A longitudinal study of computerised cardiotocography in early fetal growth restriction.

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Keywords

Fetal growth restriction; preterm; fetal monitoring; ductus venosus; cardiotocography; short term variation

Abstract

Objectives

To explore if in early fetal growth restriction (FGR) the longitudinal pattern of short-term fetal heart rate (FHR) variation (STV) can be used for identifying imminent fetal distress and if abnormalities of FHR registration associate with two-year infant outcome.

Methods

The original TRUFFLE study assessed if in early FGR the use of ductus venosus Doppler pulsatility index (DVPI), in combination with a safety-net of very low STV and / or recurrent decelerations, could improve two-year infant survival without neurological impairment in comparison to computerised cardiotocography (cCTG) with STV calculation only. For this secondary analysis we selected women, who delivered before 32 weeks, and who had consecutive STV data for more than 3 days before delivery, and known infant two-year outcome data. Women who received corticosteroids within 3 days of delivery were excluded. Individual regression line algorithms of all STV values except the last one were calculated. Life table analysis and Cox regression analysis were used to calculate the day by day risk for a low STV or very low STV and / or FHR decelerations (DVPI group safety-net) and to assess which parameters were associated to this risk. Furthermore, it was assessed if STV pattern, lowest STV value or recurrent FHR decelerations were associated with two-year infant outcome.

Results

One hundred and fourty-nine women matched the inclusion criteria. Using the individual STV regression lines prediction of a last STV below the cCTG-group cut-off had a sensitivity of 0.42 and specificity of 0.91. For each day after inclusion the median risk for a low STV(cCTG criteria) was 4% (Interquartile range (IQR) 2% to 7%) and for a very low STV and / or recurrent decelerations (DVPI safety-net criteria) 5% (IQR 4 to 7%). Measures of

STV pattern, fetal Doppler (arterial or venous), birthweight MoM or gestational age did not improve daily risk prediction usefully. There was no association of STV regression coefficients, a last low STV or /and recurrent decelerations with short or long term infant outcomes.

Conclusion

The TRUFFLE study showed that a strategy of DVPI monitoring with a safety-net delivery indication of very low STV and / or recurrent decelerations could increase infant survival without neurological impairment at two years. This post-hoc analysis demonstrates that in early FGR the day by day risk of an abnormal cCTG as defined by the DVPI protocol safety-net criteria is 5%, and that prediction of this is not possible. This supports the rationale for cCTG monitoring more often than daily in these high-risk fetuses. Low STV and/or recurrent decelerations were not associated with adverse infant outcome and it appears safe to delay intervention until such abnormalities occur, as long as DVPI is in the normal range.

Introduction

Fetal growth restriction (FGR) in the early preterm period is associated with significant risks of perinatal mortality and neonatal morbidity. The most important prognostic factors are gestational age and birthweight at delivery. The main challenge in management of FGR is the timing of delivery, where the risk of acidosis or fetal death has to be weighed against the benefits of increasing gestational age. Typically, fetuses are not delivered until it is certain that they no longer benefit from a prolonged intra-uterine stay.. Before the occurrence of terminal acidosis and absence of fetal movements a gradual decrease of fetal heart rate (FHR) variation, the occurrence of FHR decelerations and a gradual decrease of fetal movements have been described.[1,2] If this were to be a process that may be picked up timely, the additive risks of acidosis could potentially be avoided, without compromising the benefits of increasing gestational age.

The recently published TRUFFLE was designed to investigate in pregnancies complicated by early FGR if fetal monitoring using ductus venosus (DV) pulsatility index (PI) in combination with computerised cardiotocography (cCTG) with FHR short time variation (STV) calculation could improve long-term infant outcome in comparison to monitoring by cCTG only.[3] Women with FGR at a gestational age of 26 to 31 weeks were randomised between three different protocols for intervention (DVPI >p95,DV with absent a-wave or only cCTG). The study concluded that in live-born infants monitoring by DVPI in combination with a safety-net, defined by a very low STV and/or recurrent FHR decelerations, could reduce the risk of infant neurological impairment at two years in comparison to monitoring with cCTG only. This secondary analysis of data from the TRUFFLE study is intended to explore, in a group of fetuses with early FGR, the longitudinal pattern of STV measurements, the rate at which STV decreased below the intervention cut-off and if an association existed between longitudinal STV patterns or a cCTG below intervention criteria with perinatal parameters and 2-year infant outcome.

Methods

The TRUFFLE study design has been described earlier.[3] In short, women with singleton fetuses at 26-32 weeks of gestation, with fetal abdominal circumference <10th percentile and umbilical artery Doppler PI >95th percentile, were included in a twenty centre European study (ISRCTN 56204499). By randomisation women were allocated for delivery according to one of three indications: reduced STV (<3.5 ms at a gestational age below 29 weeks and <4.0 ms thereafter; 'cCTG'), early DVPI (>95th percentile 'DV p95') or late DV changes ('a' wave at or below baseline; 'DV no A'). Abnormal DVPI measurements were required to be repeated within 24 hours, if cCTG result allowed this, to demonstrate consistency. In the cCTG group delivery could also be decided if cCTG showed recurrent decelerations (cCTG group safety net criteria). In the DV groups a very low STV (<2.6 ms at a gestational age below 29 weeks and <3.0 ms thereafter) or recurrent decelerations could indicate delivery (DV group safety net criteria). The Oxford Sonicaid 8002 system or an equivalent Dawes-Redman software based algorithm were used for STV calculation.[4] The recordings were at least 45 min in duration. Most participating centres (17 of 20) performed a cCTG at least daily, the others on alternate days, but more often on indication.

