How to monitor pregnancies complicated by fetal growth restriction and delivery below 32 weeks: a post-hoc sensitivity analysis of the TRUFFLE-study

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Abstract

Objectives

In the recent TRUFFLE study it appeared that, in pregnancies complicated by fetal growth restriction (FGR) between 26 and 32 weeks, monitoring of the ductus venosus (DV) combined with computerised cardiotocography (cCTG) as a trigger for delivery, increased the chance of infant survival without neurological impairment. However, concerns in interpretation were raised as DV monitoring appeared associated with a non-significant increase in fetal death, and part of the infants were delivered after 32 weeks, after which the study protocol was no longer applied. This secondary sensitivity analysis focuses on women who delivered before 32 completed weeks, and analyses fetal death cases in detail.

Methods

We analysed the monitoring data of 317 women who delivered before 32 weeks, excluding women with absent infant outcome data or inevitable perinatal death. The association of the last monitoring data before delivery and infant outcome was assessed by multivariable analysis.

Results

The primary outcome (two year survival without neurological impairment) occurred more often in the two DV groups (both 83%) than in the CTG-STV group (77%), however the difference was not statistically significant (p=0.21). Nevertheless, in surviving infants 93% was free of neurological impairment in the DV groups versus 85% in the CTG-STV group (p=0.049). All fetal deaths (n=7) occurred in women allocated to DV monitoring, which explains this difference. Assessment of the monitoring parameters that were obtained shortly before fetal death in these 7 cases showed an abnormal CTG in only one.

Multivariable regression analysis of factors at study entry demonstrated that higher gestational age, larger estimated fetal weight 50th percentile ratio and lower U/C ratio were significantly associated with the (normal) primary outcome. Allocation to the DV groups had a smaller effect, but remained in the model ($p<0.1$). Assessment of the last monitoring data before delivery showed that in the CTG-STV group abnormal fetal arterial Doppler was significantly associated with adverse outcome. In contrast, in the DV groups an abnormal DV was the only fetal monitoring parameter that was associated with adverse infant outcome, while fetal arterial Doppler, STV below CTG-group cut-off or recurrent fetal heart rate decelerations were not.

Conclusions

In accordance with the results of the overall TRUFFLE study of the monitoring-intervention management of very early severe FGR we found that the difference in the proportion of infants surviving without neuroimpairment (the primary endpoint) was non-significant when comparing timing of delivery with or without changes in the DV waveform. However, the uneven distribution of fetal deaths towards the DV groups was likely by chance, and among surviving children neurological outcomes were better. Before 32 weeks, delaying delivery until abnormalities in DVPI or STV and/or recurrent decelerations occur, as defined by the study protocol, is therefore probably safe and possibly benefits long-term outcome.

Keywords

Fetal growth restriction; intra-uterine growth restriction, ductus venosus, cardiotocography

Introduction and objective

No cure exists for fetal growth restriction (FGR). Only timely diagnosis, fetal surveillance and the decision to deliver the baby when fetal condition deteriorates can reduce the risk of mortality and neurological impairments. No consensus exists as to the best way of monitoring and triggering delivery in early preterm FGR, although optimal timing of delivery could be crucial for the chance of healthy survival.

The TRUFFLE study, carried out in 20 European perinatal centres, explored if a monitoring method that uses abnormal ductus venosus (DV) measurements ('early' at 95th percentile or 'late' at absent A-wave) or abnormal findings of computerised cardiotocography (cCTG) as a trigger for delivery, could increase the chance of healthy infant survival compared to the standard monitoring method by cCTG in pregnancies complicated by FGR between 26 and 32 weeks.(1, 2) Survival without neurological impairment occurred more often in the group using late ductus and cCTG changes as trigger for delivery compared to the cCTG group, while differences between the early and late DV group were minimal.(2) However, reservations in data interpretation were raised by the fact that only a proportion of the fetuses allocated to delivery based on ductus venosus changes actually delivered according to this criterion, the majority having been delivered on cardiotocography safety net criteria. Also, all fetal deaths were in the DV groups. Differences in outcome between the DV groups were minimal and part of the infants were delivered after 32 weeks, the term after which the study protocol was no longer followed. This sensitivity analysis aims to focus on women delivered according to the formal protocol, thus restricted to women who delivered before 32 completed weeks, to pinpoint the effect of ductus venosus added to CTG in the monitoring of growth-restricted fetuses. The second aim is to analyse the monitoring data in the fetal deaths.

