29th World Congress on Ultrasound in Obstetrics and Gynecology

12-16 October 2019
Berlin, Germany

Ultrasound Obstet Gynecol 2017; **50:** 71–78
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17215

Longitudinal study of computerized cardiotocography in early fetal growth restriction

H. WOLF[1], B. ARABIN[2], C. C. LEES[3,4], D. OEPKES[5], F. PREFUMO[6], B. THILAGANATHAN[7], T. TODROS[8], G. H. A. VISSER[9], C. M. BILARDO[10], J. B. DERKS[9], A. DIEMERT[11], J. J. DUVEKOT[12], E. FERRAZZI[13], T. FRUSCA[14], K. HECHER[11], N. MARLOW[15], P. MARTINELLI[16], E. OSTERMAYER[17], A. T. PAPAGEORGHIOU[7], H. C. J. SCHEEPERS[18], D. SCHLEMBACH[19], K. T. M. SCHNEIDER[17], A. VALCAMONICO[6], A. VAN WASSENAER-LEEMHUIS[20] and W. GANZEVOORT[1], on behalf of the TRUFFLE group[#]

[1]*Department of Obstetrics and Gynecology, Academic Medical Centre, Amsterdam, The Netherlands;* [2]*Center for Mother and Child of the Phillips University, Marburg, Germany;* [3]*Department of Surgery and Cancer, Imperial College London, London, UK;* [4]*Department of Development and Regeneration, KU Leuven, Leuven, Belgium;* [5]*Department of Obstetrics, Leiden University Medical Center, Leiden, The Netherlands;* [6]*Maternal-Fetal Medicine Unit, University of Brescia, Brescia, Italy;* [7]*Fetal Medicine Unit, St George's, University of London and St George's University Hospitals NHS Foundation Trust, Molecular and Clinical Sciences Research Institute, London, UK;* [8]*Department of Obstetrics and Gynaecology, University of Turin, Turin, Italy;* [9]*Department of Perinatal Medicine, University Medical Center, Utrecht, The Netherlands;* [10]*Department of Obstetrics and Gynaecology, University Medical Center, University of Groningen, Groningen, The Netherlands;* [11]*Department of Obstetrics and Fetal Medicine, University Medical Center, Hamburg, Eppendorf, Germany;* [12]*Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, The Netherlands;* [13]*Department of Woman, Mother and Neonate, Buzzi Children's Hospital, University of Milan, Milan, Italy;* [14]*Department of Obstetrics and Gynecology, Maggiore Hospital, University of Parma, Parma, Italy;* [15]*Department of Neonatology, Institute for Women's Health, University College Hospitals London, London, UK;* [16]*Department of Neuroscience, Dentistry and Reproductive Sciences, University of Naples Federico II, Naples, Italy;* [17]*Division of Perinatal Medicine, Department of Obstetrics and Gynecology, Technical University, Munich, Germany;* [18]*Department of Obstetrics, Maastricht University Medical Centre, Maastricht, The Netherlands;* [19]*Department of Obstetrics, Vivantes Clinic Neukölln, Berlin, Germany;* [20]*Department of Neonatology, Emma Children's Hospital Academic Medical Centre, Amsterdam, The Netherlands*

KEYWORDS: cardiotocography; ductus venosus; fetal growth restriction; fetal monitoring; preterm; short-term variation

ABSTRACT

Objectives *To explore whether, in early fetal growth restriction (FGR), the longitudinal pattern of fetal heart rate (FHR) short-term variation (STV) can be used to identify imminent fetal distress and whether abnormalities of FHR recordings are associated with 2-year infant outcome.*

Methods *The original TRUFFLE study assessed whether, in early FGR, delivery based on ductus venosus (DV) Doppler pulsatility index (PI), in combination with safety-net criteria of very low STV on cardiotocography (CTG) and/or recurrent FHR decelerations, could improve 2-year infant survival without neurological impairment in comparison with delivery based on CTG monitoring only. This was a secondary analysis of women who delivered before 32 weeks and had consecutive STV data recorded > 3 days before delivery and known infant outcome at 2 years of age. Women who received corticosteroids within 3 days of delivery were excluded. Individual regression line algorithms of all STV values, except the last one before delivery, were calculated. Life tables and Cox regression analysis were used to calculate the daily risk for low STV or very low STV and/or FHR decelerations (below DV group safety-net criteria) and to assess which parameters were associated with this risk. Furthermore, it was assessed whether STV pattern, last STV value or recurrent FHR decelerations were associated with 2-year infant outcome.*