For reference of birthweight multiples of the median (MoM) were calculated. The 50th percentile weight from a fetal growth chart, adjusted for gestational age, maternal ethnic descent, weight, length and infant sex, was used as normalised median fetal weight.[5]

The primary TRUFFLE study outcome was infant survival with a normal neurological development at the age of two years (adjusted for prematurity), defined by a Bayley third edition infants and toddlers developmental score (PsychCorp, San Antonio, USA) higher than 85 and absence of severe vision or hearing deficiency or cerebral palsy.[3] A secondary outcome was severe neonatal morbidity, defined as bronchopulmonary dysplasia (BPD - additional oxygen at 36 weeks adjusted age), germinal matrix haemorrhage (GMH) grade 3 or 4, periventricular leucomalacia (PVL) more than grade 1, necrotising enterocolitis (NEC – confirmed by X-ray or laparotomy) or microbiologically proven sepsis.

For this secondary analysis all women were selected who had been included in the study for more than 3 days before delivery, had at least 4 cCTG STV registrations in the last week before delivery and at least one cCTG-STV registration during the last 24 hours before delivery, and were delivered before 32 completed weeks. This last restriction was necessary

because after 32 weeks the use of protocol-driven monitoring was no longer prescribed and therefore STV measurement results had no longer been entered consistently in the study database. Women who received corticosteroids within 3 days before delivery were excluded as it has been observed that STV increases shortly after corticosteroids and decreases on day 2-3 after corticosteroids administration.[6,7] Because a more prolonged effect of corticosteroids could not be excluded we analysed monitoring data separately for women who delivered within one week after corticosteroids and women who delivered later.

For overview of STV data a boxplot was made using STV values recorded during the last 3 weeks before delivery, categorised per time windows of three, two or one day intervals before delivery. If women had more than one STV measurement in a time window only the last one was selected.

For longitudinal analysis we calculated for each woman separately the STV data by day and time of registration using linear and exponential regression analysis. Goodness of fit was calculated by the average squared difference of observed and expected STV. Because linear and exponential regression did not differ in this respect, also after differentiating for a last STV above or below cCTG-group study cut-off, for perinatal mortality or for primary infant outcome (data not shown), we decided to use only linear regression for individual data analysis.

Linear regression analysis was performed for each woman using all STV data except the last one. Based on the differences of observed and expected values of STV the standard deviation (SD) from the regression line could be calculated for each woman. This allowed to assess if the last STV measurement (which was exempted from this regression line calculation) was in line with earlier measurements or diverted more than 2 SD from the expected STV value. Figure 1a and 1b demonstrate this method for two women, one with a last value below 2 SD from the previous values, and one with a last (low) value in line with expectation based on the regression line of earlier values.

For each woman an expected last STV ($STV^{expected}$) could be calculated using the individual regression algorithm based on all STV values except the last one. Sensitivity and specificity for the prediction of a STV below cCTG-group cut-off by $STV^{expected}$ were calculated.

Life table analysis was used to calculate the day by day risk of a low STV below cCTG group cut-off and of a very low STV and / or recurrent FHR decelerations (DV group safety-net criteria). Using Cox regression analysis it was assessed if the daily risk could be predicted better by using the individual regression line slope angle, randomisation group allocation, the ratio of umbilical artery PI and middle cerebral artery PI (UC ratio), absent or reversed diastolic velocity in the umbilical artery (ARED flow), gestational age and birthweight MoM. Birthweight was used as it should be similar to fetal weight during the last week of pregnancy in FGR and is more precise than fetal weight calculated by ultrasound biometry. Odds ratios (OR) were calculated with 95% confidence interval (CI). Estimation of the area under the curve (AUC) of a receiver operating characteristic (ROC) curve was used to assess the efficacy of a model.

Based on the regression coefficient of a linear model of all STV registrations of the study population during the last 3 weeks before delivery, a regression coefficient of less than -0.1 (which means a decrease of 1 ms. / 10 days or a negative angle of more than 6^{o}) was defined as decreasing pattern. If the tilt of the regression line was less the pattern was defined as stable.

Perinatal and outcome data were compared between women with or without a decreasing slope of the regression line and between women with a last STV value that was within or below 2 SD from the expected value. Combining these two classifications we could define four groups for comparison.

Odds ratios of infant survival at 2-year without neurological impairment were calculated for a decreasing STV regression line, for a last cCTG below the cCTG-group STV criteria, a cCTG below the DV-group safety-net criteria, or a cCTG with recurrent FHR decelerations, with adjustment for birth weight MoM and gestational age.

Homogeneity of data was tested by Levene statistics to decide between parametric or non-parametric testing. Groups were compared by ANOVA, Kruskal Wallis, Man-Whitney, Pearson chi square or Fisher exact as appropriate. Multivariable analysis was done by back-step procedure with p to remove at 0.1. Statistics were performed with IBM SPSS version 23 (New York, U.S.A.).

