Is middle cerebral artery Doppler related to neonatal and 2-year infant outcome in early fetal growth restriction?

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BACKGROUND: Reduced fetal middle cerebral artery Doppler impedance is associated with hypoxemia in fetal growth restriction. It remains unclear as to whether this finding could be useful in timing delivery, especially in the third trimester. In this regard there is a paucity of evidence from prospective studies.

OBJECTIVES: The aim of this study was to determine whether there is an association between middle cerebral artery Doppler impedance and its ratio with the umbilical artery in relation to neonatal and 2 year infant outcome in early fetal growth restriction (26^{+0}–31^{+6} weeks of gestation). Additionally we sought to explore which ratio is more informative for clinical use.

STUDY DESIGN: This is a secondary analysis from the Trial of Randomized Umbilical and Fetal Flow in Europe, a prospective, multicenter, randomized management study on different antenatal monitoring strategies (ductus venosus Doppler changes and computerized cardiotocography short-term variation) in fetal growth restriction diagnosed between 26^{+0} and 31^{+6} weeks. We analyzed women with middle cerebral artery Doppler measurement at study entry and within 1 week before delivery and with complete postnatal follow-up (374 of 503). The primary outcome was survival without neurodevelopmental impairment at 2 years corrected for prematurity. Neonatal outcome was defined as survival until first discharge home without severe neonatal morbidity. Z-scores were calculated for middle cerebral artery pulsatility index and both umbilicocerebral and cerebroplacental ratios. Odds ratios of Doppler parameter Z-scores for neonatal and 2 year infant outcome were calculated by multivariable logistic regression analysis adjusted for gestational age and birthweight p50 ratio.

RESULTS: Higher middle cerebral artery pulsatility index at inclusion but not within 1 week before delivery was associated with neonatal survival without severe morbidity (odds ratio, 1.24; 95% confidence interval, 1.02–1.52). Middle cerebral artery pulsatility index Z-score and umbilicocerebral ratio Z-score at inclusion were associated with 2 year survival with normal neurodevelopmental outcome (odds ratio, 1.33; 95% confidence interval, 1.03–1.72, and odds ratio, 0.88; 95% confidence interval, 0.78–0.99, respectively) as were gestation at delivery and birthweight p50 ratio (odds ratio, 1.41; 95% confidence interval, 1.20–1.66, and odds ratio, 1.86; 95% confidence interval, 1.33–2.60, respectively). When comparing cerebroplacental ratio against umbilicocerebral ratio, the incremental range of the cerebroplacental ratio tended toward zero, whereas the umbilicocerebral ratio tended toward infinity as the values became more abnormal.

CONCLUSION: In a monitoring protocol based on ductus venosus and cardiotocography in early fetal growth restriction (26^{+0}–31^{+6} weeks of gestation), the impact of middle cerebral artery Doppler and its ratios on outcome is modest and less marked than birthweight and delivery gestation. It is unlikely that middle cerebral artery Doppler and its ratios are informative in optimizing the timing of delivery in fetal growth restriction before 32 weeks of gestation. The umbilicocerebral ratio allows for a better differentiation in the abnormal range than the cerebroplacental ratio.

Key words: cerebroplacental ratio, Doppler velocimetry, intrauterine growth restriction, middle cerebral artery, neonatal, umbilicocerebral ratio

There is renewed interest in the predictive value for adverse perinatal outcome of the middle cerebral artery (MCA) Doppler, particularly in the third trimester.[1] The so-called brain-sparing effect, as evidenced by a low pulsatility index (PI), refers to vasodilatation of cerebral vessels in response to fetal hypoxemia particularly in fetal growth restriction.[2-4] Ratios of cerebral (carotid or MCA) to central or peripheral (aortic or umbilical) impedance are more closely related to antenatal blood gases and pH,[4] discriminate better between normal and risk pregnancies,[5-7] and are more predictive of perinatal fetal distress than individual Doppler parameters.[8]

To consider the opposite changes occurring in the MCA (reduced impedance) and umbilical artery (increased impedance) with progressive hypoxemia, the umbilicocerebral ratio[5-7] and its inverse, the cerebroumbilical, also known as the cerebroplacental ratio, have been established.[7,9-12] Up to now, most publications report on the cerebroplacental rather than the umbilicocerebral ratio, but the advantage of one over the other is unclear.

Although brain sparing has been traditionally considered as a protective phenomenon in fetal hypoxemia, its presence or deterioration of the ratio of the MCA Doppler PI to umbilical artery may be associated with an increased risk of adverse neurodevelopmental outcome, both in term and preterm pregnancies with fetal growth restriction.[13] The interpretation of these findings is problematic, especially for preterm fetal growth restriction, because of the paucity of prospective good-quality studies with adequate sample size and long-term follow-up.

The aim of this study was to investigate the association of the MCA PI, and cerebroplacental and umbilicocerebral ratios, normalized for gestational age,

with neonatal and 2 year infant outcome in a large predefined group with early fetal growth restriction (26^{+0}–31^{+6} weeks of gestation) as part of the multicenter Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study.[14,15] We also investigated which MCA-related ratio is most informative for clinical use.

Material and Methods

This is a secondary analysis of the association between MCA PI, and cerebroplacental and umbilicocerebral ratios with the neonatal and 2 year infant outcome from the TRUFFLE study. The TRUFFLE study design has been described earlier.[15]

In short, this was a prospective, multicenter, randomized management trial conducted in 20 European tertiary care centers from 2005 to 2010. The randomized trial was registered with the International Standard Randomized controlled Trial Number Register (number ISRCTN56204499).

