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Fetal monitoring indications for delivery and 2-year outcome in 310 infants with fetal growth restriction delivered before 32 weeks' gestation in the TRUFFLE study

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ABSTRACT

Objective *In the TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe) study on the outcome of early fetal growth restriction, women were allocated to one of three groups of indication for delivery according to the following monitoring strategies: (1) reduced fetal heart rate (FHR) short-term variation (STV) on cardiotocography (CTG); (2) early changes in fetal ductus venosus (DV) waveform (DV-p95); and (3) late changes in fetal DV waveform (DV-no-A). However, many infants per monitoring protocol were delivered because of safety-net criteria, for maternal or other fetal indications, or after 32 weeks of gestation when the protocol was no longer applied. The objective of the present* posthoc *subanalysis was to investigate the indications for delivery in relation to 2-year outcome in infants delivered before 32 weeks to further refine management proposals.*

Methods *We included all 310 cases of the TRUFFLE study with known outcome at 2 years' corrected age and seven fetal deaths, excluding seven cases with inevitable perinatal death. Data were analyzed according to the allocated fetal monitoring strategy in combination with the indication for delivery.*

Results *Overall, only 32% of liveborn infants were delivered according to the specified monitoring parameter for indication for delivery; 38% were delivered because of safety-net criteria, 15% for other fetal reasons and 15% for maternal reasons. In the CTG-STV group, 51% of infants were delivered because of reduced STV. In the DV-p95 group, 34% of infants were delivered because of abnormal DV and, in the DV-no-A group, only 10% of infants were delivered accordingly. The majority of infants in the DV groups were delivered for the safety-net criterion of spontaneous decelerations in FHR. Two-year intact survival was highest in the DV groups combined compared with the CTG-STV group ($P = 0.05$ for live births only, $P = 0.21$ including fetal death), with no difference between DV groups. A poorer outcome in the CTG-STV group was restricted to infants delivered because of FHR decelerations in the safety-net subgroup. Infants delivered because of maternal reasons had the highest birth weight and a non-significantly higher intact survival.*

Conclusions *In this subanalysis of infants delivered before 32 weeks, the majority were delivered for reasons other than the allocated monitoring strategy indication. Since, in the DV group, CTG-STV criteria were used as a safety net but in the CTG-STV group, no DV safety-net criteria were applied, we speculate that the slightly poorer outcome in the CTG-STV group might be explained by the absence of DV data. The optimal timing of delivery of fetuses with early intrauterine*

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growth restriction may therefore be best determined by monitoring them longitudinally, with both DV and CTG monitoring.

INTRODUCTION

Two-year follow-up data of the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study on the outcome of early intrauterine growth-restricted (IUGR) fetuses have shown that the overall outcome of surviving infants was more favorable than has been published previously[1]. The timing of delivery was randomized and based on reduced fetal heart rate (FHR) short-term variation (STV) on computerized cardiotocography (CTG) and early or late pulsatility changes in the ductus venosus (DV), with safety-net criteria applied in all three intervention strategies.

Impaired outcome (mortality and severe morbidity) did not differ significantly between the three arms of the trial, but data on 2-year neurological outcome showed that a conservative approach to the timing of delivery, by delaying delivery until late DV changes occur, was associated with a better outcome in survivors as compared with CTG-STV monitoring. Data were analyzed according to intention to treat. However, a considerable proportion of infants per protocol was delivered because of the so-called safety-net criteria (i.e. severely reduced STV, occurrence of spontaneous unprovoked FHR decelerations or, after 30 weeks, reversed end-diastolic velocity (REDV) in the umbilical artery, without abnormality in DV flow velocity waveform pattern). As CTG is the standard of care for monitoring IUGR fetuses at risk of impaired intrauterine conditions, CTG safety-net criteria were established for patients randomized to the DV groups only, whereas DV was not evaluated in patients randomized to CTG-STV monitoring. Moreover, in all three arms of the trial, many infants were delivered because of maternal indication or other fetal indication or after 32 weeks of gestation, when delivery occurred according to local protocols and not the intention-to-treat arms of the study.