The TRUFFLE study was ratified by the ethics committees of all participating units. The study received funding from ZonMw, The Netherlands and Dr Hans Ludwig Geisenhofer Foundation, Germany.

Results

One hundred and forty-nine women (42%) of 356 women who delivered before 32 weeks qualified for the inclusion criteria of this secondary analysis (table 1). Most exclusions (41%) were due to a delivery within 3 days after inclusion. Eight women, who complied with the cCTG frequency inclusion criteria, had been excluded because they had corticosteroids within 3 days before delivery. In five of these a second course of corticosteroids had been given shortly before delivery (including one with unexpected fetal death) and the other three had been given corticosteroid 1-5 days after randomisation. Table 2 shows perinatal data of the study population, specified for the interval from corticosteroids and includes data regarding the 8 women with a short corticosteroids to delivery interval, who were excluded from longitudinal analysis. Median gestational age at delivery was 30 weeks, mean birthweight 880 g and birthweight MoM 0.57.

Fetal death occurred in two women (1%) in the study selection (table 1), of which one was excluded from longitudinal analysis because of a short interval to delivery after corticosteroids. In both the last cCTG approximately 12 hours before fetal death was normal (average STV 5 ms), but one had a DVPI >p95 (randomised to the DV absent flow group). The remaining fetal death in the TRUFFLE study (n=10) were not included because the number of cCTG registrations was insufficient for longitudinal analysis. In one a borderline STV (2.7 ms) was recorded approximately 12 hours before fetal death. Two had a normal STV (average 5.7 ms) approximately 24 hours before fetal death, one of these had a DVPI >p95. Two women refused intervention when indicated by low STV and recurrent decelerations and fetal death was confirmed 24 hours later. In five fetal death the interval between the last cCTG and fetal death was more than 24 hours. Three of these had refused further monitoring and intervention. Neonatal mortality occurred in 6% and severe neonatal morbidity in 29 % of the infants. Eighty-two percent of the infants were classified as normal at the corrected age of two years.

Figure 2 shows a boxplot of STV categorised per time window for the last 3 weeks before delivery. A linear model of all STV registrations showed a slow decrease (algorithm 5.36 – 0.11 x [days before delivery]; 95% CI +/- 4 ms.). Other models (quadratic, cubic, logistic) gave identical or higher residuals than the linear model. As can be seen from figure 2, the

most prominent decrease of STV took place in the last day before delivery. Last day STV measurements were significantly lower than measurements in earlier days. Repeating the linear regression using all STV registrations except those from the last day showed a stable, nearly horizontal pattern (algorithm 5.71- 0.04 x [days before delivery], or a decrease of 1 ms. / 25 days).

A linear decrease of the individual STV regression line with a regression coefficient of less than -0.1 (or an angle of < -6^{o}) occurred in 61 women (41%), a regression coefficient below -0.3 (or an angle of < -17^{o}) was observed in only 24 women (16%). Using all STV data of the 88 women with a regression coefficient larger than -0.1 gave a median regression coefficient of -0.001, which can be interpreted as horizontal.

Women who had received corticosteroids 4 to 7 days before delivery (n=23; 15%) had approximately two times more often a regression coefficient of less than -0.1 and twice as often a last STV below cCTG group cut-off than women who received no corticosteroids (n=5) or had corticosteroids more than 7 days before delivery (n=121) (Table 2; $p < 0.05$). These two groups had a statistically significant difference in interval from inclusion to delivery, but did not differ in Doppler parameters, gestational age at delivery, birthweight or birthweight MoM.

The study group could be subdivided in four groups, based on the value of the individual STV regression line coefficient more or less than – 0.1 (or an angle of -6^{o}) and the last STV being more or less than 2 SD of the regression line calculated with all STV values except the last one. There were no differences between these groups in gestational age at randomisation, gestational age at delivery, birthweight, severe neonatal morbidity or infant two-year outcome (Table 3). In the first group (stable pattern with a last STV within +/- 2 SD) estimated fetal weight and birth weight MoM were lower. Only 6 women (15%) in this group had a low last STV and in these women STV had been just above the cCTG-group cut-off from start. In the other classification groups a last low STV occurred approximately three times more frequently. In those with a decreasing pattern UC ratio was higher.
Within the classification groups data were similar for women who had corticosteroids 4-7 days before delivery in comparison with the remaining women.

In 61 women (41%) the last STV value was below 2 SD of the individual regression line. In half of these (30; 49%) the last STV value was below the cCTG-group cut-off. In 88 women (59%) the last STV was between 2 SD of the regression line, and in 27 of these (31%) the STV value was below the cCTG-group cut-off.

The sensitivity of a low $STV^{expected}$ below cCTG-group cut-off for the prediction of a last STV lower than the cCTG-group cut-off was 0.42 and specificity 0.91 or an OR of 2.5 (95% CI 1.7 to 3.8). Combining a low $STV^{expected}$ with randomisation allocation, time of corticosteroid administration 4 to 7 days versus > 7 days before delivery, gestational age, birth weight and fetal Doppler measurements (arterial or venous) in a multivariable analysis did not improve prediction of a low STV below cCTG group cut-off.