Eligible women had singleton pregnancies between 26 and 31^{+6} gestational weeks diagnosed with fetal growth restriction, defined as a fetal abdominal circumference <10th centile[16] and abnormal umbilical artery Doppler (PI >95th centile)[7] with or without absent or reversed end-diastolic flow. Estimated fetal weight had to be >500 g,[17] and the ductus venosus waveform normal with a PI <95th centile[18] and a normal computerized cardiotocography short-term variation.[19]

Following informed consent, participants were randomly assigned to 1 of 3 groups in a 1:1:1 ratio to determine the timing of delivery. These groups were as follows: (1) monitoring and delivery according to computerized cardiotocography short-term variation criteria (short-term variation <3.5 ms) at <29 weeks or <4 ms at ≥29 weeks); (2a) delivery based on early changes in the ductus venosus PI (>95th centile); and (2b) delivery based on late changes of the ductus venosus (no or reverse A wave flow). For further details on patient monitoring in the TRUFFLE study, see the Supplemental Appendix. The study was ratified by the ethics committees of all the participating units, and all participants gave their written informed consent.

The primary outcome was survival without neurodevelopmental impairment at 2 years corrected for prematurity (Supplemental Appendix).

Neonatal outcome was defined as survival until first discharge home without severe neonatal morbidity (Supplemental Appendix).

For this analysis, we included only women who had measurements of the middle cerebral and umbilical arteries both at inclusion and within 1 week before delivery and who had complete 2 year follow-up. If there were more MCA Doppler measurements within the last week before delivery, only the last one was selected. The time interval of 1 week before delivery was chosen to maximize the number of observations. There were no significant differences across the MCA PI values in the last week within 2 year infant outcome groups (data presented in the Supplemental Appendix).

Z-scores were calculated for MCA PI and cerebroplacental and umbilicocerebral ratios using reference data by Arduini and Rizzo.[20] For birthweight classification an expected (median) weight was calculated, adjusted for gestational age, maternal weight, length, and ethnic descent.[21] This allowed the calculation of a birthweight to p50 ratio.

Both absolute values and Z-scores of MCA PI and cerebroplacental and umbilicocerebral ratios at study inclusion were compared for neonatal and 2 year infant outcome. This analysis was repeated using the last Doppler values. A delta value for the Doppler parameter Z-scores was calculated by subtracting the first measurement from the last, dividing this by the number of days in between, and multiplying this ratio by 100 as follows: delta ratio = 100 × (last − first)/interval in days. This value was similarly compared for outcome.

Analysis of variance, χ^2, Wilcoxon signed rank, or Kruskal-Wallis test was used as appropriate. The Levene test was used to assess for homogeneity of variables. Odds ratios with 95% confidence intervals (CIs) of each MCA-related Doppler Z-scores parameter for neonatal outcome (survival until the first discharge home without severe morbidity) and 2 year infant outcome (survival without neurodevelopmental impairment at 2 years) were calculated by multivariable logistic regression analysis, with adjustment for gestational age and birthweight p50 ratio. Data are presented as number, percentage (%), mean and standard deviation (SD) or median and interquartile range (IQR) as required. IBM SPSS statistics version 22 (New York, U.S.A.) was used for statistical calculation.

Results

Table 1 shows the selection process for this post hoc analysis. Women lost to follow-up (60 of 503, 12%) were excluded. All women with known outcome (n = 443; 88%) had MCA Doppler at inclusion and 380 (76%) in the last week before delivery. Additionally, we excluded 4 patients with fetal death who had refused intervention and 2 women whose infants died shortly after birth because of a lethal congenital abnormality (trisomy 18, complex cardiac abnormality) ("inevitable deaths," Table 1). The study population available for analysis was 374 women (74%).

Absolute values and Z-scores of MCA PI and cerebroplacental and umbilicocerebral ratios are shown in Table 2 specified for 2 year infant outcome categories. Absolute values and Z-scores of all Doppler parameters at study inclusion were significantly different between outcome categories. However, notwithstanding the significant difference between first and last Doppler parameters, neither the difference between the first and last measurement nor the last values were significantly associated with 2 year infant outcome. Other parameters that differed significantly among the 2 year infant outcome groups were estimated fetal weight, birthweight, birthweight p50 ratio, gestational age at inclusion and at delivery, nulliparity, Apgar score at 5 minutes <7, infant sex, and severe neonatal morbidity (Table 2).

Figure 1 shows the Z-scores of the first and last Doppler measurements: the umbilicocerebral ratio has a wider distribution in the abnormal range, with more

abnormal outliers, than the cerebroplacental ratio. The median of the differences between the first and last measurement was significantly different from zero for all three Doppler parameters ($P < .001$, Wilcoxon signed rank test).

Figure 2A shows the odds ratios for neonatal outcome adjusted for gestational age at delivery and birthweight p50 ratio (see also Supplemental Table 1 in the Supplemental Appendix). The MCA PI Z-score at study inclusion was the only Doppler-related parameter with a significant association with neonatal survival without severe morbidity (odds ratio, 1.24; 95% CI, 1.02−1.52) together with gestational age at delivery (odds ratio, 1.69; 95% CI, 1.46−1.95).

Figure 2B shows the adjusted odds ratios for 2 year infant outcome (see also Supplemental Table 2 in the Supplemental Appendix). Among all Doppler criteria, only the MCA PI Z-score and umbilicocerebral ratio Z-score at the study inclusion were significantly associated with 2 year infant survival with normal neurodevelopmental outcome (odds ratio, 1.33; 95% CI, 1.03−1.72, and odds ratio, 0.88; 95% CI, 0.78−0.99, respectively). Gestational age at delivery and the birthweight p50 ratio were also significantly associated with a normal outcome (odds ratio, 1.41; 95% CI, 1.20−1.66, and odds ratio, 1.86; 95% CI, 1.33−2.60, respectively).