Results *One hundred and forty-nine women from the original TRUFFLE study met the inclusion criteria. Using the individual STV regression lines, prediction of a last STV below the cut-off used by the CTG monitoring group had sensitivity of 42% and specificity of 91%. For each day after study inclusion, the median risk for low STV (CTG group cut-off) was 4% (interquartile range (IQR), 2–7%) and for very low STV and/or recurrent FHR decelerations (below DV group safety-net criteria) was 5% (IQR, 4–7%). Measures of STV pattern, fetal Doppler (arterial or venous), birth-weight multiples of the median and gestational age did not usefully improve daily risk prediction. There was no association*

Correspondence to: Prof. H. Wolf, Department of Obstetrics and Gynecology, Academic Medical Centre, H4-278, Meibergdreef 15, 1007 MB Amsterdam, The Netherlands (e-mail: h.wolf@amc.uva.nl)

[#]TRUFFLE group collaborating authors are listed at the end of the article.

Accepted: 8 July 2016

of STV regression coefficients, a low last STV and/or recurrent FHR decelerations with short- or long-term infant outcomes.

Conclusion *The TRUFFLE study showed that a strategy of DV monitoring with safety-net criteria of very low STV and/or recurrent FHR decelerations for delivery indication could increase 2-year infant survival without neurological impairment. This* post-hoc *analysis demonstrates that, in early FGR, the daily risk of abnormal CTG, as defined by the DV group safety-net criteria, is 5%, and that prediction is not possible. This supports the rationale for CTG monitoring more often than daily in these high-risk fetuses. Low STV and/or recurrent FHR decelerations were not associated with adverse infant outcome and it appears safe to delay intervention until such abnormalities occur, as long as DV-PI is within normal range. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

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 at delivery and birth weight. The main challenge in management of FGR is the timing of delivery, for which 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 intrauterine stay. Prior to the development of terminal acidosis and absence of fetal movement, a gradual decrease in fetal heart rate (FHR) short-term variation (STV), FHR deceleration and gradual decrease in fetal movement have been described[1,2]. If there was a process in place so that these could be identified in a timely manner, the additive risks of acidosis could potentially be avoided, without compromising the benefits of increasing gestational age.

The recently published Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) study was designed to investigate in pregnancies complicated by early FGR whether fetal monitoring of ductus venosus (DV) pulsatility index (PI), in combination with STV on computerized cardiotocography (CTG), could improve long-term infant outcome in comparison with monitoring by CTG only[3]. Women with FGR between 26+0 and 31+6 weeks were randomized to three different strategies for delivery intervention (DV-PI > 95th percentile, absent A-wave in the DV or low CTG only). The study concluded that monitoring of DV-PI, in combination with safety-net criteria of very low STV and/or recurrent FHR decelerations, could reduce the risk of infant neurological impairment at 2 years in comparison with monitoring by CTG only.

This secondary analysis of data from the TRUFFLE study was intended to explore, in a group of fetuses with early FGR, the longitudinal pattern of STV recordings, the rate at which STV decreased below the intervention cut-off and whether an association exists between longitudinal STV pattern or STV below intervention cut-off and perinatal parameters and 2-year infant outcome.

METHODS

The TRUFFLE study design has been described previously[3]. Briefly, women with a singleton pregnancy between 26+0 and 31+6 weeks of gestation with fetal abdominal circumference < 10th percentile and umbilical artery Doppler PI > 95th percentile were included in a 20-center European study (ISRCTN, 56204499). Women were allocated at random to one of three monitoring strategies for delivery: (1) reduced STV (< 3.5 ms before 29 weeks and < 4.0 ms thereafter) on CTG, (2) early DV Doppler changes (DV-PI > 95th percentile – 'DV-p95' group) and (3) late DV Doppler changes (A-wave at or below baseline – 'DV-no-A' group). Abnormal DV-PI measurements were to be repeated within 24 h, if CTG results allowed this, to demonstrate consistency. In all groups, the timing of delivery could also be decided by safety-net criteria if the CTG showed recurrent decelerations in FHR or when STV in the DV groups was very low (STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter). The Oxford Sonicaid 8002 system or an equivalent Dawes–Redman software-based algorithm was used for STV calculation[4]. Recordings were at least 45 min in duration. Most participating centers (17/20) performed CTG at least daily. The remaining centers performed CTG on alternate days, but more often on indication.

For birth weight, multiples of the median (MoM) were calculated. The 50th weight percentile from a fetal growth chart, adjusted for gestational age, maternal ethnicity, weight, height and neonatal sex, was used as normalized median fetal weight[5].