Life table analysis showed that for each day after inclusion the median risk of a low STV below the cCTG group cut-off was 4% (Interquartile range (IQR) 2% to 7%). The daily risk for a very low STV and / or recurrent decelerations (= DV group safety-net) was 5% (IQR 4% to 7%). Stratification of the analysis for allocation to DV group or cCTG group monitoring did not show significant differences between the allocation groups. Cox regression analysis demonstrated that only addition of the STV regression coefficient and a last $STV^{expected}$ improved the risk estimate for a low STV below cCTG group cut-off slightly ((ROC analysis AUC 0.61; 95% CI 0.51 to 0.70), while fetal Doppler (arterial or venous), birthweight MoM or gestational age were rejected from the model. A similar model for improving the prediction of a very low STV and / or decelerations (DV group safety-net) failed (AUC 0.51; 95% CI 0.41 to 0.61).

Adjusted odds ratios for survival without neurological impairment at the age of two years of the STV regression line coefficient, recurrent decelerations, a last low (cCTG group cut-of) or a very low STV with or without recurrent decelerations (DV group safety-net) are shown in figure 3. Odds ratios were adjusted for gestational age and birthweight MoM for each variable separately. Randomisation group allocation (DV or cCTG only) had been entered in these analyses, but was ejected from the model. None of these variables reached statistical significance.

We observed no association of a last STV below cCTG group cut off or / and recurrent decelerations with umbilical pH or Apgar score at birth, nor with the incidence of severe

neonatal morbidity or neurological impairment at the age of two years. Because the last STV value had no association with outcome we did not perform statistics for earlier STV values.

Discussion

In this post-hoc analysis of TRUFFLE study data 38% of the women had a last STV below cCTG-group cut-off, and 11% a last STV below DV cut-off, while recurrent FHR decelerations in a last cCTG were observed in 44% of the women. Fifty percent of the women had either a STV below DV cut-off and / or recurrent FHR decelerations and surpassed the DV safety-net criteria. The DV safety-net criteria are therefore an important part of the DV strategy as defined in the TRUFFLE protocol.

After inclusion in the study the day by day risk of a very low STV and / or recurrent decelerations (DV groups safety-net) was 5% (IQR 4 to 7%). Within this group of women with early FGR this background risk of surpassing the DV safety-net criteria could not be individually adjusted using longitudinal STV parameters, fetal Doppler parameters (arterial or venous), nor by any other perinatal characteristics. The clinical implication of this finding is that, if DV safety-net criteria are considered a valid and urgent indication for delivery, then at least a daily frequency for cCTG registration is needed. Study data have insufficient power to address the question if a higher cCTG frequency than once daily might improve detection further.

Short or long-term infant outcome was not associated with longitudinal STV pattern, a last STV below cCTG-group cut-off or below DV-group cut-off or with recurrent decelerations. Apparently, in early preterm growth restriction, if properly monitored and action is taken as specified in the TRUFFLE protocol, it is not harmful to delay delivery until cCTG monitoring shows clear abnormalities. Because two-third of this cohort had also been monitored with DVPI, this statement is probably only valid for women with early FGR who are also monitored by DVPI and delivered when DVPI is consistently abnormal. This is supported by the observation of fetal death approximately 12 hours after a normal cCTG in women with a DVPI >p95.

While we conclude that it is safe to wait for a very low STV and / or recurrent FHR decelerations as long as cCTG is recorded with sufficient frequency, and DVPI is normal, we

do not advocate to delay delivery thereafter. Our study was not designed to define the mortality risk after an abnormal cCTG. However, the occurrence of fetal death shortly after a refusal of intervention by two women, when a low STV and decelerations were observed, supports the need for delivery of the baby on this indication. These two women were excluded from the present analysis because they had insufficient STV data for longitudinal analysis. The association of low FHR variation and / or decelerations with fetal hypoxia and acidosis has been observed.[4,8,9] Older studies support the generally accepted opinion that delivery is indicated for low FHR variation and/or decelerations to prevent fetal death.[10,11]

The observed differences in STV characteristics between women who had corticosteroids 4-7 days before delivery compared to women who had a longer interval or did not get corticosteroids were probably influenced by other causes than the timing of steroids, given the significant difference of the interval between randomisation and delivery and gestational age at delivery between these groups.

One hundred and forty-nine (46%) of the women from the TRUFFLE study, who delivered before 32 completed weeks and had complete 2-year follow-up (n = 322), had sufficient data for the current analysis. They are deemed representative, because no differences were observed in demographic and perinatal data between the current selection and the complete group of women delivered before 32 completed weeks (data not shown). The only major difference of the current selection with the remaining women was in antenatal mortality: nearly all antenatal death (11 of 12; 92%) were excluded because of insufficient data for longitudinal analysis. Most of these had insufficient data either because of refusal of intervention (5) or a shorter inclusion duration than 4 days (5). In one of these latter women a more frequent cCTG might have prevented fetal death.