Methods

The study design has been described earlier.(1, 2) In short, women with singleton fetuses at 26-32 weeks of gestation, with abdominal circumference <10th percentile and umbilical artery Doppler pulsatility index (PI) >95th percentile, were included in a twenty centre European study (ISRCTN 56204499). Baseline maternal and fetal data were collected via a secure internet data entry page. Study group allocation was performed in an even ratio from randomly sized blocks, stratified for gestational age (lower or higher than 29 weeks of gestation) and for participating centres. Eligible women were allocated for delivery according to one of three monitoring arms: reduced cardiotocography (cCTG) fetal heart rate short-term variation (STV<3.5 ms at a gestational age below 29 weeks and <4.0 ms thereafter), early ductus venosus (PI>95th percentile; 'DV p95') or late ductus venosus changes ('a' wave at or below baseline; 'DV no A'). Abnormal DV measurements should be repeated within 24 hours, if cCTG results allowed this, to demonstrate consistency. In all groups delivery could also be decided on 'safety net criteria' when the cCTG showed recurrent decelerations, or in the DV groups when STV was very low (STV<2.6 ms at a gestational age below 29 weeks and <3.0 ms thereafter).

The primary outcome was survival without cerebral palsy, severe neurosensory impairment or low Bayley Scales of Infant Developmental score <85 at 2 years of age.

This post-hoc analysis targets at the association of fetal monitoring data (CTG STV, DV PI, DV a-wave, umbilical artery PI, middle cerebral artery PI and the umbilical artery / middle cerebral artery ratio (UC ratio), that were available shortly before delivery, and outcome (two years neurodevelopmental outcome, fetal, neonatal, infant death).

Because the study protocol was restricted to management before 32 weeks and monitoring data thereafter were not stored (and DV was not used), we analysed the data of women who delivered before 32 weeks only. Seven women with inevitable fetal or neonatal death, and one with absent neonatal data, who had remained in the primary published intention to treat analysis, were excluded in this analysis as these circumstances precluded any exploration of the association between monitoring data and outcome. In five of these women fetal death occurred due to refusal of intervention, and in two the babies died shortly after delivery because of lethal congenital

abnormality (one trisomy 18, one complex cardiac defect). In one no neonatal data could be provided after neonatal transfer immediately after delivery. Furthermore short-term data of 33 surviving infants (9%), who could not be examined after two years, were excluded from endpoint data analysis.

Cut-off values for fetal monitoring data were as defined by the study protocol. For reference of estimated fetal weight and birth weight a ratio was calculated with a 50th percentile (p50) weight adjusted for gestational age, maternal ethnic descent, weight and length and infant sex.(3)
The effect of the most recent monitoring registration before birth on long-term outcome was evaluated by univariable and multivariable analysis. Univariable analysis used Anova, Chi-square or Kruskal-Wallis as appropriate. Multivariable analysis allowed the adjustment for relevant clinical details that were significantly different between outcome categories in univariable analysis. Criteria for inclusion and exclusion of potential variables were set at 0.05 and 0.10 respectively. IBM SPSS version 22 (New York, USA) was used for statistics.

Results

Three-hundred and seventeen (of the original 503) FGR infants with known outcome (either with perinatal death or follow-up examination at 2 years) were delivered before 32 weeks and included in this post-hoc analysis (Table 1). For the purposes of further analysis the two DV groups were combined to assess more precisely the association of abnormal DV PI with infant outcome. The primary outcome (two-year survival without neurological impairment) occurred more often in the DV groups (both 83%) than in the CTG-STV group (77%), although this difference is not statistically significant (p=0.21). Nevertheless, when analysing the group of surviving infants, the prevalence of neurological impairment in the DV groups was half of the prevalence in the CTG groups (14/190 (7%) versus 14/95 (15%); RR 0.50 (0.25 to 1.00); p=0.049, numbers-needed-to-treat [NNT] 13).

Table 2A and 2B demonstrate demographic, obstetric and neonatal information specified for normal or abnormal neurological infant development at the corrected age of 2 years, and perinatal

mortality. Thirty-two infants (10%) had died (7 antenatal, 25 neonatal). Causes for neonatal death that were not included in the study definition of severe neonatal morbidity were acute respiratory distress, multi-organ failure or clinical sepsis. Twenty-eight infants (9%) had impaired neurological development at two years corrected age.