The primary TRUFFLE study outcome was infant survival at 2 years of age with normal neurological development (adjusted for prematurity), defined by a score > 85 on the Bayley Scales of Infant and Toddler Development (third edition) (PsychCorp, San Antonio, TX, USA) and absence of severe vision or hearing deficiency or cerebral palsy[3]. A secondary outcome was severe neonatal morbidity, defined as bronchopulmonary dysplasia (need for additional oxygen at 36 weeks adjusted age), germinal matrix hemorrhage Grade 3 or 4, periventricular leukomalacia > Grade 1, necrotizing enterocolitis (confirmed by X-ray or laparotomy) or microbiologically proven sepsis.

This secondary analysis included all women who had been included in the study for > 3 days before delivery, had at least four CTG recordings in the last week before delivery and at least one CTG recording in the last 24 h before delivery and were delivered before 32 weeks. This last inclusion criterion was necessary because, after 32 weeks, protocol-driven monitoring was no longer followed and therefore STV measurements were no longer entered consistently into the study database.

Women who received corticosteroids within 3 days before delivery were excluded as it has been observed that STV increases shortly after corticosteroid administration and decreases on day 2–3 after administration[6,7]. Because a more prolonged effect of corticosteroids could not be excluded, we analyzed monitoring data separately for women who delivered within 1 week after corticosteroid administration and women who delivered later or did not receive corticosteroids. The TRUFFLE study was approved by the ethics committees of all participating units.

For overview of STV data, a boxplot was created using STV values recorded in the last 3 weeks before delivery, grouped into time periods of 3-, 2- or 1-day intervals. If women had more than one STV measurement in a time period, only the last measurement was selected.

Individual longitudinal STV analysis was performed by linear and by exponential regression analyses, with or without adjustment for a last STV above or below the CTG group cut-off or for primary infant outcome. 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 and adjustments did not improve the fit (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 measurement before delivery. Based on the differences between observed and expected STV values, the SD from the regression line could be calculated for each woman. This allowed assessment of whether the last STV measurement (which was exempted from this regression line calculation) was in line with earlier measurements or diverted > 2 SD from the expected STV value. Figure 1 demonstrates this method for two women, one with last STV value > 2 SD below the previous values and one with last (but low) value in line with expectations, based on the regression line of earlier STV 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 of $STV^{expected}$ for prediction of STV below the CTG group cut-off were calculated.

Life table analysis was used to calculate the daily risk of low STV below the CTG group cut-off and of 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 better predicted by the individual regression line slope angle, randomization group allocation, ratio of umbilical artery PI to fetal middle cerebral artery PI (U/C ratio), absent or reversed end-diastolic velocity in the umbilical artery (ARED flow), gestational age and birth-weight MoM. Birth weight 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 (ORs) were calculated with 95% CI. Estimation of the area under the receiver–operating characteristics curve (AUC) was used to assess the efficacy of a model.