Only few studies have assessed longitudinal STV for women with early FGR. One study demonstrated a gradually decreasing STV of approximately 2.5 SD during the last 3 weeks before delivery.[2] If this cohort had the same STV variation as our cohort this must have been a decrease of approximately 4 ms. This is far larger than the slight decrease that was observed in our cohort (0.84 ms/3 weeks). In our cohort an individual decrease of more than 3 ms/10 days was rare and mostly seen with a short interval to delivery. In our cohort, most STV decrease occurred only during the last 24 hours before delivery. Because the data in the study by Hecher et al were organised by gestational age and deliveries occurred at different

gestational ages, data shortly before delivery could gradually lower the average STV. Two longitudinal studies in early FGR followed long term FHR variation, which has some relation to short term variation. One study observed that variation was stable until a decrease in the last day before delivery.[12] The other reported a slight decrease of variation during the last 3 weeks of pregnancy, again with the most significant decrease in the last day.[13] These data are in accordance with the present study.

There is no proof that cCTG with STV calculation is superior to visual analysis of CTG for fetal monitoring. However, for research purpose STV is superior to visual analysis because it enables definition of strict criteria for intervention, while visual analysis is rather subjective. Implementation of an intervention protocol benefits from well-defined criteria.

Conclusion

The TRUFFLE study showed that a strategy of DVPI monitoring with a safety-net delivery indication of very low STV and / or recurrent decelerations could increase infant survival without neurological impairment at two years. This post-hoc analysis demonstrates that in early FGR the day by day risk of an abnormal cCTG as defined by the DVPI protocol safety-net criteria is 5%, and that prediction of this is not possible. This supports the rationale for cCTG monitoring more often than daily in these high-risk fetuses. Low STV and/or recurrent decelerations were not associated with adverse infant outcome and it appears safe to delay intervention until such abnormalities occur, as long as DVPI is in the normal range.

Figure legends

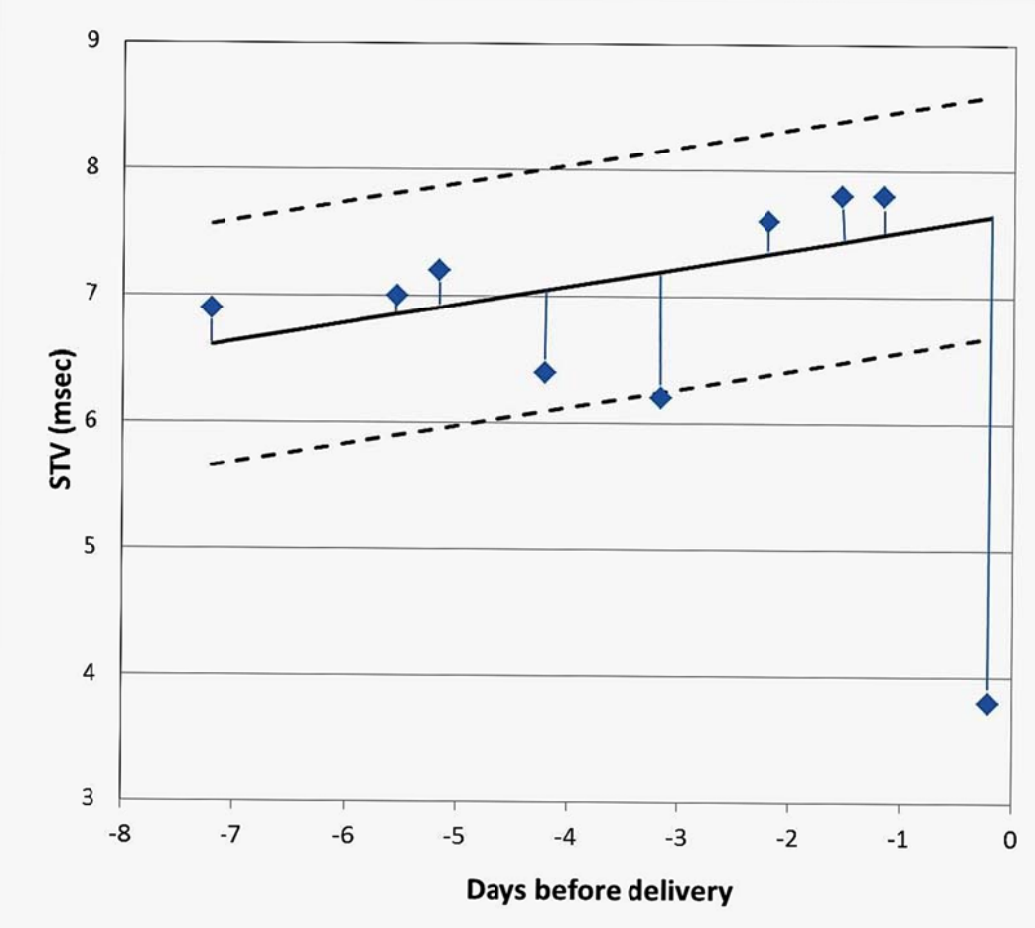

Figure 1a: Example of acute change of STV to a value below CTG-group cut-off: linear regression line, with 2 SD lines, for all STV values during the last week before delivery, except the last value, for an individual woman. Last measurement below the 2SD line.

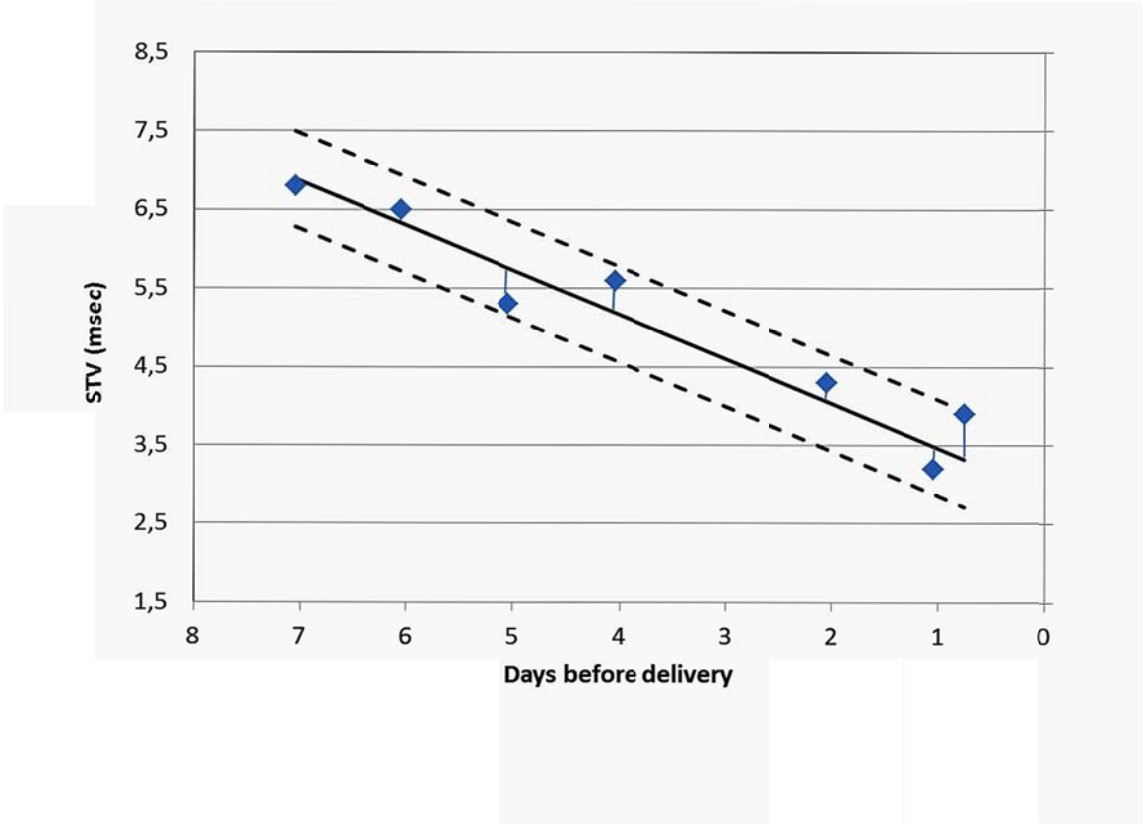

Figure 1b: Example of gradual change of STV to a value below CTG-group cut-off: linear regression line, with 2 SD lines, for all STV values during the last week before delivery, except the last value, for an individual woman. Last measurement within the 2SD lines

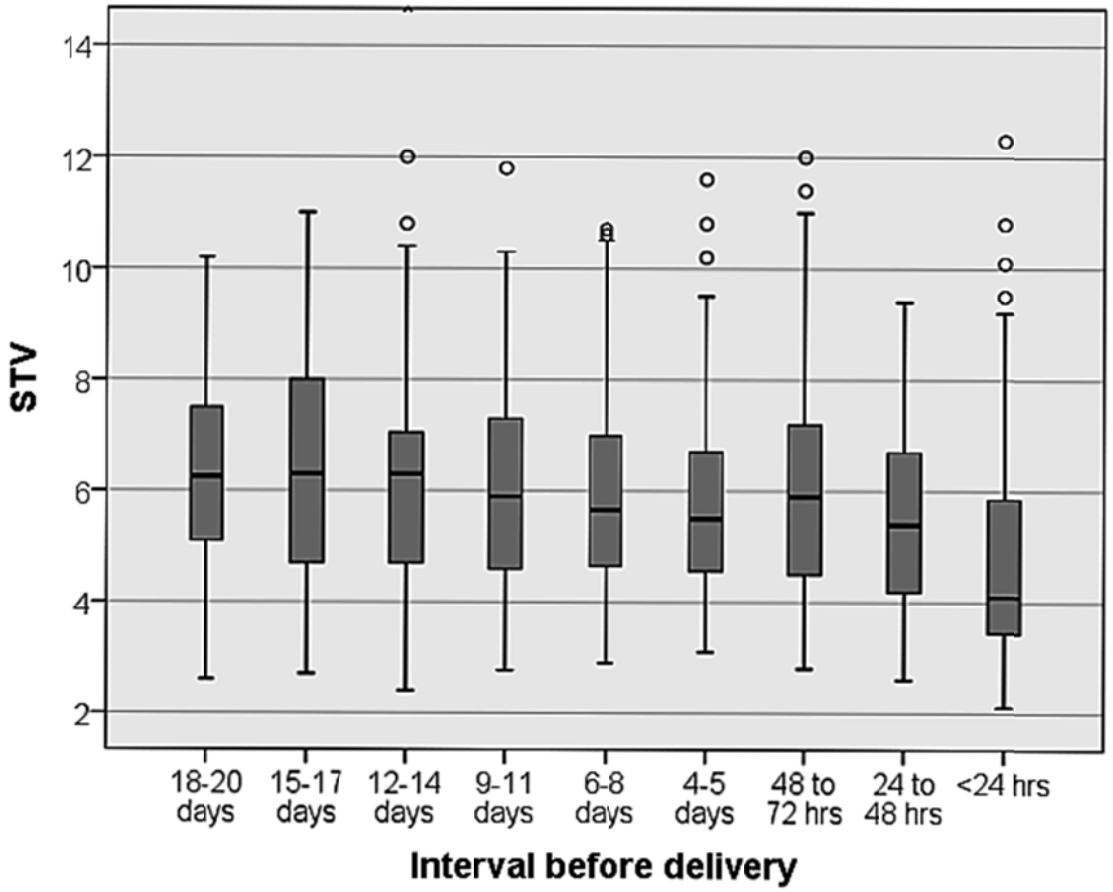

Figure 2: Boxplot of STV measurements of all women in the studygroup (n=149), specified for days before delivery (or fetal death).

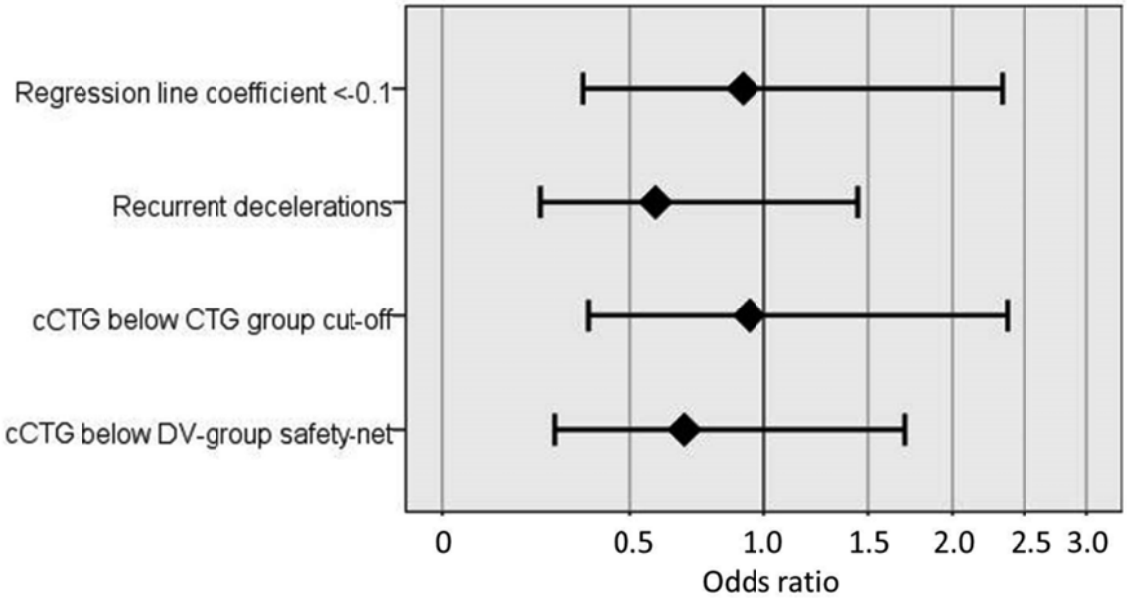

Figure 3: Odds ratios for infant survival without neurological impairment at 2 years with 95% confidence interval of a decrease of STV over time (regression line coefficient) and classification of the last cCTG before delivery. Odds ratios were calculated separately with adjustment for gestational age at delivery and birthweight MoM.

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Table 1:

Selection of the study population by stepwise application of the inclusion criteria (percentage from total number)

TRUFFLE study population delivered <32 weeks	356
Having 2-year infant follow up (or death)	322 (90%)
Delivered (or fetal death) >3 days after inclusion	175 (49%)
Having sufficient CTG data for analysis	157 (44%)
Having corticosteroids >3 days before delivery	149 (42%)

Table 2:

The classification of longitudinal STV patterns and perinatal data of the study group specified for timing of corticosteroid administration.

	Corticosteroids			
	≤3 days before delivery	4-7 days before delivery	>7 days before delivery	All
N (row%)	8 (5%)	23 (15%)	126 (85%)	157
Randomised to cCTG group	2 (25%)	9 (39%)	38 (30%)	49 (31%)
STV regression coefficient <-0.3 (=decrease)	---	12 (52%)*	12 (10%)	24 (16%)
STV regression coefficient <-0.1 (=decrease)	---	17 (74%)*	44 (35%)	61 (41%)
Last STV below 2 SD from earlier registrations	---	8 (35%)	53 (42%)	61 (41%)
Last STV below cCTG-group cut-off	3 (38%)	16 (70%)*	46 (37%)	65 (41%)
Last STV very low and/or decelerations	3 (38%)	14 (61%)	61 (48%)	78 (50%)
Umbilical artery absent or reversed flow	4 (50%)	13 (57%)	56 (44%)	69 (46%)
UC ratio	1.4 (0.38)	1.7 (0.7)	1.5 (0.5)	1.5 (0.5)
Days from randomisation to delivery	12 (7 to 15)	5 (5 to 6)*	11 (8 to 17)	11 (7 to 16)
Fetal death	1 (13%)	0 (--)	1 (1%)	2 (1%)
Gestational age at delivery	30.9 (29.2 to 31.5)	29.0 (28.3 to 30.4)*	30.1 (29.0 to 31.0)	30.0 (28.9 to 30.9)
Birthweight	927 (239)	836 (218)	884 (194)	880 (200)
Birthweight MoM	0.56 (0.07)	0.56 (0.09)	0.57 (0.09)	0.57 (0.09)
Severe neonatal morbidity	2 (25%)	9 (39%)	34 (27%)	45 (29%)
Neonatal mortality	1 (13%)	3 (13%)	6 (5%)	10 (6%)
Normal 2-year outcome	6 (75%)	15 (65%)	108 (86%)	129 (82%)