Women with a normal infant outcome had been randomised at a higher gestational age and the estimated fetal weight and birthweight p50 ratio were larger than in women with an infant who died or had abnormal development. All fetal deaths (n=7) occurred in women allocated to DV monitoring. Assessment of the monitoring parameters obtained shortly before fetal death showed that in only one case STV was below the CTG group cut-off, whereas DV was still normal (Table 3). All other fetal death cases had either no STV assessment within 24 hours before fetal death or a normal CTG according to CTG-group protocol. In two cases the most recent DV PI before death had been higher than 95th percentile (but these cases had been allocated to the DV no A group).

At delivery, infants with a normal outcome were born at later gestational age, with a higher birth weight and birth weight ratio, and less frequently had a low APGAR score. At discharge, severe composite morbidity was less likely in infants with a normal outcome (definition of composite morbidity and results given in Table 2b). Especially cerebral haemorrhage and periventricular leucomalacia (PVL) were more frequent in infants with an abnormal outcome (17%) than in the normal outcome group (2%). Eighty-three percent of the live-born infants survived without neurological impairment, although 28% of these infants had severe morbidity in the neonatal period. In contrast, thirteen of the 28 infants (46%) with neurological impairment did not have severe morbidity during the neonatal period.

There were no differences in inclusion characteristics, or in obstetric and neonatal details between the randomisation groups and between infants with or infants without follow-up at two years age corrected for prematurity (data published previously(2)). Infants delivered after 32 weeks were included at a later gestational age, and a larger estimated fetal weight and had better outcomes than those included earlier, as can be expected.

Multivariable regression analysis of factors at study entry demonstrated that gestational hypertension, larger estimated fetal weight p50 ratio and lower U/C ratio were significantly

associated with the (normal) primary outcome (Figure 1A). Allocation to the DV groups had a smaller effect, but remained in the model ($p<0.1$). Multivariable analysis with parameters known at delivery demonstrated that women with a normal outcome were more likely to have been allocated to the DV-groups, had a lower U/C ratio, and their babies had a higher birth weight, a higher APGAR score and were more often female (Figure 1B). If this analysis was repeated including DV PI only in those women who had a last DV measurement within 3 days of delivery or fetal death (n=180) then only a last DV measurement higher than 95th percentile was negatively associated with the primary endpoint and a larger birth weight p50 ratio had a positive effect, while the other parameters were ejected from the model (Figure 1C).

The association between the last fetal monitoring before birth (or fetal death) and primary outcome is specified in greater detail in Table 4 separately for participants of the CTG-STV group and the DV groups. There appeared a difference of the impact of abnormal monitoring results on the primary outcome between these groups. In the CTG group, umbilical artery Doppler ARED flow and high U/C-ratio were negatively associated with the primary outcome (Figure 2A). In the DV groups an abnormal DV PI > 95th percentile was negatively associated with the primary outcome and this effect was more pronounced after recurrent elevated DV PI > 95th percentile with a longer interval than 1 day (which was allowed by the study protocol) (Figure 2B). The negative effect of an abnormal DV PI >95th percentile was not further affected by a combination with a STV below CTG-STV group cut-off, below DV safety-net cut-off or decelerations. Although the U/C ratio in the DV groups was of the same value as in the CTG group and the incidence of umbilical artery ARED flow was similar, the negative association of these parameters with the primary endpoint that was observed in the CTG-STV group was absent in the DV groups.

Discussion

This secondary sensitivity analysis of TRUFFLE strengthens the conclusion of the primary intention-to-treat analysis, that perinatal outcomes are improved if ductus venosus measurements are added to CTG-STV in the monitoring of fetuses with severe early-onset FGR. The analysis targeted those infants that were delivered before 32 weeks to focus on the effect of the different

monitoring techniques and looked in-depth at the perinatal deaths and the association between the most recent fetal monitoring parameters with the primary outcome.