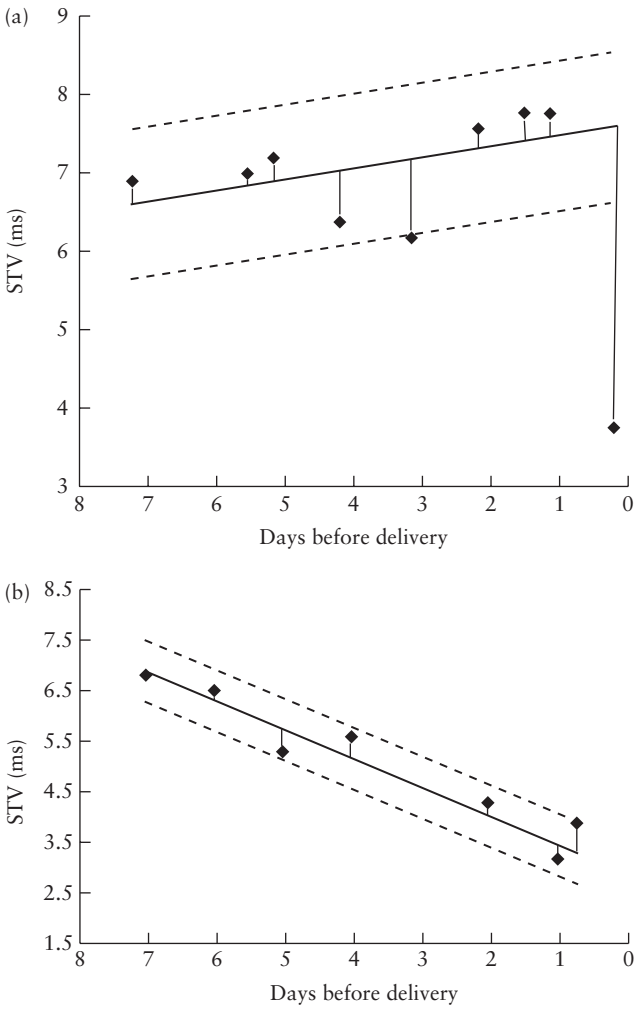

Figure 1 Examples of acute (a) and gradual (b) change in fetal heart rate short-term variation (STV) in two individual pregnancies to a value below the cardiotocography group cut-off for indication for delivery. Linear regression line ± 2 SD is shown for all STV values in last week before delivery, excluding last STV value before delivery. Last STV measurement is below 2 SD in (a) and within 2 SD in (b).

Based on the regression coefficient of a linear model of all STV recordings of the study population during the last 3 weeks before delivery, a regression coefficient < -0.1 (a decrease of 1 ms per 10 days or negative slope angle $> 6°$) was defined as a decreasing STV pattern. If the regression coefficient was ≥ -0.1 or the angle of the regression line was $< 6°$, the STV pattern was defined as stable.

Perinatal and outcome data were compared between women with and those without a decreasing STV regression line and women with a last STV value within the expected range and those with STV more than 2 SD below the expected value. By combining these two classifications, we could define four groups for comparison.

ORs of 2-year infant survival without neurological impairment were calculated for a decreasing STV regression line, a last STV below the CTG group criteria, a last STV below the DV group safety-net criteria and last

STV 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 and non-parametric testing. Groups were compared by ANOVA, Kruskal–Wallis, Mann–Whitney *U*, Pearson's chi-square or Fisher's exact test, as appropriate. Multivariable analysis was performed by a backwards stepwise procedure with $P < 0.1$ to exclude potential variables from the model. Statistical analyses were performed with SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

One hundred and forty-nine (42%) women of the 356 women who delivered before 32 weeks qualified for inclusion in this secondary analysis (Table 1). The main reason for exclusion (41%) was delivery or fetal death within 3 days after study inclusion. Eight women who complied with the CTG frequency inclusion criteria were excluded from longitudinal analysis because they had received 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 received corticosteroids 1–5 days after randomization. Table 2 shows perinatal data of the study population, grouped according to the time interval from administration of corticosteroids to delivery. This table includes data on the eight women with a short corticosteroid-to-delivery interval who were excluded from the longitudinal analysis. Median gestational age at delivery was 30 weeks, mean birth weight was 880 g and birth-weight MoM was 0.57.

Fetal death occurred in two (1%) cases (Table 2), of which one was excluded from longitudinal analysis because of a short corticosteroid-to-delivery interval. In both cases, the last CTG performed approximately 12 h before fetal death was normal (mean STV, 5 ms), but one case had a DV-PI > 95th percentile (randomized to DV-no-A group). The additional fetal deaths in the TRUFFLE study ($n = 10$) were not included in the analysis because the number of CTG recordings was insufficient for longitudinal analysis. In one case, a borderline STV (2.7 ms) was recorded approximately 12 h before fetal death. Two cases had normal STV (mean, 5.7 ms) approximately 24 h before fetal death, one of which had a DV-PI > 95th percentile. Two women refused intervention when indicated for delivery by low STV and recurrent FHR decelerations and fetal death was confirmed 24 h later. In five fetal deaths, the interval between the last CTG and fetal death was more than 24 h. 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 infants were classified as normal at the corrected age of 2 years.

Table 1 Selection of women for analysis by stepwise application of inclusion criteria to TRUFFLE study population of 356 women who delivered < 32 weeks' gestation

Inclusion criterion	n *(%)*
Two-year infant follow-up (or known death)	322 (90)
Delivered or fetal death > 3 days after study inclusion	175 (49)
Sufficient cardiotocography data for analysis	157 (44)
Corticosteroids administered > 3 days before delivery or not received	149 (42)

Table 2 Longitudinal fetal heart rate (FHR) short-term variation (STV) patterns and perinatal outcome in 157 pregnancies with fetal growth restriction, according to timing of corticosteroid administration

