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

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Condensation: Middle cerebral artery Doppler and umbilico-cerebral ratio are less strongly associated with outcome than birth weight or gestation at delivery in early fetal growth restriction.

Short version of title: Middle cerebral artery Doppler in early fetal growth restriction.

Abstract

BACKGROUND

Reduced fetal middle cerebral artery Doppler impedance is associated with hypoxemia in fetal growth restriction. This finding is increasingly recommended to guide delivery timing decisions despite 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. Additionally we sought to explore which ratio is more informative for clinical use.

STUDY DESIGN

This is a secondary analysis from TRUFFLE, 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 (374/503). 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 umbilico-cerebral and cerebro-placental 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 birth weight 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 to 1.52). Middle cerebral artery pulsatility index Z-score and umbilico-cerebral 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 cerebro-placental ratio against umbilico-cerebral ratio, the incremental range of the cerebro-placental ratio tended towards zero whereas the umbilico-cerebral ratio tended towards infinity as the values became more abnormal.

CONCLUSIONS

In a monitoring protocol based on ductus venosus and cardiotocography in early fetal growth restriction, the impact of middle cerebral artery Doppler and its ratios on outcome is modest and less marked than birth weight and delivery gestation. It is unlikely that middle cerebral artery Doppler and its ratios are informative in optimizing timing of delivery in early fetal growth restriction. The umbilico-cerebral ratio allows for a better differentiation in the abnormal range than the cerebro-placental ratio.

Introduction

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] In order to consider the opposite changes occurring in the MCA (reduced impedance) and umbilical artery (increased impedance) with progressive hypoxemia, the umbilico-cerebral ratio[5-7] and its inverse, the cerebro-umbilical also known as the cerebro-placental ratio have been established.[7,9-12] Up to now, most publications report on the cerebro-placental rather than the umbilico-cerebral 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 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, due to paucity of prospective good-quality studies with adequate sample size and long-term follow-up. The aim of this study is to investigate the association of the MCA PI, cerebro-placental and umbilico-cerebral ratios, normalized for gestational age, with neonatal and 2-year infant outcome in a large predefined group with early fetal growth restriction as part of the

multicenter 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, cerebro-placental and umbilico-cerebral 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 – 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 grams,[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 one of three groups in a 1:1:1 ratio to determine the timing of delivery. These groups were: 1) monitoring and delivery according to computerized cardiotocography short term variation criteria (short term variation <3.5 milliseconds (msec) at <29 weeks or <4 msec 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

Supplementary Appendix. The study was ratified by the ethics committees of all participating units, and all participants gave their written informed consent.

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

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

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

Both absolute values and Z-scores of MCA PI, cerebro-placental and umbilico-cerebral 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 multiply this ratio by 100: Delta ratio = 100 x (last – first) / Interval in days. This value was similarly compared for outcome.

Anova, Chi-square, Wilcoxon signed rank or Kruskal-Wallis test were used as appropriate. Levene test was used to assess for homogeneity of variables. Odds ratios with 95% confidence intervals (CI) 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 birth weight 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 (60/503, 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 due to a lethal congenital abnormality (trisomy 18, complex cardiac abnormality) ("inevitable deaths", Table 1). The study population available for analysis was 374 (74%) women.

Absolute values and Z-scores of MCA PI, cerebro-placental and umbilico-cerebral 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 2-year infant outcome groups were estimated fetal weight, birth weight, birth weight p50, 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 umbilico-cerebral ratio has a wider distribution in the abnormal range, with more abnormal outliers, than the cerebro-placental ratio. The median of the differences between the first and last measurement was significantly different from zero for all three Doppler parameters (p<0.001, Wilcoxon signed rank test).

Figure 2a shows the odds ratios for neonatal outcome adjusted for gestational age at delivery and birth weight p50 ratio (see also Table S1 in the Supplementary 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 to 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 Table S2 in the Supplementary Appendix). Among all Doppler criteria, only MCA PI Z-score and umbilico-cerebral ratio Z-score at 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 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 cerebro-placental ratio did not reach statistical significance despite the fact that it is the inverse of the umbilico-cerebral ratio, and that Z-scores were calculated from the same reference table. To explore this further, we plotted umbilico-cerebral ratio against cerebro-placental ratio and observed that in the abnormal range for cerebro-placental ratio (<1), the incremental change is far more compressed than for umbilico-cerebral ratio (>1) (Figure 3).

Comment

Principal findings of the study

We show that, for MCA related Doppler parameters, only MCA PI Z-score at study inclusion is associated with neonatal survival until discharge home without severe morbidity, and that MCA PI and the umbilico-cerebral ratio Z-scores at study inclusion are associated with 2-year infant survival without neurodevelopmental impairment. Cerebro-placental ratio Z-score at study inclusion, MCA PI, umbilico-cerebral and cerebro-placental 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 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, fetuses with less severe cerebral vasodilatation at study inclusion had a higher chance of avoiding mortality and severe neonatal morbidity, and of 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 birth weight 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 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 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 umbilico-cerebral ratio at study inclusion and 2-year survival without neurodevelopmental impairment, not for its inverse the cerebro-placental ratio.

Several reports have shown the advantage of umbilico-cerebral[5-6] and cerebro-placental 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 feto-placental hemodynamic profiles.

Though one study revealed an association between abnormal umbilico-cerebral 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 impacts 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] Further, the fact that changes in MCA, the cerebro-placental or umbilico-cerebral ratios Z-scores with respect to time were not associated with normal outcome at 2 years suggests that there is no rationale for delivering babies on the basis of MCA Doppler impairment. It is in fact plausible that the reverse may be true given the stronger effect of gestational age and birth weight on outcome.

It might be of interest that the umbilico-cerebral ratio Z-score at study inclusion showed an association with the 2-year infant outcome, but the cerebro-placental 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 MCA PI falls. Therefore, the umbilico-cerebral ratio will increase and tend towards an asymptote leading to infinity, while the cerebro-placental ratio will tend towards zero (Figure 3). A worsening in the fetal condition will have a very small effect on the cerebro-placental ratio but conversely a large one on the umbilico-cerebral ratio. Therefore, the umbilico-cerebral 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 high majority of these babies represented a true growth restriction as reflected not only by the low estimated fetal weight but also a high umbilical artery PI. Furthermore, all women were followed by a clearly defined monitoring protocol and all investigators were experienced in fetal Doppler assessment. None of MCA related Doppler parameters played a part in 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 birth weight, fetal sex, and others.

Factors affecting the generalizability of the results include that not all women entered into the study were considered as not all underwent MCA Doppler assessment within one week before delivery. Of eligible women, we were able to consider three quarters. Again, this is unlikely to be associated with a systematic bias as 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 cerebro-placental ratio and adverse neonatal outcome has been found not only in late fetal growth restriction,[33,34] but also in fetuses with

normal birth weight.[9] An association has been described between lower fetal cerebro-placental ratio and the need for operative delivery for fetal compromise at term with suspected late placental diffusion disturbances regardless of the fetal size.[35] We interpret these findings with caution since 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.[36]

Several studies evaluated the association between MCA related Doppler parameters and short-term outcome in early fetal growth restriction.[1,13,37] 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 fact, the majority of studies examined the role of cerebral vasodilatation on long-term outcome in preterm fetuses, both growth restricted and appropriate for gestational age.[38-40]

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 early fetal growth restriction. 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 early fetal growth restriction 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, birth weight and sex were the most important predictors of survival without morbidity.[41]

In conclusion, despite some associations with adverse outcome, it is unlikely that MCA PI, cerebro-placental and umbilico-cerebral ratios will be helpful for targeting the best time of delivery in early fetal growth restriction monitored by short term fetal heart rate variation and ductus venosus PI. Where indicated, the umbilico-cerebral ratio is preferable for clinical use over cerebro-placental ratio as this allows better differentiation in the abnormal range.

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Tables

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

	cCTG-STV	DV p95	DV no A	Total
All (Row%)	166 (33%)	167 (33%)	170 (34%)	503
With known outcome at 2 years	144 (87%)	142 (85%)	157 (92%)	443 (88%)
Perinatal and infant death <2 years †	13 (9%)	11 (8%)	17 (11%)	41 (9%)
Neurological impairment*	20 (15%)	12 (9%)	7 (5%)	39 (10%)
Doppler within 1 week 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 years †	10 (8%)	10 (9%)	12 (9%)	32 (9%)
Neurological impairment*	15 (14%)	11 (10%)	6 (5%)	32 (10%)

† Including 2 deaths after first discharge home and before 2 years.

*The denominator is represented by infants with known outcome minus perinatal and infant death <2 years.

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

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

	Normal neuro-development outcome	Abnormal neuro-development outcome	Death < 2 years	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	31 (5)	31 (5)	30 (6)	31 (5)
Nulliparous*	192 (62%)	16 (50%)	27 (84%)	235 (63%)
Gestational age at inclusion*	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*	895 (213)	831 (237)	718 (182)	875 (218)
Estimated fetal weight p50 ratio *	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 *	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 *	-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 *	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 *	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 *	0.7 (0.6-0.9)	0.6 (0.5-0.8)	0.7 (0.5-0.8)	0.7 (0.6-0.9)
CPR Z-score *	-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 week before delivery †				
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 *	30.6 (29.1-32.0)	30.1 (28.4-31.4)	28.6 (27.8-29.8)	30.4 (29.0-31.9)
Birth weight *	1000 (269)	870 (266)	759 (233)	968(276)
Birth weight p50 ratio*	0.59 (0.09)	0.55 (0.08)	0.56 (0.10)	0.59 (0.10)
Male sex*	149 (48%)	20 (63%)	18 (56%)	187 (50%)
Apgar score 5' <7 *	24 (8%)	8 (25%)	5 (16%)	37 (10%)
pH <7.0 (n=359)	2 (1%)	1 (4%)	1(5%)	4 (1%)
Severe neonatal morbidity*	80 (26%)	14 (44%)	24 (75%)	118 (32%)
Neonatal death			24 (75%)	24 (6%)
Late death <2 years			1 (3%)	1 (0%)

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

*p<0.05 (Anova, Chi-square or Kruskal-Wallis test).

† Last measurements differing significantly from the first measurements (p<0.05; Wilcoxon signed rank test).

cCTG-STV: computerized cardiotocography short-term variation; DV p95: early changes in the ductus venosus (DV-PI>95th percentile);

DV no A: late changes in ductus venosus (no or reverse A wave flow);

MCA-PI: middle cerebral artery pulsatility index;

UCR: umbilico-cerebral ratio;

CPR: cerebro-placental ratio.

Figure legends

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

The umbilico-cerebral ratio (UCR), the cerebro-placental ratio (CPR) and middle cerebral artery (MCA) pulsatility index at inclusion (first) and within 1 week before delivery (last), n=374.

Differences between first and last measurements are all statistically significant (p<0.001, Wilcoxon signed rank test).

Figure 2. Odds ratios with 95% confidence intervals for neonatal and 2-year infant outcome.

The upper panel (a) represents odds ratios for neonatal outcome (survival until the first discharge home without severe morbidity) and the lower panel (b) represents odds ratios for 2-year infant outcome (survival without neurological impairment at 2 years) of the Z-scores of the middle cerebral artery (MCA) pulsatility index, umbilico-cerebral ratio (UCR) and cerebro-placental ratio (CPR) at inclusion (first) and within one week before delivery (last), adjusted for birthweight p50 ratio and gestational age. The odds ratios of the adjusting parameters are shown below the horizontal line.

DV p95: early changes in the ductus venosus (DV-PI>95th percentile);

DV no A: late changes in ductus venosus (no or reverse A wave flow).

Figure 3: Umbilico-cerebral ratio (UCR) versus cerebro-placental ratio (CPR) at study inclusion in the TRUFFLE study (n=374).

The shaded area defines an abnormal test with a cut-off at 1.0.

Figure legends