The cerebroplacental ratio did not reach statistical significance despite the fact that it is the inverse of the umbilicocerebral ratio and that the Z-scores were calculated from the same reference table. To explore this further, we plotted the umbilicocerebral ratio against the cerebroplacental ratio and observed that in the abnormal range for the cerebroplacental ratio (<1), the incremental change is far more compressed than for the umbilicocerebral ratio (>1) (Figure 3).

TABLE 1
Selection of the final study group (n = 374) by stepwise application of the inclusion criteria

Variables	cCTG-STV	DV p95	DV no A	Total
All (row, %)	166 (33%)	167 (33%)	170 (34%)	503
With known outcome at 2 y	144 (87%)	142 (85%)	157 (92%)	443 (88%)
Perinatal and infant death <2 y[a]	13 (9%)	11 (8%)	17 (11%)	41 (9%)
Neurological impairment[b]	20 (15%)	12 (9%)	7 (5%)	39 (10%)
Doppler within 1 wk before delivery	121 (73%)	118 (71%)	141 (83%)	380 (76%)
Inevitable death excluded	1 (1%)	1 (1%)	4 (3%)	6 (2%)
Study population	120 (72%)	117 (70%)	137 (81%)	374 (74%)
Perinatal and infant death <2 y[a]	10 (8%)	10 (9%)	12 (9%)	32 (9%)
Neurological impairment[b]	15 (14%)	11 (10%)	6 (5%)	32 (10%)

cCTG-STV, computerized cardiotocography short-term variation; *DV no A*, late changes in ductus venosus (no or reverse A wave flow); *DV p95*, early changes in the ductus venosus (DV-PI >95th percentile).

[a] Including 2 deaths after first discharge home and before 2 years; [b] The denominator is represented by infants with known outcome minus perinatal and infant death <2 years.

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Comment

Principal findings of the study

We show that in fetal growth restriction from 26^{+0} to 31^{+6} weeks of gestation monitored by ductus venosus Doppler and computerized cardiotocography (short-term variation) for MCA-related Doppler parameters, only the MCA PI Z-score at study inclusion is associated with neonatal survival until discharge home without severe morbidity and that the MCA PI and the umbilicocerebral ratio Z-scores at study inclusion are associated with 2 year infant survival without neurodevelopmental impairment.

The cerebroplacental ratio Z-score at study inclusion, the MCA PI, and the umbilicocerebral and cerebroplacental ratio Z-sores shortly before birth and the change of these parameters with time were not associated with neonatal or 2 year infant outcome. Moreover, our data show that, in this subgroup of growth-restricted fetuses (before 32 weeks of gestation) and in this monitoring scenario, gestational age at delivery remains the most important factor in determining neonatal survival without adverse outcome and, together with birthweight, in determining 2 year infant outcome without neurodevelopmental impairment.

Results of the study in the context of other observations

Brain sparing in early fetal growth restriction and neonatal and 2 year infant outcome

In this study of fetuses whose mothers were enrolled into a large prospective, randomized management trial of early fetal growth restriction (26^{+0}−31^{+6} weeks of gestation), fetuses with less severe cerebral vasodilatation at study inclusion had a higher chance of avoiding mortality and severe neonatal morbidity and 2 year survival without neurodevelopmental impairment. This observation is consistent with recent reports of an increased prevalence of adverse outcomes in fetal growth restriction with cerebral vasodilatation,[13] suggesting that, although cerebral vasodilatation is thought to be protective, its presence reveals fetal hypoxemia[22] that might be associated with brain damage.

Importantly, in our study, gestational age and birthweight were the main factors in determining neonatal and infant outcome, respectively. Moreover, similarly to other studies that evaluated brain sparing and delivery in early growth restriction,[23,24] the MCA PI measured close to delivery and its change over time had no impact on neonatal or 2 year infant outcome.

These findings confirm that in early fetal growth restriction between 26^{+0} and 31^{+6} weeks of gestation, the impact of placental disease on neonatal and infant outcome depends mainly on gestational age and severity of growth restriction.[23,24] The impact of MCA

TABLE 2

Demographic, obstetric, Doppler, and neonatal data specified for 2 year infant outcome categories for women with a Doppler measurement at the inclusion and within 1 week before delivery

Variables	Normal neurodevelopment outcome	Abnormal neurodevelopment outcome	Death <2 y	Total
Number of women (row, %)	310 (83%)	32 (9%)	32 (9%)	374
Allocation				
cCTG-STV	95 (31%)	15 (13%)	10 (8%)	120 (32%)
DV p95	96 (31%)	11 (9%)	10 (9%)	117 (31%)
DV noA	119 (38%)	6 (4%)	12 (9%)	137 (37%)
Maternal age, y	31 (5)	31 (5)	30 (6)	31 (5)
Nulliparous[a]	192 (62%)	16 (50%)	27 (84%)	235 (63%)
Gestational age at inclusion, wks[a]	29.3 (28.0–30.2)	29.0 (26.9–30.7)	27.9 (27.0–28.7)	29.1 (27.9–30.1)
Estimated fetal weight at inclusion, wks[a]	895 (213)	831 (237)	718 (182)	875 (218)
Estimated fetal weight p50 ratio[a]	0.65 (0.10)	0.62 (0.08)	0.61 (0.08)	0.64 (0.10)
Gestational hypertensive disease	237 (77%)	25 (78%)	24 (75%)	286 (77%)
Doppler parameters at study inclusion				
MCA-PI[a]	1.4 (1.2–1.7)	1.3 (1.1–1.5)	1.4 (1.1–1.5)	1.4 (1.2–1.7)
MCA-PI Z-score[a]	−2.0 (−2.6 to −1.1)	−2.2 (−3.3 to −1.7)	−2.1 (−3.1 to −1.6)	−2.0 (−2.7 to −1.1)
UCR[a]	1.3 (1.1–1.6)	1.6 (1.2–1.9)	1.4 (1.2–2.2)	1.4 (1.1–1.7)
UCR Z-score[a]	2.7 (1.8–3.9)	3.6 (2.1–5.0)	3.0 (2.2–5.9)	2.8 (1.9–4.2)
CPR[a]	0.7 (0.6–0.9)	0.6 (0.–0.8)	0.7 (0.–0.8)	0.7 (0.6–0.9)
CPR Z-score[a]	−2.0 (−2.4 to −1.7)	−2.3 (−2.6 to −1.8)	−2.1 (−2.7 to −1.8)	−2.1 (−2.4 to −1.7)
Doppler parameters (last) within 1 wk before delivery[b]				
MCA-PI	1.3 (1.1–1.5)	1.4 (1.1–1.5)	1.3 (1.1–1.6)	1.3 (1.1–1.5)
MCA-PI Z-score	−2.3 (−2.9 to −1.5)	−2.2 (−3.2 to −1.7)	−2.4 (−3.1 to −1.5)	−2.3 (−2.9 to −1.6)
UCR	1.5 (1.2–2.0)	1.6 (1.2–2.3)	1.7 (1.3–2.4)	1.5 (1.2–2.1)
UCR Z-score	3.4 (2.4–5.3)	3.8 (2.3–6.3)	4.0 (2.5–6.6)	3.5 (2.4–5.6)
CPR	0.7 (0.5–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.7 (0.5–0.8)
CPR Z-score	−2.2 (−2.6 to −1.9)	−2.3 (−2.7 to −1.9)	−2.4 (−2.8 to −2.0)	−2.2 (−2.6 to −1.9)
Doppler difference between last and first, adjusted for number of days in between and multiplied by 100				
Delta MCA-PI ratio Z-score	0.0 (−8.3 to 0.0)	0.0 (−2.9 to 1.3)	0.0 (−0.9 to 2.3)	0.0 (−6.6 to 0.0)
Delta UCR Z-score	0.0 (0.0–16.3)	0.0 (0.0–18.1)	0.0 (0.0–18.2)	0.0 (0.0–16.8)
Delta CPR Z-score	0.0 (−4.9 to 0.0)	0.0 (−2.9 to 0.0)	0.0 (−4.9 to 0.0)	0.0 (−4.5 to 0.0)
Neonatal outcome				
Fetal death	——	——	7 (22%)	7 (2%)
Gestational age at delivery[a]	30.6 (29.1–32.0)	30.1 (28.4–31.4)	28.6 (27.8–29.8)	30.4 (29.0–31.9)
Birthweight[a]	1000 (269)	870 (266)	759 (233)	968 (276)
Birthweight p50 ratio[a]	0.59 (0.09)	0.55 (0.08)	0.56 (0.10)	0.59 (0.10)
Male sex[a]	149 (48%)	20 (63%)	18 (56%)	187 (50%)

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(continued)

TABLE 2
Demographic, obstetric, Doppler, and neonatal data specified for 2 year infant outcome categories for women with a Doppler measurement at the inclusion and within 1 week before delivery *(continued)*

Variables	Normal neurodevelopment outcome	Abnormal neurodevelopment outcome	Death <2 y	Total
Apgar score, 5 min, <7[a]	24 (8%)	8 (25%)	5 (16%)	37 (10%)
pH <7.0 (n = 359)	2 (1%)	1 (4%)	1 (5%)	4 (1%)
Severe neonatal morbidity[a]	80 (26%)	14 (44%)	24 (75%)	118 (32%)
Neonatal death			24 (75%)	24 (6%)
Late death <2 y			1 (3%)	1 (0%)

Data are presented as number (percentage), mean (SD), or median (interquartile range).

cCTG-STV, computerized cardiotocography short-term variation; *CPR*, cerebroplacental ratio; *DV no A*, late changes in ductus venosus (no or reverse A wave flow); *DV p95*, early changes in the ductus venosus (DV-PI >95th percentile); *MCA-PI*, middle cerebral artery pulsatility index; *UCR*, umbilicocerebral ratio.

[a] $P < .05$ (analysis of variance, χ^2, or Kruskal-Wallis test); [b] Last measurements differing significantly from the first measurements ($P < .05$; Wilcoxon signed rank test).

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Doppler at study inclusion on neonatal and 2 year infant outcome, though not strong, was mechanistically interesting. Given that it is impossible to know in advance whether a MCA Doppler measurement is the last for a given fetus, the finding is likely to be of very limited clinical utility and apparently not useful for the decision when to deliver the fetus.