	Interval between corticosteroid administration and delivery			
Parameter	*≤ 3 days* (n = *8)*	*4–7 days* (n = *23)*	*> 7 days* (n = *126)*†	*All* (n = *157)*
Randomized to CTG monitoring group	2 (25)	9 (39)	38 (30)	49 (31)
STV regression coefficient < −0.3 (decrease)	—	12 (52)*	12 (10)	24 (15)
STV regression coefficient < −0.1 (decrease)	—	17 (74)*	44 (35)	61 (39)
Last STV before delivery > 2 SD below earlier recordings	—	8 (35)	53 (42)	61 (39)
Last STV below CTG group cut-off	3 (38)	16 (70)*	46 (37)	65 (41)
Last STV below DV group safety-net criteria‡	3 (38)	14 (61)	61 (48)	78 (50)
Umbilical artery ARED flow	4 (50)	13 (57)	56 (44)	73 (46)
U/C ratio	1.4 ± 0.38	1.7 ± 0.7	1.5 ± 0.5	1.5 ± 0.5
Days from randomization to delivery	12 (7–15)	5 (5–6)*	11 (8–17)	11 (7–16)
Fetal death	1 (13)	0 (0)	1 (1)	2 (1)
Gestational age at delivery (weeks)	30.9 (29.2–31.5)	29.0 (28.3–30.4)*	30.1 (29.0–31.0)	30.0 (28.9–30.9)
Birth weight (g)	927 ± 239	836 ± 218	884 ± 194	880 ± 200
Birth-weight 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 infant outcome	6 (75)	15 (65)	108 (86)	129 (82)

Data are given as *n* (%), mean ± SD or median (range). Comparison of women with corticosteroids 4–7 days *vs* > 7 days before delivery by Fisher's exact test or Mann–Whitney *U*-test: *$P < 0.05$. †Five women in this group did not receive corticosteroids. ‡Very low STV and/or FHR decelerations. ARED, absent or reversed end-diastolic; CTG, cardiotocography; DV, ductus venosus; MoM, multiples of the median; U/C ratio, umbilical artery pulsatility index to fetal middle cerebral artery pulsatility index ratio.

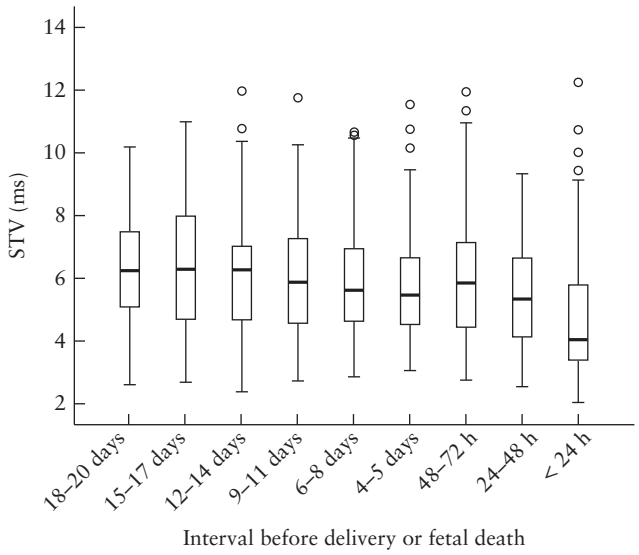

Figure 2 Boxplot of fetal heart rate short-term variation (STV) measurements in all women in study group ($n = 149$), according to length of time before delivery or fetal death. Median, interquartile range, range and outliers are shown.

Figure 2 shows a boxplot of STV recordings, grouped according to the time period at which the measurement was taken in the last 3 weeks before delivery. A linear model of all STV recordings showed a slow decrease in STV values (algorithm: 5.36 – 0.11 × (days before delivery); 95% CI, ±4 ms). Other models (quadratic, cubic, logistic) gave residuals identical to or higher than those of the linear model. As can be seen in Figure 2, the most prominent decrease in STV was on the day before delivery. The last STV measurements before delivery were significantly lower than earlier measurements. Repeating the linear regression of STV recordings, excluding those obtained on the day before delivery, showed a stable, nearly horizontal pattern (algorithm: 5.71 – 0.04 × (days before delivery) or a decrease of 1 ms/25 days).