Therefore, there is a need for *posthoc* subanalysis of the TRUFFLE data, especially for infants delivered before 32 weeks, to investigate outcome at 2 years in relation to the indication for delivery in order to further refine management proposals.

METHODS

In the multicenter, unblinded, randomized TRUFFLE study, women with a singleton pregnancy at 26–32 weeks of gestation with very preterm fetal growth restriction (i.e. abdominal circumference < 10th percentile and umbilical artery Doppler pulsatility index (PI) > 95th percentile) were included. Eligible women were allocated at an even 1: 1: 1 ratio from randomly sized blocks, stratified for gestational age (< 29 or ≥ 29 weeks of gestation) and for participating center, to one of three timing-of-delivery plans, which differed according to the prenatal monitoring strategy: (1) reduced FHR STV (< 3.5 ms before 29 weeks and < 4.0 ms thereafter) on CTG; (2) early DV Doppler changes (PI > 95th percentile – 'DV-p95' group); and (3) late DV Doppler changes (A-wave at or below baseline – 'DV-no-A' group). In all groups, the timing of delivery could also be decided by joint safety-net criteria of recurrent decelerations in FHR on CTG or, after 30 weeks, REDV in the umbilical artery and, for the DV groups, when STV was very low (STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter). The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley-III developmental score > 85 at 2 years of age. The study was registered with ISRCTN (number 56204499). Between January 2005 and October 2010, 503 women were included in the TRUFFLE study. The results on direct neonatal and 2-year outcome have been published previously[1,2].

In this *posthoc* subanalysis of the TRUFFLE study, we included all 310 liveborn infants with known outcome at 2 years' corrected age that were delivered before 32 weeks of gestation and seven cases that resulted in fetal death. Cases in which intervention before birth was not performed because of suspected poor prognosis of the infant ($n = 5$) and two cases born with a lethal congenital malformation were not included[2]. Twenty-five cases that resulted in neonatal death were included in the analyses. The majority of the analyses were on the 310 liveborn infants with known 2-year outcome. However, for comparison with data from the original TRUFFLE study, where appropriate, data are also shown only for those with 2-year survival. Data were analyzed according to the allocated monitoring strategy and for the intervention indication. Data were analyzed by ANOVA or chi-square test, as appropriate, using IBM SPSS version 22 (IBM Corp., New York, NY, USA).

RESULTS

In total, 310 liveborn infants that were delivered before 32 weeks of gestation and seven cases that resulted in fetal death were included. The number of live births according to allocated fetal monitoring group and indication for delivery is shown in Table 1. Overall, two-thirds of liveborn infants were delivered according to the specified criteria of the monitoring strategy and just over half of these were delivered because of safety-net criteria. The remaining one-third of the study population was delivered because of non-protocol fetal indication or for maternal indication. In the CTG-STV group, 51% of infants were delivered because of reduced STV. In 19 of these cases, FHR decelerations were also present. In the DV groups, delivery because of DV-PI > 95th centile was the indication for delivery in 34% of cases allocated to the DV-p95 group and only 10% of cases were delivered for absent or reversed A-wave in the DV-no-A group. In the DV-no-A group, more than 50% of cases were delivered because of safety-net criteria and almost 40%

because of other fetal or maternal indications. The seven fetal deaths occurred in the two DV groups (three in DV-p95 and four in DV-no-A).

Table S1 shows gestational age and weight at delivery according to allocated fetal monitoring group and indication for delivery. There were no significant differences between the subgroups, although birth weight was higher in infants delivered for maternal indication (ANOVA, corrected for multiple testing, $P = 0.02$), but gestational age was similar compared with the other indication groups.