* $p < 0.05$ (Fisher's Exact test or Mann-Whitney U test between Corticosteroids 4-7 days and > 7 days before delivery)

Table 3:

Perinatal data of the study group with specification for the last STV having a value within or below 2 SD of all previous STV values (Last ±2 SD or Last < 2 SD) and having a regression coefficient of more than -0.1 (slope angle -6° or more = Stable) or a coefficient at or below -0.1 (= Decrease) for all STV registrations except the last.

* P < 0.05 (Anova or Pearson Chi-square)

	Regression line classifications				
	Stable, Last ±2 SD	Stable, Last <2SD	Decrease; Last ±2 SD	Decrease; Last <2SD	Total
N (row%)	40 (27%)	48 (32%)	48 (32%)	13 (9%)	149
At inclusion					
Gestational age (w)	28.0 (26.9 to 29.0)	28.1 (27.2 to 29.4)	28.1 (27.0 to 29.4)	28.1 (27.0 to 29.4)	28.1 (27.0 to 29.3)
Randomisation cCTG group	14 (35%)	17 (35%)	13 (27%)	3 (23%)	47 (32%)
Estimated fetal weight *	730 (134)	791 (173)	840 (180)	774 (171)	789 (170)
Estimated fetal weight MoM *	0.61 (0.10)	0.66 (0.09)	0.67 (0.08)	0.63 (0.07)	0.65 (0.09)
Corticosteroids within 4-7 days*	2 (5%)	4 (8%)	13 (27%)	4 (31%)	23 (15%)
After inclusion					
UC ratio (highest)*	1.8 (0.9)	1.8 (0.7)	3.0 (1.8)	2.7 (1.3	2.2 (1.2)
Absent-reversed EDF	19 (48%)	21 (44%)	24 (50%)	5 (39%)	69 (46%)
Last cCTG: Recurrent decelerations	21 (53%)	21 (44%)	20 (42%)	4 (31%)	66 (44%)
STV < cCTG group cut-off *	6 (15%)	23 (48%)	21 (44%)	7 (54%)	57 (38%)
STV < DV groups cut-off	1 (3%)	5 (10%)	8 (17%)	3 (23%)	17 (11%)
DV safety-net criteria	22 (55%)	23 (48%)	25 (52%)	5 (39%)	75 (50%)
Gest hypertensive morbidity	27 (68%)	38 (79%)	42 (88%)	12 (92%)	119 (80%)
Days from inclusion to delivery*	13 (9 to 17)	11 (6 to 17)	8 (5 to 11)	8 (6 to 17)	10 (7 to 16)
Fetal death	1 (3%)	0 (---)	0 (---)	0 (---)	1 (1%)
Live-born neonates (row%)	39 (26%)	48 (32%)	48 (32%)	13(9%)	148
Gestational age (w)	30.1 (29.6 to 30.9)	30.4 (28.9 to 31.0)	29.8 (28.5 to 30.9)	29.7 (28.6 to 31.2)	30.0 (28.8 to 30.9)
Birthweight (g)	834 (173)	899 (206)	892 (211)	862 (196)	877 (198)
Birthweight MoM *	0.53 (0.10)	0.58 (0.09)	0.59 (0.09)	0.55 (0.08)	0.57 (0.09)
Male	16 (41%)	26 (54%)	26 (54%)	9 (69%)	77 (52%)
Umbilical artery pH < 7.0 (n=124)	0	0	0	1 (8%)	1 (1%)
Severe neonatal morbidity†	13 (33%)	10 (21%)	14 (29%)	6 (46%)	43 (29%)
Neonatal death	4 (10%)	2 (4%)	3(6%)	0 (---)	9 (6%)
Neurological impairment at 2 years	6 (15%)	3 (6%)	4 (8%)	3 (23%)	16 (11%)
Alive and normal	29 (73%)	43(90%)	41 (85%)	10 (77%)	123 (83%)

‡ DV safety-net: very low STV or recurrent fetal heart rate decelerations

† Components of severe morbidity were bronchopulmonary dysplasia (BPD - additional oxygen at 36 weeks adjusted age), germinal matrix haemorrhage (GMH) grade 3 or 4, periventricular leucomalacia (PVL) more than grade 1, necrotising enterocolitis (NEC – confirmed by X-ray or laparotomy) or microbiologically proven sepsis.