A linear decrease in the individual STV regression line with a regression coefficient <−0.1 (or a slope angle <−6°) occurred in 61 (41%) women and a regression coefficient <−0.3 (or a slope angle <−17°) was observed in only 24 (16%) of these. Using all STV data of the 88 women with a regression coefficient ≥−0.1 gave a median

Table 3 Perinatal data of 149 pregnancies with fetal growth restriction, according to last fetal heart rate (FHR) short-term variation (STV) value before delivery within 2 SD (last STV ± 2 SD) or more than 2 SD below (last STV < 2 SD) all previous STV values, and STV regression coefficient ≥ −0.1 (or slope angle ≥ −6°, stable) or < −0.1 (decreasing) for all STV recordings except last STV

	Regression line classification				
	Stable STV		*Decreasing STV*		
Parameter	*Last STV ± 2 SD*	*Last STV < 2 SD*	*Last STV ± 2 SD*	*Last STV < 2 SD*	*All*
n (%)	40 (27)	48 (32)	48 (32)	13 (9)	149 (100)
At inclusion					
Gestational age (weeks)	28.0 (26.9–29.0)	28.1 (27.2–29.4)	28.1 (27.0–29.4)	28.1 (27.0–29.4)	28.1 (27.0–29.3)
Randomization to CTG group	14 (35)	17 (35)	13 (27)	3 (23)	47 (32)
Estimated fetal weight (g)*	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 4–7 days before delivery*	2 (5)	4 (8)	13 (27)	4 (31)	23 (15)
After inclusion					
Highest U/C ratio*	1.8 ± 0.9	1.8 ± 0.7	3.0 ± 1.8	2.7 ± 1.3	2.2 ± 1.2
Umbilical artery ARED flow	19 (48)	21 (44)	24 (50)	5 (38)	69 (46)
Last CTG					
Recurrent FHR decelerations	21 (53)	21 (44)	20 (42)	4 (31)	66 (44)
STV < CTG group cut-off*	6 (15)	23 (48)	21 (44)	7 (54)	57 (38)
STV < DV group cut-off	1 (3)	5 (10)	8 (17)	3 (23)	17 (11)
STV < DV group safety-net criteria†	22 (55)	23 (48)	25 (52)	5 (38)	75 (50)
Gestational hypertension	27 (68)	38 (79)	42 (88)	12 (92)	119 (80)
Days from inclusion to delivery*	13 (9–17)	11 (6–17)	8 (5–11)	8 (6–17)	10 (7–16)
Fetal death	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
Liveborn (% of all liveborn)	39 (26)	48 (32)	48 (32)	13 (9)	148 (100)
Gestational age at delivery (weeks)	30.1 (29.6–30.9)	30.4 (28.9–31.0)	29.8 (28.5–30.9)	29.7 (28.6–31.2)	30.0 (28.8–30.9)
Birth weight (g)	834 ± 173	899 ± 206	892 ± 211	862 ± 196	877 ± 198
Birth-weight MoM*	0.53 ± 0.10	0.58 ± 0.09	0.59 ± 0.09	0.55 ± 0.08	0.57 ± 0.09
Male neonate	16 (40)	26 (54)	26 (54)	9 (69)	77 (52)
Umbilical artery pH < 7.0 ($n = 124$)	0 (0)	0 (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 (0)	9 (6)
Neurological impairment at 2 years	6 (15)	3 (6)	4 (8)	3 (23)	16 (11)
Alive and normal at 2 years	29 (73)	43 (90)	41 (85)	10 (77)	123 (83)

Data are given as *n* (%), median (range) or mean ± SD. Groups compared by ANOVA or Pearson's chi-square test: *$P < 0.05$. †Very low STV and/or recurrent FHR decelerations. ‡Components include bronchopulmonary dysplasia (need for additional oxygen at 36 weeks adjusted age), germinal matrix hemorrhage Grade 3 or 4, periventricular leukomalacia > Grade 1, necrotizing enterocolitis (confirmed by X-ray or laparotomy) or microbiologically proven sepsis. ARED, absent or reversed end-diastolic; CTG, cardiotocography; DV, ductus venosus; MoM, multiples of the median; U/C ratio, umbilical artery pulsatility index to fetal middle cerebral artery pulsatility index ratio.

regression coefficient of −0.001, which can be interpreted as horizontal.

Women who received corticosteroids 4–7 days before delivery ($n = 23$; 15%) had both a regression coefficient <-0.1 and a last STV below CTG group cut-off approximately twice as often as women who received no corticosteroids ($n = 5$) or had corticosteroids more than 7 days before delivery ($n = 121$) (Table 2; $P < 0.05$). There was a statistically significant difference in the time interval from inclusion to delivery between these two groups, but there was no difference in Doppler parameters, gestational age at delivery, birth weight or birth-weight MoM.