Infant outcome at 2 years is shown in Table 2. Overall, 83% of liveborn infants were alive without neurological impairment at 2 years of age. This value was 86% in both DV groups and 77% in the CTG-STV group ($P = 0.049$ for CTG-STV compared with DV groups combined). There were seven fetal deaths, all occurring in the DV groups. When these deaths were included in the analysis, 2-year survival without neurological impairment in the DV arms decreased to 83% ($P = 0.21$ when compared with the CTG-STV group). Overall, the most favorable outcome (91%) occurred in infants delivered because of maternal reasons and this held true for all three fetal monitoring groups ($P = 0.09$ for maternal *vs* all other indications, excluding fetal death). The lowest incidence of 2-year intact survival without neurological impairment (58%) occurred in infants in the CTG-STV group that were delivered because of safety-net criteria. The outcome in this group was significantly poorer than that in the DV groups in which delivery was on the basis of safety-net criteria ($P = 0.001$). In fact, the overall poorer outcome in the CTG-STV group was only due to a poorer outcome in the safety-net subgroup. There was no difference in 2-year intact survival between infants that were delivered based on the CTG-STV criteria (81%) as compared with those delivered based on DV criteria (DV groups combined: 80%).

The results were similar when the 25 neonatal deaths were excluded. In the CTG-STV group, 81/95 (85%) survivors had a normal neurological outcome as compared with 176/190 (93%) in the combined DV groups (Table 2; $P = 0.049$). The lowest incidence of 2-year intact survival occurred among infants in the CTG-STV group that were delivered because of safety-net criteria (15/22 (68%) *vs* 80/85 (94%) in the combined DV groups). There was no difference in 2-year intact survival in cases delivered based on the specified STV abnormality in the CTG-STV group (44/50 (88%)) or DV abnormality in the DV groups combined (36/41 (88%)).

Table 3 shows infant outcome according to subdivisions of the safety-net criteria in the allocated fetal monitoring groups; low STV was a safety-net criterion only in the DV groups. Sixty-seven percent of infants that were delivered because of safety-net criteria were for FHR decelerations only, 12% for low STV only, another 15% for a combination of both and only 6% because of REDV in the umbilical artery at > 30 weeks. In the combined DV

Table 1 Number of liveborn infants delivered before 32 weeks of gestation in each fetal monitoring strategy for delivery: fetal heart rate (FHR) short-term variation on cardiotocography (CTG-STV), ductus venosus (DV) pulsatility index > 95th percentile (DV-p95) or absence of A-wave in the DV (DV-no-A), according to indication for delivery

Indication for delivery	*CTG-STV* (n = *105*)	*DV-p95* (n = *99*)	*DV-no-A* (n = *106*)	*All* (n = *310*)
Specified CTG or DV abnormality	54 (51)	34 (34)	11 (10)	99 (32)
Safety-net criteria	26 (25)	37 (37)	55 (52)	118 (38)
DV groups safety-net criteria of reduced STV*	—	11	21	
Joint safety-net criteria				
Spontaneous FHR decelerations	24	22	33	
UA-REDV > 30 weeks	2	4	1	
Other fetal indication	9 (9)	15 (15)	22 (21)	46 (15)
Maternal indication	16 (15)	13 (13)	18 (17)	47 (15)

Data are given as *n* or *n* (%). *STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter. REDV, reversed end-diastolic velocity; UA, umbilical artery.

Table 2 Number of infants with normal neurological outcome at 2 years of age in each fetal monitoring strategy for delivery: fetal heart rate short-term variation on cardiotocography (CTG-STV), ductus venosus (DV) pulsatility index > 95th percentile (DV-p95) or absence of A-wave in the DV (DV-no-A), according to indication for delivery

Indication for delivery	*CTG-STV*	*DV-p95*	*DV-no-A*	*All*
Specified CTG or DV abnormality	44/54 (81)	26/34 (76)	10/11 (91)	80/99 (81)
Safety-net criteria	15/26 (58)	34/37 (92)	46/55 (84)	95/118 (81)
Other fetal indication*	7/9 (78)	14/15 (93)	18/22 (82)	39/46 (85)
Maternal indication	15/16 (94)	11/13 (85)	17/18 (94)	43/47 (91)
Total liveborn infants with known outcome	81/105 (77)	85/99 (86)	91/106 (86)	257/310 (83)
Total infants including cases of fetal death†	81/105 (77)	85/102 (83)	91/110 (83)	257/317 (81)
Total survivors	81/95 (85)	85/93 (91)	91/97 (94)	257/285 (90)

Data are given as *n*/*N* (%). Only infants delivered before 32 weeks were included and fetal death due to inevitable poor prognosis and neonatal death due to lethal anomaly were excluded. *Including eight cases of partial placental abruption (two in CTG-STV, two in DV-p95 and four in DV-no-A); all these infants did well. †Seven antepartum deaths included.

Table 3 Indication for delivery and neurological outcome at 2 years of age in 118 infants delivered for safety-net criteria, according to fetal monitoring strategy for delivery: fetal heart rate (FHR) short-term variation on cardiotocography (CTG-STV), ductus venosus (DV) pulsatility index > 95th percentile (DV-p95) or absence of A-wave in the DV (DV-no-A)

Safety-net indication for delivery	*CTG-STV*	*DV-p95*	*DV-no-A*	*Total*
Low STV only*	—	2	12	14
Normal outcome	—	1	9	10 (71)
Abnormal outcome	—	1	3	4 (29)
FHR decelerations only	24	22	33	79
Normal outcome	13	20	27	60 (76)
Abnormal outcome	11	2	6	19 (24)
Low STV with FHR decelerations*	—	9	9	18
Normal outcome	—	9	9	18 (100)
Abnormal outcome	—	0	0	0 (0)
UA-REDV > 30 weeks only	2	4	1	7
Normal outcome	2	4	1	7 (100)
Abnormal outcome	0	0	0	0 (0)
Total	26	37	55	118
Normal outcome	15 (58)	34 (92)	46 (84)	95 (81)
Abnormal outcome	11 (42)	3 (8)	9 (16)	23 (19)

Data are given as *n* or *n* (%). Percentages for outcome were calculated from number of infants delivered for that indication. *Criterion applied only in DV groups. REDV, reversed end-diastolic velocity; UA, umbilical artery.

groups, very low STV alone was an indication for delivery in only 14/92 (15%) cases and very low STV combined with FHR decelerations in another 18/92 cases (20%); FHR decelerations, with or without low STV, were by far the most important determinant for delivery in the DV groups (79%). When delivery was indicated by FHR decelerations, adverse 2-year infant outcome was significantly more frequent in the CTG-STV group than in the DV groups ($P = 0.003$). For the other safety-net criteria, outcome was not significantly different from the overall 2-year infant outcome (Table 3), although all seven cases that were delivered because of REDV in the umbilical artery after 30 weeks did well.

In 19 of the 54 infants in the CTG-STV group that were delivered because of STV criteria (Table 1), FHR decelerations were also present. In a further 24 infants in the CTG-STV group that were delivered because of safety-net criteria, only FHR decelerations were present (Table 3). Therefore, in the CTG-STV group, slightly more fetuses were delivered because of reduced STV than because of FHR decelerations.

When excluding infants that were delivered because of maternal reasons, REDV in the umbilical artery or non-protocol indications (i.e. infants in which there was no recorded CTG or DV abnormality), 210 infants were delivered because of CTG abnormalities (reduced STV and FHR decelerations) or DV abnormalities. Of these, 165 were delivered because of CTG abnormalities and 45 because of DV abnormalities. Of the infants delivered because of an abnormal DV waveform, 80% (36/45) were normal at follow-up, and of those delivered because of CTG abnormalities, also 80% (132/165) were normal.

The only fetuses monitored for both CTG and DV were those in the two DV groups. Even in these groups, twice as many infants ($n = 87$) were delivered because of CTG-STV safety-net criteria (reduced STV and/or FHR decelerations) than because of DV abnormalities ($n = 45$). Slightly more infants that were delivered because of CTG-STV abnormalities were normal at follow-up (75/87, 86%; Table 3), as compared with 80% of those that were delivered because of DV abnormalities (36/45; Table 2). These data indicate that the overall outcome of infants delivered because of CTG-STV changes was at least similar to that in those delivered because of DV abnormalities. However, in the subgroup with CTG-STV monitoring only (without DV monitoring), outcome was poorer.

DISCUSSION

We carried out a *posthoc* subanalysis of outcomes in infants from the TRUFFLE study that were delivered before 32 weeks of gestation. By doing so, we excluded infants born ≥ 32 weeks that were probably at lower risk for impaired outcome and were delivered according to local management criteria and not according to the initial monitoring group protocol[1]. This analysis was carried out to obtain additional insight into 2-year outcome in relation to the actual indication for delivery. A limitation of the smaller size of this study was the fact that it was not powered for the questions raised. Conclusions, therefore, have to be drawn with caution.

We found that the 2-year outcome was better in the DV groups as compared with the CTG-STV group and this is in line with the total study population[1]. In the original TRUFFLE study, the primary outcome, i.e. survival without cerebral palsy or neurosensory impairment, was not significantly different between the monitoring groups, but neurological outcome in survivors was significantly better in the DV-no-A group as compared with the CTG-STV group, with a trend towards better outcome in the DV-p95 group.

When analyzed according to the actual indication for delivery (specified CTG or DV abnormality, safety-net criteria, other fetal indication, maternal indication), we found no differences between groups in 2-year outcome, although those delivered for maternal indication had

a non-significantly better outcome. The latter may be related to a significantly higher birth weight at the same gestational age at delivery.

In the DV-no-A group, more fetuses were delivered because of other fetal indications or maternal indications than in the other monitoring groups. The reason for this is unclear as other fetal indications were not specified thoroughly by the participating centers, apart from partial placental abruption. Waiting for late DV changes to occur may have increased the chance for CTG abnormalities and other fetal indications to develop.

The better outcome in the DV groups seems to be initially somewhat difficult to explain given the fact that only 35% and 10% of infants in the DV-p95 and DV-no-A groups, respectively, were actually delivered because of the allocated DV criteria, whereas 53% and 73%, respectively, were delivered because of safety-net criteria or other fetal indication. The safety-net criteria largely relate to the occurrence of FHR decelerations or a highly reduced STV, i.e. CTG-STV criteria. In total, more infants in the DV groups were delivered on the basis of CTG-STV safety-net criteria than on the basis of an abnormal DV pattern. This implies that, in the majority of cases, CTG abnormalities (reduced STV and/or FHR decelerations) precede DV changes. From longitudinal studies, it is known that CTG-STV and DV changes occur more or less at the same time in early IUGR fetuses[3,4]. In other words, in half the cases, changes in CTG-STV precede DV changes, but also the opposite holds true. The differences in outcome may, therefore, be related to the study design in which, in the DV groups, CTG-STV safety-net criteria were included, whereas in the CTG-STV group, no DV measurements were obtained. From earlier studies, we know that survival in cases with early IUGR is higher if either CTG or DV anomalies had been present, as compared with cases in which both had been present[3–5]. The poorer outcome in the CTG-STV group may therefore be due to the fact that, in a substantial number of cases in this monitoring group, both CTG and DV abnormalities had been present.

The outcome of fetuses in the CTG-STV group that were delivered on the basis of CTG-STV was identical to that of those in the combined DV groups that were delivered on the basis of DV abnormalities. It therefore seems essential to include CTG-STV monitoring when determining the timing of delivery. The significantly poorer outcome in infants in the CTG-STV group delivered because of safety-net criteria, specifically FHR decelerations, as compared with those in the DV groups delivered because of this criterion, may indicate that an absence of knowledge of DV flow in this subgroup delayed delivery and was causal to the poorer outcome. In this context, it has to be realized that the TRUFFLE study was a comparison of CTG monitoring only with combined DV and CTG monitoring. Our data stress the importance of monitoring early IUGR fetuses for both CTG and DV.

In clinical practice this implies that, when monitoring early IUGR fetuses with both techniques, the majority will be delivered because of CTG abnormalities before DV changes occur. DV may therefore be considered the safety net for CTG monitoring. Such a safety net seems useful, as data from the original TRUFFLE study and data from the present subanalysis have shown that monitoring with CTG alone (without a DV safety net), resulted in a poorer outcome than when combining both assessment techniques.

STV threshold values for normality may not be clear at this moment. We have defined normal STV as > 3.5 ms at before 29 weeks and > 4.0 ms thereafter[1]. These threshold values were set taking into account the increase in STV with increasing gestational age[6,7], the absence of fetal acidemia in cases with STV > 4.0 ms[8] and the presence of acidemia or hypoxemia in the majority of cases with STV between 3.5 and 4.0 ms[9]. The 2.5th centile of STV in normal populations has been found to be around 4.0–5.0 ms in the early third trimester in recordings of variable length[10] or around 4.4–5.4 ms in CTG recordings of 1-h duration[6,7]. Therefore, we used a lower STV threshold value in the present study. However, it is known that FHR decelerations occur on average at the same time as heart rate STV falls below normal range[11]. As, in the present study, slightly more fetuses in the CTG-STV group were delivered on the basis of reduced STV than because of FHR decelerations, it seems unlikely that the STV threshold values in the CTG-STV group were set too low.

The fact that most fetuses in the DV groups that were delivered for safety-net indications were delivered on the basis of FHR decelerations and not on the applied very low STV cut-off values suggests that the latter values might have been set too low. Therefore, it may be that the same criteria used in the CTG-STV group should be used, and more so, as the outcome in the CTG-STV group of fetuses delivered according to the specified monitoring parameter was identical to that of cases delivered in the DV groups because of an abnormal DV. However, the optimal STV cut-off values might be subject to further analysis, as we had no information on DV in the CTG-STV group and it may therefore be that cases with a reduced STV according to the CTG-STV group might have been identified by DV abnormalities. It should also be noted that the TRUFFLE STV threshold values were based on 1-h CTG recordings. Shorter recordings may give less accurate results[1,2,6]. Moreover, possible effects of medication, such as betamethasone and magnesium sulfate, should be taken into account, as both drugs may reduce STV without affecting the occurrence of FHR decelerations[12–16].

Taking into account the restriction that the present *posthoc* subanalysis was not powered for the questions raised in this paper, the data suggest some refinement in the management protocol of early IUGR fetuses delivered before 32 weeks of gestation: (1) the optimal timing of delivery may best be achieved by combined longitudinal monitoring using both CTG and DV. Given that low STV (< 2.6 ms before 29 weeks and < 3.0 ms between 30 and 32 weeks) does not appear to be associated with an increase in adverse outcome, it may be safe to wait for such abnormalities to occur, as long as DV remains normal. (2) The favorable outcome in the small group of fetuses delivered because of REDV in the umbilical

artery after 30 weeks of gestation supports the use of this criterion after this gestational age.

The data from this subanalysis based on the actual indications for delivery in infants delivered before 32 weeks of gestation support those of the whole TRUFFLE study, whereby it has to be realized that almost two-thirds of cases will be delivered per protocol because of indications other than CTG abnormalities in the CTG-STV group or abnormal DV in the DV groups. This held true especially for fetuses allocated to the DV groups. Overall, the outcome of IUGR fetuses delivered before 32 weeks seems to be better than historical data have shown and this is probably due to the close multimodality (Doppler and CTG) monitoring.

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SUPPORTING INFORMATION ON THE INTERNET

Table S1 may be found in the online version of this article.