In this post-hoc analysis both DV groups were combined because we wanted to explore the association of 2-year infant outcome with DV measurement results. It was deemed justified because survival with normal neurodevelopment at 2 years corrected for prematurity was equal in both DV groups (both 83% in infants with known outcome). Normal 2 year outcome was less frequent in the CTG-STV group (77%), but this difference was not statistically significant. Perinatal mortality was similar between the CTG-STV and the DV groups (10%), however all antenatal deaths (n=7) occurred in the DV groups. Analysis of this antenatal mortality suggested this was a spurious result: 6 of 7 cases would probably also not have been delivered timely if they had been allocated to the CTG-STV group as the last STV results were above the CTG-group cut-off limits. Two cases of fetal death might have benefited from a DVPI cut-off at the 95th percentile instead of absent a-wave.

Multivariable analysis did not demonstrate a significant benefit for normal primary outcome in those randomised to the DV groups after adjustment for gestational age and fetal weight p50 ratio. If the analysis is restricted to those that are born alive, assuming that fetal death had occurred unbalanced by chance, there is a statistically significant benefit for DV monitoring. This is in line with aggregated cohort evidence as systematically reviewed by Morris et al.(4) who showed moderate predictive accuracy of longitudinal DV measurements for fetal/neonatal wellbeing in high-risk pregnancies (likelihood ratio 3.15; 95% CI 2.19-4.54).

Analysis of the results of the different monitoring techniques shows that with CTG monitoring decelerations and umbilical artery ARED flow are negatively associated with outcome while this is not so with combined DV and CTG monitoring. It might be that those at risk for neurological impairment with ARED flow are delivered more timely in the DV groups because of abnormal DV measurement, although we cannot prove this because DV was not measured in the CTG-STV group after inclusion.

Typically, umbilical artery / middle cerebral artery flow abnormalities precede abnormalities of DV flow pattern.(5, 6) Elevated U/C ratio and umbilical artery ARED flow are known predictors of adverse outcome in pregnancies with FGR.(7) Our findings confirmed this but only in the CTG-STV group.

Possibly, Doppler assessment of ductus venosus allowed 'fine tuning' of the timing of delivery, and selection of a sub-group of fetuses with severe redistribution (U/C ratio) and severe placental impairment (umbilical ARED flow) who were most at risk for cerebral damage.

The observation that elevated DV PI or absent / reversed a-wave is associated with increased neonatal morbidity and adverse long-term infant outcome and that DV flow abnormalities are a stronger predictor of these outcomes than umbilical artery flow abnormalities have been described earlier.(8, 9) The current analysis, where in the DV groups abnormal DV flow pattern is associated with abnormal neurological outcome is consistent with these observations.

The difference in association between monitoring data and outcome between the CTG-STV group and the DV groups, and the lower prevalence of neurological impairment in survivors in the DV groups, may support the hypothesis that in some early preterm growth restricted infants cardiac dysfunction (abnormal DV assessment) can precede cerebral dysfunction (low CTG-STV). Thus, timely detection of these changes by DV measurement (and subsequent action) can prevent neurological impairment in some fetuses. In others this sequence can be opposite with earlier STV abnormality or recurrent heart rate decelerations as indication for delivery. In four cases with fetal death the most recent DV was in the normal range, but in two it was higher than the 95th percentile. Frauenschuh et al. found that in 4 cases of severe placental insufficiency ductus venosus blood flow prior to intrauterine fetal death can be unaffected.(10) Thus it is well possible that there is some variation in the effect of malnutrition and hypoxia on the FGR fetus and the onset of organ damage may not follow the same pattern in all fetuses.

We only included babies delivered before 32 weeks because by protocol and in practice, ductus venosus Doppler only contributed to the delivery decision before 32 weeks gestation. The potential bias introduced by excluding differential delivery after 32 weeks by trial allocation group is likely to be small, since the post 32 week numbers were equally distributed between the groups. Results from this analysis can therefore only be applied to women with FGR before 32 weeks.

This post-hoc analysis highlights some of the effects of DV-monitoring that were obscured by the original intention-to-treat analysis. However, just like all post-hoc analyses there should be caution regarding the possibility of bias. Nonetheless, the current findings are consistent with the original data.

Conclusions

In accordance with the results of the overall TRUFFLE study of the monitoring-intervention management of very early severe FGR we found that the difference in the proportion of infants surviving without neuroimpairment (the primary endpoint) was non-significant when comparing timing of delivery with or without changes in the DV waveform. However, we speculate that the uneven distribution of fetal deaths towards the DV groups was likely by chance, and we found that among surviving children the neurological outcomes at two years of age were better. Adverse neurodevelopmental outcome was significantly associated with abnormal DVPI before delivery and lower birth weight in surviving babies. Before 32 weeks, delaying delivery until abnormalities in DVPI or STV and/or recurrent decelerations occur, as defined by the study protocol, is therefore probably safe and possibly benefits long-term outcome.