The study group was subdivided into four groups based on the value of the individual STV regression line coefficient being more or less than −0.1 (or slope angle of −6°) and the last STV being more or less than 2 SD below the regression line calculated using all STV values except the last measurement before delivery. There were no differences between these groups for gestational age at randomization, gestational age at delivery, birth weight, severe neonatal morbidity or 2-year infant outcome (Table 3). In the first group (stable STV pattern with a last STV within 2 SD), estimated fetal weight and birth-weight MoM were lower. Only six (15%) women in this group had a low last STV and in these women STV was just above the CTG group cut-off at inclusion. In the other classification groups, a low last STV occurred approximately three times more frequently. In those with a decreasing STV pattern, U/C ratio was higher. Within the classification groups, data were similar for women who received corticosteroids 4–7 days before delivery in comparison with the remaining women.

In 61 (41%) women, the last STV value was more than 2 SD below the individual regression line. In half of these women ($n = 30$; 49%), the last STV value was below the CTG group cut-off. In 88 (59%) women, the last STV was within 2 SD of the regression line, and in 27 of these (31%), the STV value was below the CTG group cut-off (Table 3).

The sensitivity of $STV^{expected}$ below the CTG-STV group cut-off for prediction of a last STV lower than the CTG group cut-off was 42% and specificity was 91%, with an OR of 2.5 (95% CI, 1.7–3.8). Combining low $STV^{expected}$ with randomization allocation, time of corticosteroid administration of 4–7 days *vs* > 7 days before delivery, gestational age, birth weight and fetal Doppler measurements (arterial or venous) in a multivariable analysis did not improve prediction of low STV below the CTG group cut-off.

Life table analysis showed that, for each day after inclusion, the median risk for low STV below the CTG group cut-off was 4% (interquartile range (IQR), 2–7%). The daily risk for very low STV and/or recurrent FHR decelerations (DV group safety-net criteria) was 5% (IQR, 4–7%). Stratification of the analysis for allocation to DV or CTG monitoring groups 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 slightly the risk estimate for a low STV below the CTG group cut-off (AUC, 0.61 (95% CI, 0.51–0.70)), while fetal Doppler (arterial or venous), birth-weight MoM and gestational age were rejected from the model. A similar model for improving the prediction of very low STV and/or recurrent FHR decelerations (below DV group safety-net criteria) failed (AUC, 0.51 (95% CI, 0.41–0.61)).

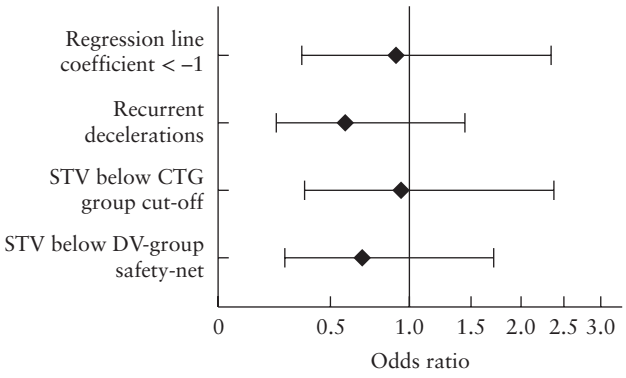

Figure 3 Odds ratios with 95% CIs for 2-year infant survival without neurological impairment for a longitudinal decrease in fetal heart rate (FHR) short-term variation (STV) (regression line coefficient), recurrent FHR decelerations and last STV before delivery below cardiotocography (CTG) group cut-off and below ductus venosus (DV) group safety-net criteria cut-off for indication of delivery. Odds ratios were calculated separately with adjustment for gestational age at delivery and birth-weight multiples of the median.

Adjusted ORs for 2-year survival without neurological impairment of the STV regression line coefficient, recurrent FHR decelerations, a low last STV (below CTG group cut-off) or very low STV and/or recurrent FHR decelerations (below DV group safety-net criteria) are shown in Figure 3. ORs were adjusted for gestational age and birth-weight MoM for each variable separately. Group allocation (DV or CTG monitoring) had been entered into this analysis but was rejected from the model. None of these variables reached statistical significance.

We observed no association of a last STV below the CTG group cut-off and/or recurrent FHR decelerations with umbilical pH or Apgar score at birth, nor with the incidence of severe neonatal morbidity or neurological impairment at the age of 2 years. Because the last STV value before delivery had no association with outcome, we did not perform statistical analysis on earlier STV values.