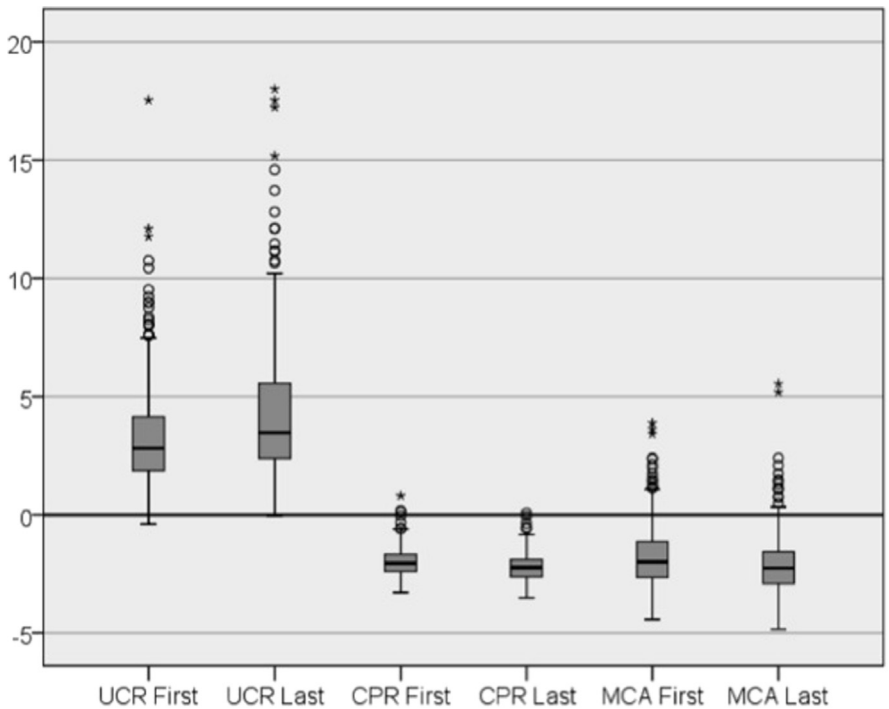
Middle cerebral artery related ratios

For MCA-related ratios, we found significant differences for absolute values and Z-scores at study inclusion, but these differences were not observed close to delivery. After adjustment for other relevant factors, a significant association persisted only between the umbilicocerebral ratio at study inclusion and 2 year survival without neurodevelopmental impairment, not for its inverse the cerebroplacental ratio.

Several reports have shown the advantage of the umbilicocerebral[5-6] and cerebroplacental ratios[7,25-29] over an isolated MCA PI measurement in differentiating fetal growth restriction from small for gestational age or appropriately grown fetuses and in predicting adverse neonatal outcome in fetal growth restriction. However, most studies were performed in both early and late fetal growth restriction, while in our cohort only pregnancies with early (<32 weeks) fetal growth restriction were included, characterized by both smallness and umbilical Doppler abnormalities. Early and late fetal growth restriction are associated with different fetoplacental hemodynamic profiles.

Though one study revealed an association between the abnormal

FIGURE 1
Box plots of middle cerebral artery-related Doppler parameters Z-scores



The UCR, the CPR, and MCA pulsatility index at inclusion (first) and within 1 week before delivery (last) (n = 374). Differences between the first and last measurements are all statistically significant ($P < .001$, Wilcoxon signed rank test).

CPR, cerebroplacental ratio; *MCA*, middle cerebral artery; *UCR*, umbilicocerebral ratio.

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umbilicocerebral ratio and adverse neurodevelopmental infant outcome,[30] our findings suggest that this association is dominated by gestational age and birthweight.

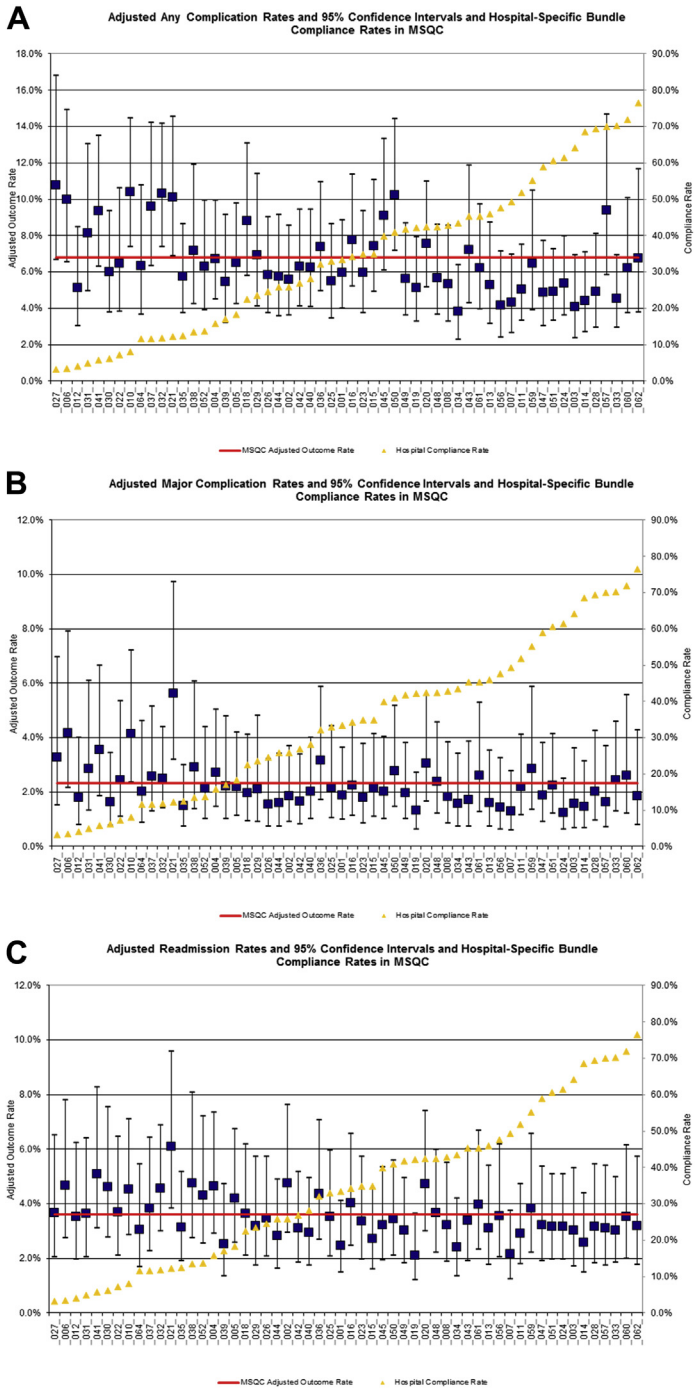
Interestingly, we found no association between change in MCA-related Doppler parameters with time, or measured close to delivery, and neonatal or 2 year infant outcome, suggesting that it is not the change in MCA-related Doppler parameters that has an impact on the outcome in early fetal growth restriction. In fact, it has been shown that the MCA PI may be abnormal for many weeks before the fetus becomes compromised.[31,32] The trend with time of MCA PI z score and UC ratio z score in relation to infant outcome within 2 weeks of delivery is shown in Supplementary Figures 1 and 2.

It might be of interest that the umbilicocerebral ratio Z-score at study inclusion showed an association with the 2 year infant outcome, but the cerebroplacental ratio Z-score did not. We have shown that although both ratios describe the same phenomenon, they behave differently in the abnormal range. This can be explained mathematically: as umbilical and MCA Doppler become abnormal, the umbilical artery PI increases and the MCA PI falls. Therefore, the umbilicocerebral ratio will increase and tend toward an asymptote, leading to infinity, while the cerebroplacental ratio will tend toward zero (Figure 3). A worsening in the fetal condition will have a very small effect on the cerebroplacental ratio but conversely a large one on the umbilicocerebral ratio. Therefore, the umbilicocerebral ratio discriminates better in the context of progressive fetal hypoxia.

Strengths and limitations

Our results are robust for several reasons. First of all, this is by far the largest cohort (n = 374) of early fetal growth restriction in which MCA-related parameters were evaluated in relation to neonatal and 2 year infant outcome. Moreover, women enrolled in the TRUFFLE study were carefully phenotyped: the large majority of these babies represented a true growth restriction as reflected not only by the low estimated

FIGURE 2
Odds ratios with 95% confidence intervals for neonatal and 2 year infant outcome



Odds ratios of MCA, UCR, and CPR z-scores on inclusion (first) and within one week before delivery (last) for short term outcome **(A)** survival of the neonatal period without severe morbidity, and for long-term outcome **(B)** survival without neurological impairment at 2 years, adjusted for gestational age at delivery per week and birth weight p50 ratio per 0.1. The odds ratios of the adjusting parameters are shown below the *horizontal line.*

CPR, cerebroplacental ratio; *DV no A*, late changes in ductus venosus (no or reverse A wave flow); *DV p95*, early changes in the ductus venosus (DV-PI >95th percentile); *MCA*, middle cerebral artery; *UCR*, umbilicocerebral ratio.

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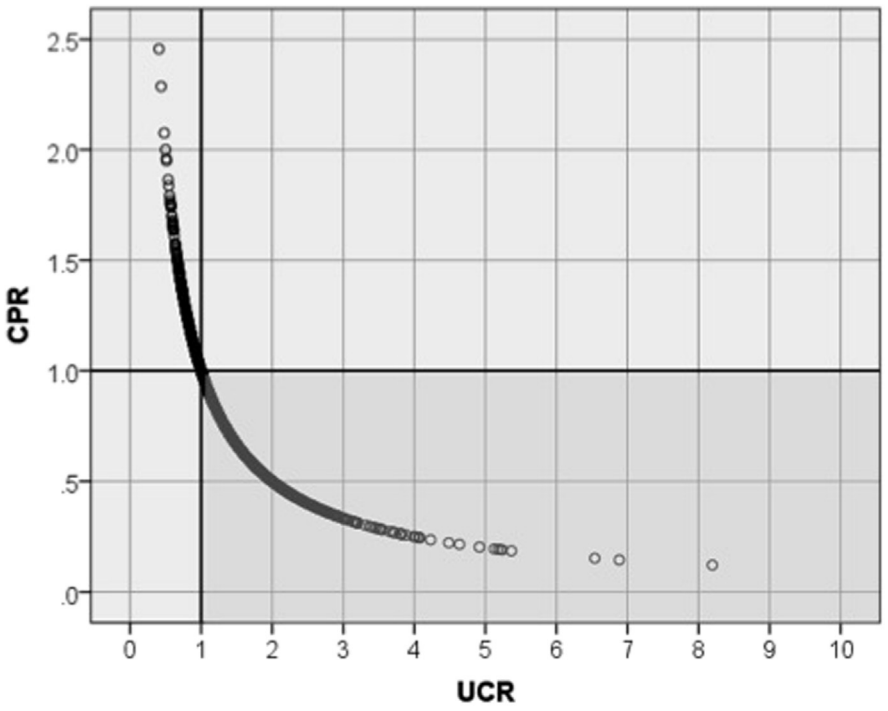
FIGURE 3
UCR vs CPR at study inclusion



UCR vs CPR at study inclusion in the TRUFFLE study (n = 374). The *shaded area* defines an abnormal test with a cutoff at 1.0.

CPR, cerebroplacental ratio; *TRUFFLE*, Trial of Randomized Umbilical and Fetal Flow in Europe; *UCR*, umbilicocerebral ratio.

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fetal weight but also a high umbilical artery PI. This definition of fetal growth restriction does not rely only on biometric smallness but also on abnormal umbilical artery Doppler and was suggested both by a large prospective observational study[33] and expert consensus[34] to distinguish true fetal growth restriction and small for gestational age. Furthermore, all women were followed up by a clearly defined monitoring protocol and all investigators were experienced in fetal Doppler assessment. None of the MCA-related Doppler parameters played a part in the obstetric decision making, and their values were adjusted for relevant parameters associated with neonatal and infant outcome, such as gestational age at study entry or at delivery, estimated fetal weight or birthweight, fetal sex, and others.

Factors affecting the generalizability of the results include that not all women entered into the study were considered because not all underwent MCA Doppler assessment within 1 week before delivery. Of eligible women, we were able to consider three quarters. Again, this is unlikely to be associated with a systematic bias because MCA Doppler was not a component of delivery decision making.

The fact that all fetuses with early growth restriction already had increased umbilical artery PI at inclusion is different from a situation in late fetal growth restriction when umbilical artery waveforms may still be within the normal range. Therefore, we caution in generalizing these results to later gestation.

Conclusions and clinical implications

In term pregnancies an association between cerebroplacental ratio and adverse neonatal outcome has been found not only in late fetal growth restriction[35,36] but also in fetuses with normal birthweight.[9] An association has been described between a lower fetal cerebroplacental ratio and the need for operative delivery for fetal compromise at term with suspected late placental diffusion disturbances, regardless of the fetal size.[37] We interpret these findings with caution because retrospective results showing a relationship between MCA Doppler-related parameters and short-term outcome cannot be considered as robust evidence on how to influence perinatal practice.[38]

Several studies evaluated the association between MCA-related Doppler parameters and short-term outcome in early fetal growth restriction.[1,13,39] However, there is a paucity of prospective studies that evaluated long-term neurodevelopmental outcome in a large cohort of preterm growth-restricted babies.[30] In the series of reports by Scherjon et al,[40-42] prematurely born babies were followed up longitudinally up to 11 years. The brain-sparing effect, defined as an umbilicocerebral ratio >0.72, was not associated with adverse neurodevelopmental outcome at 3 years,[40] was associated with poorer cognitive outcome at 5 years,[41] and was not associated with behavioral problems at 11 years,[42] respectively.

However, in this cohort, as in others,[43] the role of cerebral vasodilatation on long-term outcome was examined in preterm fetuses, both growth restricted and appropriate for gestational age,[40-43] making the comparison difficult with the present data.

Although this study was not designed to evaluate the role of MCA-related Doppler parameters in delivery decision making, based on our results, there is no compelling evidence to support its use in the follow-up or timing of delivery in fetal growth restriction between 26^{+0} and 31^{+6} weeks of gestation. Given that we have shown that monitoring and delivery based on late ductus venosus changes combined with computerized cardiotocography confers the best 2 year neurodevelopmental outcome,[15] it is important to wait if possible before delivering the fetus.

Our data show that the gestational age at delivery in fetal growth restriction between 26^{+0} and 31^{+6} weeks of gestation remains the most important factor in

determining neonatal and 2 year infant outcome. This accords with the findings of a study of 17,148 babies born at 22−32 weeks. Though not limited to growth restriction, gestation, birthweight, and sex were the most important predictors of survival without morbidity.[44]

In conclusion, despite some associations with adverse outcome, it is unlikely that MCA PI and cerebroplacental and umbilicocerebral ratios will be helpful for targeting the best time of delivery in fetal growth restriction between 26^{+0} and 31^{+6} weeks of gestation monitored by short-term fetal heart rate variation and ductus venosus PI. Where indicated, the umbilicocerebral ratio is preferable for clinical use over cerebroplacental ratio because this allows better differentiation in the abnormal range. ■

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Supplemental Appendix

Appendix 1: details on the TRUFFLE study[1]

Monitoring of the participants

Monitoring in all groups was recommended at least once a week and included umbilical artery Doppler and computerized cardiotocography short-term variation. The safety net criteria for delivery were irrespective of the randomized group, if any of the following conditions were met based on computerized cardiotocography: short-term variation <2.6 ms before 29 weeks; and <3 ms thereafter or if, irrespective of short-term variation, there were repeated unprovoked decelerations. After 32 weeks, the decision to deliver was based on local criteria because ductus venosus waveforms were no longer considered. The protocol allowed delivery if there was reversed umbilical artery end diastolic flow at ≥30 weeks or if there was absent umbilical artery end diastolic flow at ≥32 weeks. The timing of steroid administration was according to local protocols.

Evaluation and definition of the neurodevelopmental impairment

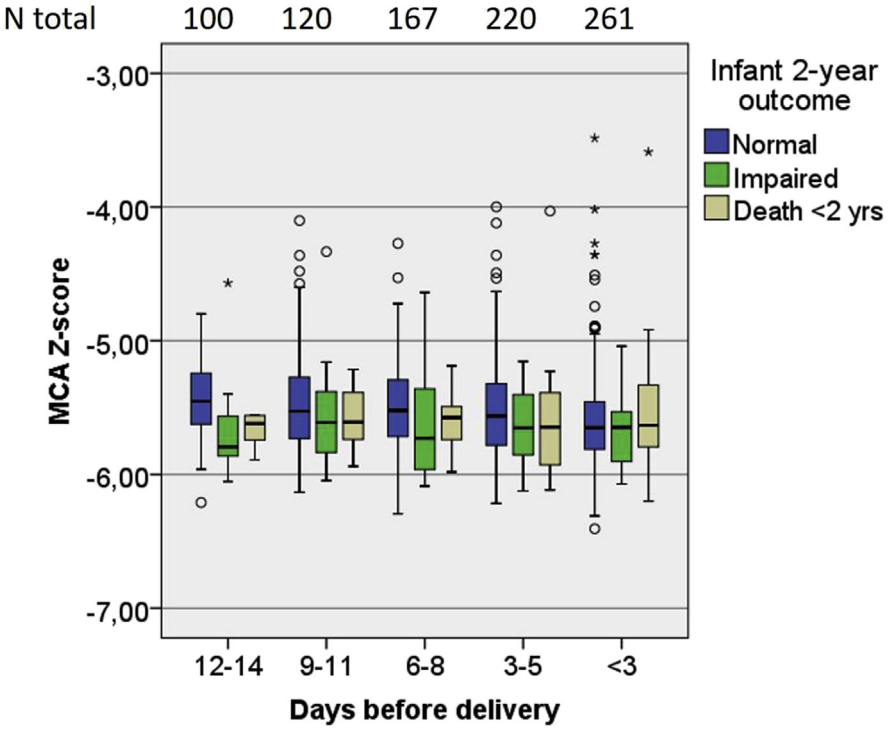
Development was assessed using the Bayley III Scales of Infant and Toddler Development.[2] Published normative scores were used in all centers and instructions translated locally.[3] All children had a formal neurological examination to determine the presence of cerebral palsy, which was classified according to the Surveillance of Cerebral Palsy in Europe classification. The functional severity of cerebral palsy was scored by the Gross Motor Function Classification System.[4] Neurodevelopmental impairment was defined as a Cognitive Bayley III score or corrected Bayley II mental development index score of <85 or an estimated cognitive delay of >3 months, cerebral palsy with a Gross Motor Function Classification System >1, hearing loss requiring hearing aids or severe visual loss (certifiable as blind or partially sighted).

Definition of neonatal morbidity

The neonatal morbidity was defined as bronchopulmonary dysplasia (additional oxygen at 36 weeks adjusted age), germinal matrix hemorrhage grade 3 or 4, periventricular leukomalacia >1, necrotizing enterocolitis (confirmed by X-ray or laparotomy), or microbiologically proven sepsis.

Appendix 2: additional results

SUPPLEMENTAL FIGURE 1
MCA pulsatility index Z-score trend before delivery



MCA pulsatility index Z-score trend before delivery divided by 2-year outcome groups is shown.

MCA, middle cerebral artery.

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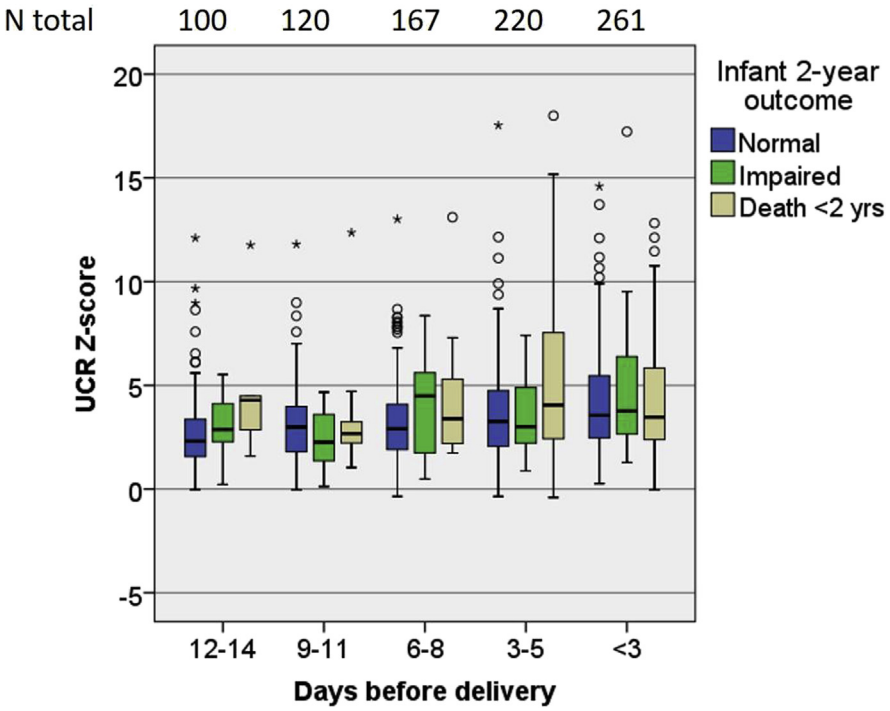
SUPPLEMENTAL FIGURE 2
UCR Z-score trend before delivery



UCR Z-score trend before delivery divided by 2 year outcome groups is shown.

UCR, umbilicocerebral ratio.

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SUPPLEMENTAL TABLE 1

Odds ratios with 95% confidence limits for neonatal outcome (infant survival until first discharge home without severe neonatal morbidity)

Variables	*P* value	OR	P5	P95
UCR Z-score first	.11	0.92	0.83	1.02
CPR Z-score first	.10	1.44	0.94	2.20
MCA Z-score first	.03	1.24	1.02	1.52
UCR Z-score last	.50	0.98	0.91	1.05
CPR Z-score last	.61	1.12	0.73	1.72
MCA Z-score last	.71	1.04	0.86	1.26
UCR Z-delta	.39	1.00	0.99	1.00
CPR Z-delta	.72	1.00	0.98	1.03
MCA Z-delta	.58	1.00	0.99	1.01
Adjusting parameters				
Gestational age at delivery/week	< .0001	1.69	1.46	1.95
Birthweight p50 ratio/0.1	.14	1.21	1.94	1.57

The model was adjusted for gestational age and birthweight p50 ratio.

CPR, cerebroplacental ratio; *MCA*, middle cerebral artery; *UCR*, umbilicocerebral ratio.

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SUPPLEMENTAL TABLE 2

Odds ratios with 95% confidence limits for 2-year infant outcome (infant survival without neuro-developmental impairment at 2-year)

Variables	*P* value	OR	P5	P95
UCR Z-score first	.04	0.88	0.78	0.99
CPR Z-score first	.10	1.58	0.92	2.71
MCA Z-score first	.03	1.33	1.03	1.72
UCR Z-score last	.74	0.99	0.92	1.06
CPR Z-score last	.99	1.00	0.61	1.64
MCA Z-score last	.62	1.06	0.85	1.32
UCR Z-delta	.63	1.00	1.00	1.00
CPR Z-delta	.50	0.99	0.97	1.02
MCA Z-delta	.05	0.99	0.98	1.00
Adjusting parameters				
Gestational age at delivery/week	< .0001	1.41	1.20	1.66
Birthweight p50 ratio/0.1	< .0001	1.86	1.33	2.60

The model was adjusted for gestational age and birthweight p50 ratio.

CPR, cerebroplacental ratio; *MCA*, middle cerebral artery; *UCR*, umbilicocerebral ratio.

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Appendix 3

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