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Table 1

Randomisation allocation, with selection for post-hoc analysis and primary study outcome.

		CTG-STV	DV p95	DV noA	Total
Total study group (row%)		166 (33%)	167 (33%)	170 (34%)	503
Excluded	Inevitable perinatal death	2	1	4	7
	Neonatal data missing	1	--	--	1
	Alive, but no follow-up at 2 years	21 (13%)	25 (15%)	13 (8%)	59 (12%)
	Delivered at 32 weeks or later	37 (22%)	39 (23%)	43 (25%)	119 (24%)
Delivered before 32 weeks		105 (63%)	102 (61%)	110 (65%)	317 (63%)
	Gestational age (median (IQR))	29.7 (28.5 to 30.9)	29.9 (28.7 to 30.9)	29.9 (28.7 to 30.7)	29.9 (28.6 to 30.9)
	Birthweight (mean (SD))	888 (202)	887 (220)	876 (208)	884 (209)
	Fetal death	0 (--)	3 (3%)	4 (4%)	7 (2%)
	Neonatal death	10 (10%)	6 (6%)	9 (8%)	25 (8%)
	Alive and evaluated at 2 years	95 (90%)	93 (91%)	97 (88%)	285 (90%)
	Alive without neurological impairment % of evaluated live infants (p=0.049)* % of all infants with known outcome (p=0.21)*	81 (85%) (77%)	85 (91%) (83%)	91 (94%) (83%)	257 (90%) (81%)

*Pearson's chi-square for comparison of the CTG-STV group with both DV groups combined

Table 2a.

Demographic and obstetric characteristics at study entry, specified for study primary outcome for all infants with known outcome (omitting 33 lost to follow-up) – percentages for each row.

	Normal	Impaired	Dead	All known outcome
Delivered <32 weeks (row%)	257 (81%)	28 (9%)	32 (10%)	317
Maternal age	31 (5)	31 (5)	30 (5)	31 (5)
Caucasian ethnicity	220 (86%)	25 (89%)	29 (91%)	274 (86%)
Nulliparity *	159 (62%)	14 (50%)	27 (84%)	200 (63%)
BMI (kg/m^2)	25 (6)	25 (6)	25 (5)	25 (6)
Smoking	30 (12%)	6 (21%)	4 (13%)	40 (13%)
GA (w+d) *	28+6 (26+0 to 31+5)	28+1 (26+0 to 31+0)	27+6 (26+0 to 31+4)	28+4 (26+0 to 31+5)
EFW (g) *	852 (193)	778 (180)	703 (178)	833 (202)
EFW p50 ratio *	0.65 (0.09)	0.62 (0.08)	0.60 (0.08)	0.64 (0.09)
Uterine artery notch	131 (51%)	19 (68%)	20 (63%)	170 (54%)
UA PI	2.0 (0.5)	2.2 (0.7)	2.2 (0.7)	2.1 (0.6)
UA ARED flow	111 (43%)	15 (54%)	18 (56%)	144 (45%)
UA RED flow	15 (6%)	1 (4%)	3 (9%)	19 (6%)
U/C ratio*	1.5 (0.5)	1.8 (0.6)	1.7 (0.8)	1.5 (0.6)

* between groups $p < 0.05$;

Abbreviations: BMI = body mass index; GA = gestational age; EFW = estimated fetal weight; p50 = 50^{th} percentile; UA = umbilical artery; PI = pulsatility index; AREDflow = absent/reversed end-diastolic flow; U/C-ratio = umbilical artery / middle cerebral artery PI ratio;

Table 2b

Obstetric data after inclusion and neonatal data, specified for study primary outcome for all infants with known outcome