DISCUSSION

In this *post-hoc* analysis of the TRUFFLE study data, 38% of women had a last STV below the CTG group cut-off and 11% had a last STV below the DV group cut-off, while recurrent FHR decelerations in the last CTG were observed in 44% of women. Fifty percent of women had a STV below the DV group cut-off and/or recurrent FHR decelerations and surpassed the DV group 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 daily risk of very low STV and/or recurrent FHR decelerations (DV group safety-net) was 5% (IQR, 4–7%). Within this group of women with early FGR, this background risk of surpassing the DV group safety-net criteria could not be adjusted individually using longitudinal STV parameters, fetal Doppler parameters (arterial or venous), nor any other perinatal characteristics. The clinical implication of this finding is that, if DV group safety-net criteria are considered a valid and urgent indication for delivery, then at least daily CTG recordings are needed. The study data have insufficient power to address the question of whether performing CTG more often than once daily might improve detection.

Short- or long-term infant outcome was not associated with longitudinal STV pattern, a last STV below the CTG group cut-off or below the DV-group cut-off or with recurrent FHR decelerations. In early preterm FGR, if monitored properly and action is taken as specified in the TRUFFLE protocol, it is not harmful to delay delivery until CTG monitoring shows clear abnormalities. Because two-thirds of this cohort had also been monitored for DV-PI, this statement is probably only valid for women with early FGR who were also monitored for DV-PI and delivered when DV-PI was consistently abnormal. This is supported by the observation of fetal death approximately 12 h after a normal CTG in women with DV-PI > 95th percentile.

While we conclude that it is safe to delay intervention until very low STV and/or recurrent FHR decelerations occur, as long as CTG is recorded with sufficient frequency and DV-PI is normal, we do not advocate delaying delivery thereafter. Our study was not designed to define the mortality risk after an abnormal CTG. However, the occurrence of fetal death shortly after refusal of intervention by two women, when low STV and FHR decelerations were observed, supports the need for delivery 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 STV variation and/or FHR 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 STV variation and/or FHR decelerations to prevent fetal death[10,11].

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

One hundred and forty-nine (46%) of the 322 women from the TRUFFLE study who delivered before 32 weeks and had complete 2-year follow-up 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 who delivered before 32 weeks (data not shown). The only major difference of the current selected cohort with the remaining women was in antenatal mortality; nearly all antenatal deaths (11/12; 92%) were excluded because of insufficient data for longitudinal analysis. Most of these had insufficient data because of either refusal of intervention[5] or inclusion to delivery interval shorter than 4 days[5]. In one of these women, more frequent CTG might have prevented fetal death.

Few studies have assessed longitudinal STV in 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 variation in STV as did ours, this must have been an overall 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 > 3 ms/10 days was rare and seen mostly in cases with a short interval to delivery. In our cohort, most decreases in STV occurred only during the last 24 h before delivery. Because the data in the study of Hecher *et al.*[2] were organized by gestational age, and deliveries occurred at different gestational ages, data obtained shortly before delivery could lower the average STV. Two longitudinal studies in early FGR followed long-term FHR variation, which has some relation to STV. One study observed that variation was stable until a decrease on the last day before delivery[12]. The other reported a slight decrease in variation during the last 3 weeks of pregnancy, again with the most significant decrease being on the last day[13]. These data are in accordance with those of the present study.

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

In conclusion, the TRUFFLE study showed that a strategy of DV-PI monitoring with safety-net delivery indication of very low STV and/or recurrent FHR decelerations could increase infant survival without neurological impairment at 2 years of age. This *post-hoc* analysis demonstrates that, in early FGR, the daily risk of abnormal CTG, as defined by the DV-PI group safety-net criteria, is 5% and that prediction of this is not possible. This supports the rationale for CTG monitoring more often than daily in these high-risk fetuses. Low STV and/or recurrent FHR decelerations were not associated with adverse infant outcome and it appears safe to delay intervention until such abnormalities occur, as long as DV-PI is within the normal range.

ACKNOWLEDGMENTS

C.C.L. is supported by the National Institute for Health Research Biomedical Research Centre based at Imperial College Healthcare National Health Service Trust and Imperial College London. The Trial of Randomized

Umbilical and Fetal Flow in Europe study was supported by ZonMw, 2509 AE Den Haag, The Netherlands (grant 94506556), in The Netherlands. In other countries, the study was not funded. A contribution was made to study funding from the Dr Hans Ludwig Geisenhofer Foundation, Munich, Germany.

TRUFFLE GROUP COLLABORATING AUTHORS

Ayse Aktas, Center for Mother and Child of the Phillips University, Marburg, Germany; Silvia Borgione, University of Turin, Sant' Anna Hospital, