 weeks in the absence of proteinuria. Pre-eclampsia was defined as hypertension and proteinuria, or hypertension and clinical signs of pre-eclampsia[11]. HELLP syndrome was defined as alanine aminotransferase > 70 IU/L with platelets $< 100 \times 10^9$/L and with evidence of hemolysis from blood film or lactate dehydrogenase > 600 IU/L.

Outcomes

The primary outcome was a composite of abnormal condition at birth or major neonatal morbidity. Abnormal condition at birth was defined as at least one of the following: Apgar score < 7 at 5 min, umbilical artery pH < 7.0 or umbilical vein pH < 7.1, resuscitation with intubation, chest compressions or medication, or stillbirth. Major neonatal morbidity until first discharge home was defined as at least one of the following:

neurological abnormality (intracerebral hemorrhage Grade 3 or 4, periventricular leukomalacia Grade 2 or 3, encephalopathy, or seizures necessitating antiepileptic drug treatment); cardiovascular abnormality (hypotensive treatment, ductus arteriosus treatment or disseminated coagulopathy); respiratory morbidity (respiratory support for more than 1 week, mechanical ventilation, meconium aspiration or persistent pulmonary hypertension); or sepsis (clinical sepsis with positive blood culture, necrotizing enterocolitis (Bell's stage 2 or greater) or meningitis).

Data collection

Data were collected on a secure cloud-based electronic data capture platform (Castor EDC, Amsterdam, The Netherlands) curated by H.W. The database carried no personal identifiers. Participants and their infants could be identified only using unique study identifiers that were stored in their recruiting center.

Analysis

Two analyses were undertaken. First, based on the last fetal Doppler assessment within 1 week before delivery, fetal Doppler parameters were compared between women whose infant had composite adverse outcome and those with normal outcome. Second, based on the first abnormal fetal Doppler assessment after inclusion, several fetal Doppler parameters and values were selected as potential dichotomous predictors of the composite primary outcome.

The selected dichotomous predictors were: absolute MCA-PI < 5th percentile (equivalent to a Z-score of −1.645) at any gestational age; gestational-age-specific MCA-PI Z-score of < −2 at 32–33 weeks, < −1.5 at 34–35 weeks or < −1 at 36 weeks; absolute UCR value $\geq 95^{th}$ percentile (Z-score, 1.645) at any gestational age; UCR Z-score of $\geq$ 1.0 or $\geq$ 1.5 at any gestational age; and three gestational-age-specific UCR Z-score ranges: (1) $\geq$ 1.5 at 32–33 weeks or $\geq$ 1.0 at 34–36 weeks, (2) $\geq$ 1.5 at 32–33 weeks, $\geq$ 1.0 at 34–35 weeks or $\geq$ 0.5 at 36 weeks, and (3) $\geq$ 2.0 at 32–33 weeks, $\geq$ 1.5 at 34–35 weeks or $\geq$ 1.0 at 36 weeks.

The gestational-age-specific ranges were proposed allowing a graduated range on the basis that clinical decisions for delivery would require a more severely abnormal Doppler at an early gestational age, and the criteria for delivery would be more permissive closer to term. For each cut-off, we compared the incidence of composite adverse outcome between those women who had an abnormal Doppler at least once and those who never had an abnormal Doppler.

Statistical methods

Groups were compared with two-sided tests for statistical significance using the Mann–Whitney U-test or Pearson's chi-square test, as appropriate. Relative risks for

composite adverse outcome were calculated unadjusted. In women who had the last Doppler measurement obtained within 1 week before delivery, the association of UCR with composite adverse outcome was adjusted using logistic regression analysis for those parameters that differed significantly between women with and those without composite adverse outcome. Heterogeneity between centers was tested using multilevel logistic regression analysis. Data are presented as number (%) or median (interquartile range (IQR)), as required. Statistical calculations were performed using SPSS Statistics software (version 25; IBM Corp., Armonk, NY, USA).

Ethical approval

This study was observational and practice (monitoring, delivery, steroid administration) was based on existing local guidance. Data were recorded anonymously after delivery. In the UK, the Health Research Authority (HRA) did not require the study to undergo ethical review, which was the case in four further countries (14 centers). In six countries (19 centers), ethical approval was required and obtained, and participating women gave informed signed consent.

RESULTS

Population

Complete delivery and outcome data were recorded for 873 patients with late preterm singleton pregnancy at risk of fetal growth restriction in the study database. Seventeen cases were excluded because of the presence of major congenital abnormality, leaving 856 women and their fetuses for the final cohort analysis. Demographic, obstetric and fetal Doppler velocimetry characteristics of the women included in the cohort are shown in Table 1. Median gestational age and EFW at inclusion were 34 (IQR, 33–35) weeks and 1894 (IQR, 1624–2145) g, respectively. Indication for inclusion was EFW and/or AC < 10th percentile or a drop in AC growth velocity of more than 40 percentiles in 842 (98%) fetuses, while in 98 (11%) an abnormal fetal arterial Doppler (umbilical artery or MCA), according to local reference charts, was observed.

Outcome

Median gestational age at delivery was 38 (IQR, 37–39; range, 32–42) weeks and birth weight was 2478 (IQR, 2140–2790; range, 1080–4255) g. The primary composite adverse outcome occurred in 93 (11%) infants, and its components are detailed in Table 2.

Abnormal condition at birth was present in 27 (3%) fetuses. Among these, there were two (0.2%) antenatal deaths, of which one was diagnosed at 33 + 3 weeks (1 week after inclusion) and the second at 34 + 6 weeks (2 weeks after inclusion). In both cases, umbilical artery PI and UCR were < 95th percentile, while MCA-PI was

Table 1 Demographic, obstetric and Doppler variables in study population of 856 late preterm singleton pregnancies at risk of fetal growth restriction

Variable	Value
Maternal age (years)	31 (28 to 35)
Nulliparous	524 (61)
BMI (kg/m²)	22.5 (20.3 to 26.0)
Smoker	68 (8)
Diabetes Type 1, 2 or gestational	70 (8)
Chronic hypertension	19 (2)
Other disease	246 (29)
At inclusion	
Gestational age (weeks)	34 (33 to 35)
Inclusion indication*	
EFW and/or AC < 10th percentile	792 (93)
AC growth velocity drop > 40 percentiles	50 (6)
Doppler abnormality	98 (11)
EFW (g)	1894 (1624 to 2145)
EFW Z-score	−1.52 (−2.0 to −1.1)
Umbilical artery PI Z-score	0.1 (−0.3 to 0.6)
Umbilical artery PI ≥ 95th percentile	34 (4)
Middle cerebral artery PI Z-score	−0.4 (−1.2 to 0.5)
Middle cerebral artery PI < 5th percentile	116 (14)
UCR Z-score	0.0 (−0.4 to 0.5)
UCR ≥ 95th percentile	35 (4)
Pre-eclampsia or HELLP	79 (9)
Any hypertensive disorder of pregnancy	119 (14)
Antihypertensive medication	103 (12)
Corticosteroids for fetal lung maturation (> 24 h before delivery)	98 (11)
Total number of arterial Doppler measurements	2751
Number of arterial Doppler measurements per woman	4 (3 to 5)
Inclusion-to-delivery interval (days)	27 (14 to 37)
Delivery	
Planned Cesarean section	219 (26)
Indication	
Fetal condition (CTG or Doppler)	155/219 (71)
Fetal growth/EFW	25/219 (11)
Maternal condition	39/219 (18)
Induction of labor	369 (43)
Indication	
Fetal condition (CTG or Doppler)	112/369 (30)
Fetal growth/EFW	213/369 (58)
Maternal condition	44/369 (12)
Spontaneous onset of labor	268 (31)
Cesarean section after onset of labor	117 (14)

Data are given as median (interquartile range), *n* (%), *n* or *n*/*N* (%). *Multiple indications possible. AC, abdominal circumference; BMI, body mass index; CTG, cardiotocogram; EFW, estimated fetal weight; HELLP, hemolysis, elevated liver enzymes and low platelet count; PI, pulsatility index; UCR, umbilicocerebral ratio.

< 5th percentile and birth weight Z-score was < −2. There were no neonatal deaths before discharge. Major neonatal morbidity occurred in 77 (9%) cases; the major contributors were respiratory morbidity (53/77; 69%) and infection (17/77; 22%).

Figure 1 shows the proportion of infants with abnormal condition at birth and/or major neonatal morbidity before discharge, according to gestational age at delivery and birth weight Z-score. In comparison with infants with normal outcome, composite adverse perinatal outcome

Table 2 Perinatal outcome in study population of 856 late preterm singleton pregnancies at risk of fetal growth restriction
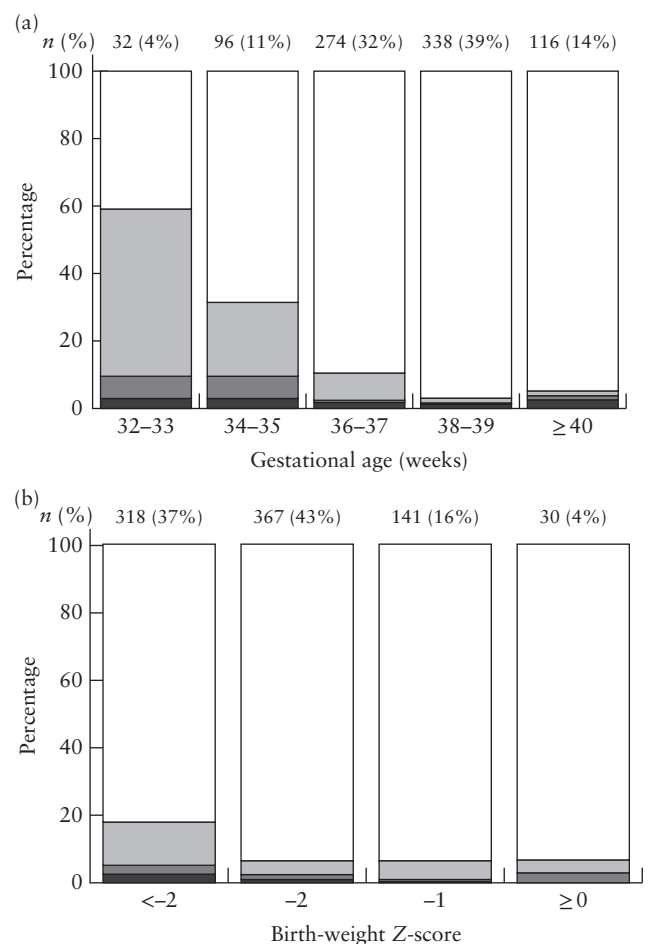
Variable	Value
Gestational age at delivery (weeks)	38 (37–39) [32–42]
Birth weight (g)	2478 (2140–2790) [1080–4255]
Birth-weight Z-score	−1.7 (−2.3 to −1.1) [−5.6 to 3.2]
Birth weight < 10th percentile	596 (70)
Male fetal sex	372 (43)
Composite adverse outcome*	93 (11)
Abnormal condition at birth†	27 (3)
Fetal death	2 (0)
Cord arterial pH < 7.0 or venous pH < 7.1	7/712 (1)
5-min Apgar score < 7	15 (2)
Resuscitation with intubation or medication	10 (1)
Major neonatal morbidity†	77 (9)
Cerebral	7 (1)
Cardiovascular	7 (1)
Respiratory	53 (6)‡
Infection	17 (2)
Abnormal condition at birth and major neonatal morbidity	11 (1)
Neonatal death	0 (0)

Data are given as median (interquartile range) [range], *n* (%) or *n/N* (%). *Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. †Multiple conditions possible. ‡39/53 (74%) had only some respiratory support for short duration in first week.

Figure 1 Incidence of composite adverse outcome in 856 late preterm singleton pregnancies at risk of fetal growth restriction, according to gestational age at delivery (a) and birth-weight Z-score (b). Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. Eleven infants had both abnormal condition at birth and major neonatal morbidity. □, normal; ▨, major neonatal morbidity; ▦, abnormal condition at birth + major neonatal morbidity; ■, abnormal condition at birth.

was associated strongly with lower gestational age at delivery (36 (IQR, 34–38) *vs* 38 (IQR, 37–39) weeks) and lower birth weight (1900 (IQR, 1557–2355) *vs* 2540 (IQR, 2220–2810) g). Infants with birth weight Z-score < −2 had a significantly higher risk of composite adverse outcome than did those with a higher birth weight Z-score (RR, 2.7 (95% CI, 1.8–4.0); $P < 0.01$).

A Doppler evaluation was recorded within 1 week before delivery in 584 (68%) women, of whom, 75 (13%) had composite adverse outcome and 509 (87%) did not. Those with composite adverse outcome had higher umbilical artery PI and lower MCA-PI at the last assessment before delivery, were born at an earlier gestational age and had lower birth weight (Table 3).

The Doppler velocimetry criteria were assessed by comparing women who had an abnormal fetal Doppler at least once at or after inclusion with women who never had an abnormal fetal Doppler, according to the different criteria (Table 4). Pregnancies with abnormal Doppler were delivered earlier in gestation compared with those in which the Doppler velocimetry results remained in the normal range, regardless of the criterion used ($P < 0.05$ for each comparison). Middle cerebral artery PI < 5th percentile and four of the UCR Z-score criteria were associated with an increased prevalence of composite adverse outcome. The highest RR of abnormal Doppler for composite adverse outcome was for MCA-PI < 5th percentile (RR, 2.2 (95% CI, 1.5–3.2)) and high gestational-age-specific UCR Z-score (≥ 1.5

at 32–33 weeks and ≥ 1.0 at 34–36 weeks) (RR, 2.0 (95% CI, 1.4–3.0)).

Compared with women with normal Doppler, those who had an abnormal Doppler at any point after inclusion, based on either the 5th percentile cut-off of MCA-PI or the gestational-age-specific UCR Z-score range, underwent prelabor Cesarean section more frequently, had a lower gestational age at delivery and a lower birth weight, and their infants had more frequently composite adverse outcome (Table 5). Table 6 shows that an abnormal Doppler occurred more frequently at an earlier gestational age and that abnormal Doppler before 36 weeks was associated significantly with a higher rate of composite adverse outcome.

Multilevel logistic regression analysis with an unconditional mean model using the participating centers and composite adverse outcome showed a random intercept variance of 0.21 (95% CI, 0.03–1.59; $P = 0.06$). Calculated from this value, the intraclass correlation coefficient was 0.06. This indicated that only 6% of the

chance of having an abnormal composite endpoint was explained by differences between centers, and that further assessment of confounders using logistic regression analysis without taking center into account was appropriate. This analysis was performed in the subgroup of 584 women with the last Doppler measurement obtained within 1 week before delivery, using UCR Z-score and those variables that differed significantly between women with and those without composite adverse outcome (Table 3). The adjusted odds ratio for composite adverse

Table 3 Univariate analysis of demographic, obstetric and Doppler variables in 584 late preterm singleton pregnancies at risk of fetal growth restriction that had last fetal Doppler measurement obtained within 1 week before delivery, according to presence or absence of composite adverse outcome

	Composite adverse outcome	
Parameter	*Present (n = 75)*	*Not present (n = 509)*
Maternal age (years)	33 (29 to 37)	32 (28 to 35)*
Maternal age $\geq$ 35 years	30 (40)	138 (27)*
Nulliparous	49 (65)	311 (61)
Smoker	11 (15)	38 (7)
BMI (kg/m^2)	21.8 (20.1 to 25.9)	22.3 (20.2 to 26.1)
Gestational hypertension or pre-eclampsia	24 (32)	78 (15)*
Umbilical artery PI Z-score	0.5 (−0.2 to 1.1)	0.1 (−0.3 to 0.6)*
Umbilical artery PI $\geq$ 95th percentile	9 (12)	31 (6)
Umbilical artery PI $\geq$ 90th percentile	13 (17)	53 (10)
Umbilical artery A/REDF	3 (4)	5 (1)
Middle cerebral artery PI Z-score	−1.4 (−2.0 to −0.4)	−1.0 (−1.6 to −0.3)*
Middle cerebral artery PI < 5th percentile	32 (43)	125 (25)*
UCR Z-score	0.6 (0.2 to 1.3)	0.4 (0.0 to 1.0)
UCR $\geq$ 95th percentile	9 (12)	65 (13)
UCR $\geq$ 90th percentile	18 (24)	95 (19)
Gestational age at delivery (weeks)	35 (34 to 37)	38 (37 to 39)*
Birth weight (g)	1820 (1520 to 2240)	2420 (2125 to 2725)*
Birth-weight Z-score	−2.5 (−3.1 to −1.5)	−1.8 (−2.3 to −1.2)*
Birth weight < 10th percentile	68 (91)	373 (73)*
Male sex	35 (47)	220 (43)

Data are given as median (interquartile range) or n (%). Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. *$P < 0.05$ by Mann–Whitney U-test or Fisher's exact test. A/REDF, absent or reversed end-diastolic flow; BMI, body mass index; PI, pulsatility index; UCR, umbilicocerebral ratio.

Table 4 Effect of different Doppler velocimetry criteria to define abnormal result in 856 late preterm singleton pregnancies: comparison of participants who had abnormal Doppler observation at least once in study with those who never had abnormal Doppler

	Doppler abnormal at least once				Doppler always normal			RR for composite adverse outcome	
Abnormal Doppler criterion	*Pregnancies*	*First abnormal Doppler to delivery interval (days)*	*Composite adverse outcome*	*GA at delivery (weeks)*	*Pregnancies*	*Composite adverse outcome*	*GA at delivery (weeks)*	*Value (95% CI)*	*P*
Middle cerebral artery PI									
< 5th percentile	287 (34)	11 (4–20)	49/287 (17)*	38 (36–39)*	569 (66)	44/569 (8)	38 (37–39)	2.2 (1.5–3.2)	< 0.01
Low GA-specific Z-score	329 (38)	12 (6–22)	43/329 (13)	37 (37–38)*	527 (62)	50/527 (9)	39 (37–40)	1.4 (0.9–2.0)	0.06
Umbilicocerebral ratio									
$\geq$ 90th percentile	168 (20)	7 (3–13)	25/168 (15)	37 (35–38)*	688 (80)	68/688 (10)	38 (37–39)	1.5 (1.0–2.3)	0.07
Z-score $\geq$ 1.0	223 (26)	8 (3–14)	34/223 (15)*	37 (36–38)*	633 (74)	59/633 (9)	38 (37–39)	1.6 (1.1–2.4)	0.02
Z-score $\geq$ 1.5	134 (16)	6 (2–11)	24/134 (18)*	37 (35–38)*	722 (84)	69/722 (10)	38 (37–39)	1.9 (1.2–2.9)	< 0.01
High GA-specific Z-score 1	162 (19)	9 (3–14)	30/162 (19)*	37 (35–37)*	694 (81)	63/694 (9)	38 (37–39)	2.0 (1.4–3.0)	< 0.01
High GA-specific Z-score 2	233 (27)	10 (5–16)	35/233 (15)*	37 (36–38)*	623 (73)	58/623 (9)	38 (37–40)	1.6 (1.1–2.4)	0.02
High GA-specific Z-score 3	126 (15)	7 (3–12)	19/126 (15)	37 (36–37)*	730 (85)	74/730 (10)	38 (37–39)	1.5 (0.9–2.4)	0.12

Data are given as n (%), median (interquartile range) or n/N (%), unless stated otherwise. Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. Low GA-specific Z-score: < −2 at 32–33 weeks, < −1.5 at 34–35 weeks, < −1 at 36 weeks; high GA-specific Z-score 1: $\geq$ 1.5 at 32–33 weeks, $\geq$ 1.0 at 34–36 weeks; high GA-specific Z-score 2: $\geq$ 1.5 at 32–33 weeks, $\geq$ 1.0 at 34–35 weeks, $\geq$ 0.5 at 36 weeks; high GA-specific Z-score 3: $\geq$ 2.0 at 32–33 weeks, $\geq$ 1.5 at 34–35 weeks, $\geq$ 1.0 at 36 weeks. *$P < 0.05$ by Mann-Whitney U-test or Fisher's exact test, compared with pregnancies with Doppler assessment always normal. GA, gestational age; PI, pulsatility index; RR, relative risk.

Table 5 Gestational age (GA) at delivery, birth weight and perinatal outcome in 856 singleton pregnancies at risk of late preterm fetal growth restriction, according to whether Doppler assessment was abnormal

| | Middle cerebral artery pulsatility index | | GA-specific UCR Z-score* | |
| | < 5th percentile at least once (n = 287) | Always normal (n = 569) | High at least once (n = 162) | Always normal (n = 694) |
Variable				
Inclusion-to-delivery interval (days)	25 (11–35)‡	28 (16–39)	17 (7–28)‡	29 (17–39)
First abnormal Doppler to delivery interval (days)	11 (4–21)	—	9 (3–14)	—
CS before labor	87 (30)‡	132 (23)	75 (46)‡	144 (21)
Induction of labor	146 (51)‡	223 (39)	68 (42)	301 (43)
Spontaneous onset of labor	54 (19)‡	214 (38)	19 (12)‡	249 (36)
CS during labor	44 (15)	73 (13)	27 (17)	90 (13)
Vaginal delivery	156 (54)	364 (64)	60 (37)‡	460 (66)
GA at delivery (weeks)	38 (36–39)‡	38 (37–39)	37 (35–37)‡	38 (37–39)
Birth weight (g)	2380 (2000–2655)‡	2555 (2213–2850)	2045 (1800–2391)‡	2577 (2260–2830)
Birth weight < 10th percentile	219 (76)‡	377 (66)	132 (81)‡	464 (67)
Composite adverse outcome†	49 (17)‡	44 (8)	30 (19)‡	63 (9)
Abnormal condition at birth only	10 (3)§	6 (1)	3 (2)¶	13 (2)¶
Major neonatal morbidity only	38 (13)‡	28 (5)	26 (16)‡	40 (6)
Abnormal condition at birth and major neonatal morbidity	1 (0)	10 (2)	1 (1)	10 (1)

*GA-specific UCR Z-score cut-offs: ≥ 1.5 at 32–33 weeks and ≥ 1.0 at 34–36 weeks. †Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. ‡$P < 0.05$ by Mann–Whitney U-test or Fisher's exact test, compared with pregnancies with Doppler assessment always normal. §Two cases of fetal death. ¶One case of fetal death. CS, Cesarean section; UCR, umbilicocerebral ratio.

Table 6 Composite adverse outcome and gestational age (GA) at delivery in 856 singleton pregnancies at risk of late preterm fetal growth restriction, according to whether Doppler assessment was abnormal and GA at assessment

| | Doppler abnormal at least once | | Doppler always normal | | RR for composite adverse outcome | |
Abnormal Doppler criterion/GA at assessment	Composite adverse outcome	GA at delivery (weeks)	Composite adverse outcome	GA at delivery (weeks)	Value (95% CI)	P
MCA-PI < 5th percentile						
32–33 weeks	24/63 (38)†	36 (34–38)†	26/282 (9)	38 (37–39)	4.1 (2.6–6.7)	< 0.01
34–35 weeks	14/94 (15)†	37 (36–38)†	37/508 (7)	38 (37–40)	2.0 (1.2–3.6)	0.02
36 weeks	6/63 (10)	38 (37–38)†	27/562 (5)	39 (38–40)	2.0 (0.9–4.6)	0.1
High GA-specific UCR Z-score*						
32–33 weeks	12/31 (39)†	34 (33–36)†	34/316 (11)	38 (37–39)	4.1 (2.2–7.9)	< 0.01
34–35 weeks	15/86 (17)†	36 (35–37)†	46/558 (8)	39 (37–40)	2.1 (1.2–3.7)	0.02
36 weeks	3/45 (7)	37 (37–38)†	34/620 (5)	39 (38–40)	1.2 (0.4–3.8)	0.7

Data are given as n/N (%) or median (interquartile range), unless stated otherwise. Women who had abnormal Doppler ultrasound were counted only once at gestational age epoch in which first abnormal Doppler was registered. Women with normal Doppler could have ultrasound at more than one gestational age epoch after inclusion; totals are therefore higher than total number of included women. Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. *GA-specific UCR Z-score cut-offs: ≥ 1.5 at 32–33 weeks and ≥ 1.0 at 34–36 weeks. †$P < 0.05$ by chi-square test or Mann–Whitney U-test, compared with pregnancies with Doppler assessment always normal. MCA, fetal middle cerebral artery; PI, pulsatility index; RR, relative risk; UCR, umbilicocerebral ratio.

outcome of UCR Z-score was 1.3 per SD of UCR (95% CI, 1.0–1.8; $P = 0.04$) (Figure 2). This model had sensitivity of 79% at specificity of 75%. Gestational age and birth weight Z-score had the greatest proportional contribution to the model (0.45 and 0.29, respectively), while that of UCR Z-score was 0.12, calculated using multilayer perceptron analysis. In a similar analysis with MCA-PI Z-score, it was observed that, after adjustment, this parameter was not associated significantly with the composite adverse endpoint.

DISCUSSION

In this study, we have shown that, in late preterm singleton pregnancies at risk of fetal growth restriction, fetal cerebral blood flow redistribution detected on Doppler ultrasound within 1 week prior to delivery and the first abnormal Doppler result at any time after inclusion were both associated with composite adverse outcome. The strength of our study is that a wide range of centers were involved, which resulted in rapid prospective recruitment of a large cohort of babies at risk of growth
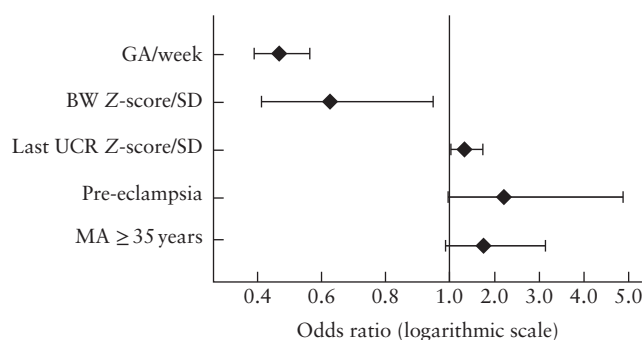
Figure 2 Adjusted odds ratios with 95% CI for composite adverse outcome in 584 late preterm singleton pregnancies at risk of fetal growth restriction and with Doppler measurement obtained within 1 week before delivery, calculated by logistic regression analysis, using parameters that were statistically significant on univariate analysis (Table 3). Missing variables from Table 3 were ejected from analysis when $P > 0.1$. Model had sensitivity of 79% at specificity of 75%, and area under receiver-operating-characteristics curve of 0.84 (95% CI, 0.79–0.89). Composite adverse outcome defined as abnormal condition at birth and/or major neonatal morbidity. BW, birth weight; GA, gestational age at delivery; MA, maternal age; UCR, umbilicocerebral ratio.

restriction. The data provide a snapshot of the natural history of late preterm growth restriction in relation to fetal cerebral redistribution in contemporary practice. We have also defined the prevalence of composite adverse perinatal outcome in these fetuses and infants, according to prespecified outcomes. The main weakness, as with any observational study, is that the Doppler results were revealed to the clinicians, thus making the results susceptible to the treatment paradox.

With the above proviso, which also affects all previous similar series, our results largely confirm the association between fetal cerebral blood flow redistribution and short-term adverse outcome in fetal growth restriction[4–6,12,13]. Our findings are also consistent with those of recent meta-analyses[4,5], in which the accuracy of fetal Doppler for the prediction of composite adverse outcome was low, with sensitivity of 45–70% and specificity of 75–95%, depending on the Doppler parameter and thresholds used.

There was a significant association between these predefined markers of abnormal Doppler velocimetry and gestational age at delivery and the frequency of our composite primary outcome (Tables 3, 5 and 6). Gestational age at delivery and birth weight Z-score should be interpreted in this cohort as a proxy measure of the severity of fetal growth restriction (Figures 1 and 2). We might hypothesize that the most severe cases will reach the limits of the uteroplacental supply earlier, which may ultimately result in fetal asphyxia or death and increase the risk of neonatal morbidity. The higher incidence of the first finding of an abnormal Doppler parameter at an earlier gestational age epoch, which was associated with more preterm deliveries and a higher rate of composite adverse outcomes, supports this (Table 6). Adjustment for gestational age at delivery, birth weight, maternal age and pre-eclampsia reduced the importance of the association

of UCR Z-score with the composite adverse endpoint, but it remained statistically significant (Figure 2).

These data cannot be used to ascertain when delivery should occur in the context of abnormal Doppler and CTG findings. This can be evaluated only in a well-conducted randomized trial before fetal MCA Doppler can be recommended for this purpose. Hence, these results have important implications for research, in particular for the design of such a trial. The parameters that dichotomized most effectively between normal outcome and composite adverse perinatal outcome were MCA-PI $< 5^{th}$ percentile or a graduated gestational-age-specific range of UCR Z-score (≥ 1.5 at 32–33 weeks, ≥ 1.0 at 34–36 weeks). The rationale behind choosing gestational-age-specific ranges reflects the higher level of concern about fetal condition that is required to trigger delivery at an earlier gestational age compared with near term at a stage at which neonatal morbidity and mortality are normally very low, extrapolating from population studies[14]. However, long-term morbidity from late preterm birth is not negligible[15,16]. The extent to which this excess morbidity is caused by late fetal growth restriction is unknown.

Furthermore, a ratio between the PI of the umbilical and middle cerebral arteries may have a closer association with perinatal outcome than does each parameter alone[4,5]. Most studies on cerebral blood flow redistribution have reported on the cerebroplacental ratio (CPR), which is the inverse of UCR. We have used UCR as we believe this ratio allows for better differentiation in the abnormal range than does CPR[10]. A brief justification for this is that, as fetal Doppler changes become more abnormal with lower cerebral and higher umbilical artery impedance, CPR tends towards an asymptote approximating to zero, while UCR tends towards infinity, thus accentuating the differences between abnormal values. Furthermore, most commonly used ratios in medicine become larger with increasing abnormality, similar to UCR.

In conclusion, a randomized trial is required to answer the uncertainties in relation to triggering delivery based on different parameters in late-preterm fetuses with, or those at risk of, growth restriction. These data will help in the selection of the potentially most effective diagnostic method and its cut-off value to guide the design of such a trial.

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