	Normal	Impaired	Dead	All known outcome
All (row%)	257 (81%)	28 (9%)	32 (10%)	317
Any hypertensive morbidity	203 (79%)	22 (79%)	23 (72%)	248 (78%)
Preeclampsia-HELLP	155 (60%)	15 (54%)	16 (40%)	286 (59%)
Antihypertensive medication	162 (63%)	16 (57%)	16 (50%)	194 (61%)
Magnesium treatment *	63 (25%)	3 (11%)	3 (9%)	69 (22%)
Interval to delivery (days)	7 (6)	8 (7)	6 (6)	7 (7)
GA (w+d) *	30+0 (26+2 to 31+6)	29+5 (26+1 to 31+3)	28+5 (26+1 to 31+6)	29+6 (26+1 to 31+6)
Fetal death	--	--	7 (22%)	7 (2%)
Live-born (row%)	257 (83%)	28 (9%)	25 (8%)	310
Birth weight (g) *	910 (203)	804 (170)	736 (231)	887 (209)
Birth weight p50 ratio *	0.59 (0.09)	0.54 (0.07)	0.55 (0.10)	0.59 (0.09)
Male sex *	118 (46%)	20 (71%)	12 (48%)	150 (48%)
Apgar score <7 *	29 (11%)	9 (32%)	6 (24%)	44 (14%)
UA pH (n=280)	7.3 (6.8 to 7.4)	7.3 (7.0 to 7.4)	7.3 (6.9 to 7.3)	7.3 (6.8 to 7.4)
UA pH <7.0	2 (1%)	1 (5%)	1 (5%)	4 (1%)
Composite severe morbidity † *	73 (28%)	15 (54%)	16 (64%)	104 (34%)
BPD *	32 (13%)	8 (29%)	2 (8%)	42 (14%)
Sepsis (Proven) *	43 (17%)	7 (25%)	12 (48%)	62 (20%)
NEC *	6 (3%)	0 (--)	5 (20%)	11 (4%)
GMH Grade III or IV *	4 (2%)	4 (14%)	3 (12%)	11 (4%)
PVL Grade II or III	2 (1%)	2 (7%)	0 (--)	4 (1%)

* between groups $p < 0.05$

* row% = the percentage of the row (horizontal) total

†Components of severe morbidity: BPD (supplemental oxygen at 36 weeks gestational age), GMH grade III or IV, PVL grade II or III, NEC (diagnosed by X-ray or laparotomy) or proven sepsis.

Abbreviations: CTG = cardiotocography; STV = short-term variation; DV = ductus venosus; BMI = body mass index; GA = gestational age; p50 = 50th percentile; EFW = estimated fetal weight; UA = umbilical artery; MCA = middle cerebral artery; PI = pulsatility index; AREDflow = absent/reversed end-diastolic flow; U/C-ratio = umbilical artery / middle cerebral artery PI ratio; HELLP = hemolysis elevated liver enzymes low platelets; BPD = bronchopulmonary dysplasia; GMH = germinal matrix haemorrhage; PVL = periventricular leucomalacia; NEC = necrotizing enterocolitis;

[Authors would prefer to combine join table 2a and 2b, but this may not improve clarity]

Table 3.

Characteristics of the seven cases of fetal death. Last CTG registered < 24 hours before death, last DV registered within 3 days before death, last umbilical Doppler within 1 week before death

Case	Allocation	GA at birth	Last CTG < 24 hrs	Last STV	Last STV low	Last CTG decel	Last DV PI	Last DV high	Last DV a-wave	Last PI UA	Last U/C	Last EDF	Comment
1	DV no A	29	Yes	5,1	No	No	,30	No	present	1,6	1,2	present	
2	DV p95	29	Yes	2,7	Yes	No	,57	No	present	3,8	3,5	absent	
3	DV no A	28	Yes	5,2	No	No	1,01	>p95	present	2,2	1,5	absent	
4	DV p95	27	No	6,9	No	No	,77	No	present	1,9	1,3	absent	Abruptio plac.
5	DV p95	29	No	7,5	No	No	,66	No	present	4,8	5,4	reversed	
6	DV no A	27	Yes	5,6	No	No	1,10	>p95	present	1,6	1,3	present	
7	DV no A	28	Yes	5,8	No	No	,74	No	present	2.0	1,7	present	

Abbreviations: GA = gestational age; CTG = cardiotocography; STV = short-term variation; DV = ductus venosus; UA = umbilical artery; PI = pulsatility index; EDF = end-diastolic flow; U/C-ratio = umbilical/cerebral ratio;

Table 4.

Last results of fetal monitoring before delivery or fetal death, for participants allocated to the CTG-STV group or to either of the DV groups. The latter groups have been combined. Participants are included in the table if the last CTG was within 24 hours, the last DV within 3 days or the last fetal arterial Doppler within 1 week of delivery or fetal death. Percentages are calculated from column totals. Numbers add up to more than 100 because many foetuses had multiple test results recorded within the relevant time period.

8 cases from STV group and 8 cases from DV groups excluded because they had no last CTG < 24 hours before birth. 20 cases from DV groups excluded because they had no last DV PI within 3 days before delivery.

Group allocation		Normal neuro dev.	Abnormal neuro dev	Neonatal death	Fetal death	Total
CTG	N with last STV<24 hrs	78	13	8	--	99
	STV (range)	4.5 (1.8)	5.0 (2.8)	3.7 (1.9)	--	4.5 (2.0)
	Low STV†	43 (55%)	6 (46%)	4 (50%)		53 (55%)
	Decelerations (%)	26 (33%)	7 (54%)	3 (38%)	--	36 (37%)
	Low STV† or/and decelerations	53 (68%)	11 (85%)	7 (88%)	--	71 (73%)
	UA PI	2.0 (0.6)	2.8 (1.3)	2.6 (1.0)	--	2.2 (0.8)
	U/C ratio *	1.6 (0.5)	2.0 (1.2)	2.0 (1.1)	--	1.7 (0.7)
	UA ARED flow *	32 (41%)	8 (62%)	7 (88%)	--	47 (49%)
DV PI	N with last STV<24 hrs	172	13	15	5	205
	STV (range)	4.6 (2.0)	4.5 (2.0)	5.1 (2.2)	4.9 (1.2)	46 (2.0)
	Low STV†	70 (41%)	6 (46%)	4 (27%)	1 (20%)	81 (40%)
	Decelerations (%)	69 (40%)	4 (31%)	5 (33%)	0 (--)	78 (38%)
	Low STV† or/and decelerations	97 (56%)	9 (70%)	9 (60%)	1 (20%)	116 (57%)
	UA PI	2.3 (0.9)	2.1 (0.8)	2.7 (1.4)	2.2 (0.9)	2.3 (0.9)
	U/C ratio	1.8 (1.0)	1.9 (0.6)	2.0 (1.0)	1.8 (0.9)	1.8 (1.0)
	UA ARED flow	104 (60%)	10 (77%)	10 (67%)	2 (40%)	126 (62%)
	N with last DVPI ≤3 days	152	14	14	7	187
	DV PI	0.80 (0.45)	1.00 (0.32)	1.03 (0.36)	0.84 (0.27)	0.82 (0.44)
	DV PI > p95 *	50 (33%)	8 (57%)	9 (64%)	2 (29%)	69 (37%)
	DV A wave abs/rev	12 (8%)	1 (7%)	1 (7%)	0 (--)	14 (8%)
	DV PI >p95 + (Low STV† or/and decelerations) *	21 (14%)	4 (29%)	6 (43%)	0 (--)	31 (17%)
	Recurrent DV PI >p95 > 1 day before birth *	12 (8%)	4 (29%)	3 (14%)	1 (14%)	20 (11%)
	DV PI > p95 once, later normal	4 (2%)	2 (14%)	0 (---)	0 (---)	6 (3%)
	DV PI <p95 + (Low STV† or/and decelerations)	62 (41%)	5 (36%)	4 (29%)	1 (14%)	72 (39%)
	DV PI <p95 + (Low STV‡ or/and decelerations)	54 (36%)	4 (29%)	3 (14%)	0 (--)	61 (33%)

* P<0.05

† STV cut-off by CTG-STV group criteria

‡ STV cut-off by DV groups safety-net criteria

Abbreviations: CTG = cardiotocography; STV = short-term variation; DV = ductus venosus; UA = umbilical artery; PI = pulsatility index; AREDflow = absent/reversed end-diastolic flow; U/C-ratio = umbilical/cerebral ratio.

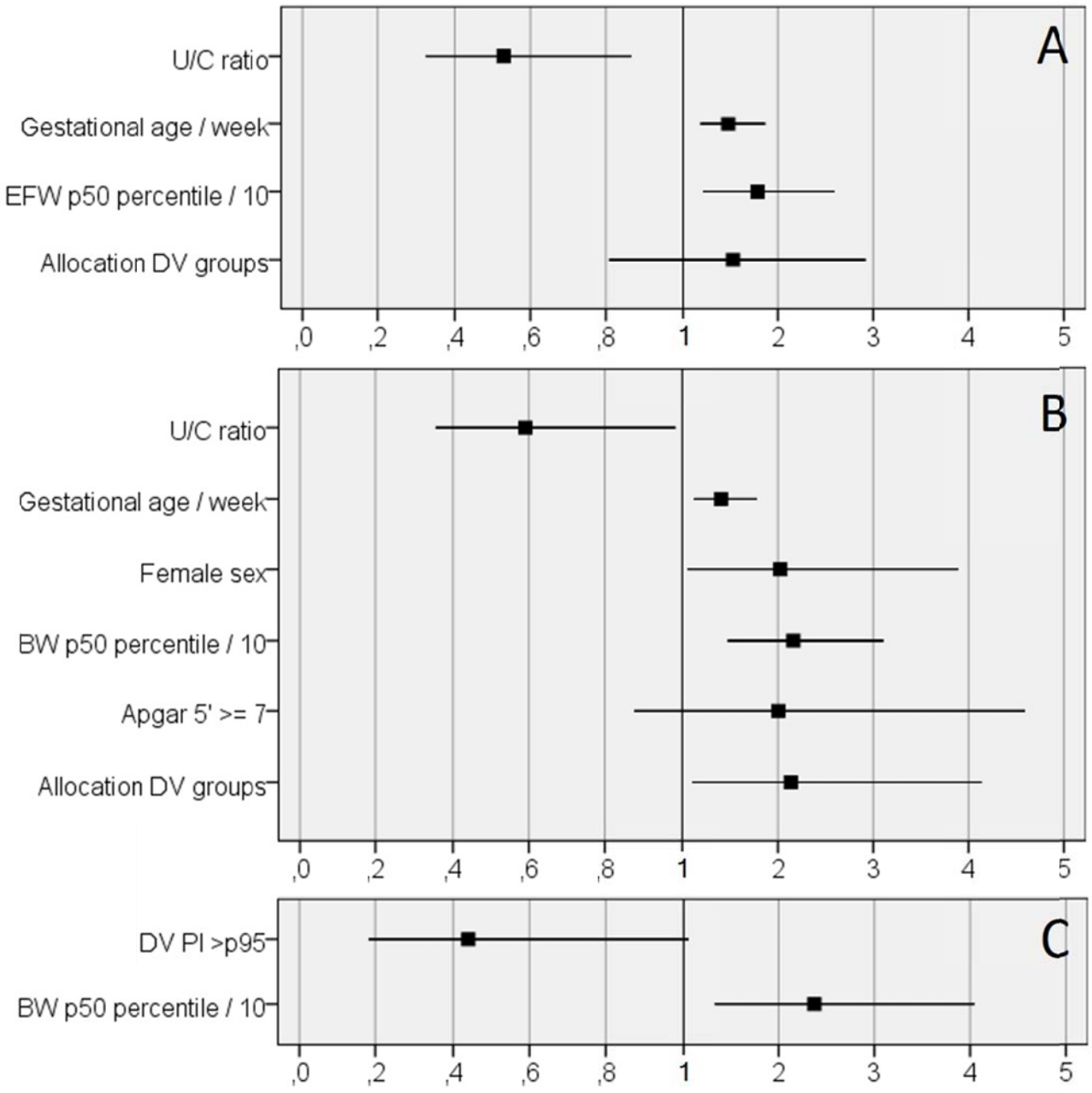

Figure 1. Graphic representations of odds ratios for normal outcome at corrected age of 2 years, calculated by multivariable analysis, in infants with fetal growth restriction before 32 weeks. P in 0.05, p out 0.10; Group allocation forced to stay in the model; Underlying data as supplemental material.

1A. analysis with factors at inclusion; AUC 0.69

1B. analysis with factors at delivery; AUC 0.75

1C. analysis 1B. restricted to women in the DV groups with a DV measurement <3 days before delivery (n=180; AUC 0.75)

Figure 2

2A: Univariable Odds ratios with 95% confidence limits for normal outcome at corrected age of 2 years specified for the last CTG within 24 hours before delivery, the last fetal arterial PI within 7 days or the last DVPI within 3 days before delivery for women randomised to cCTG monitoring (A) or to DVPI + cCTG monitoring (B).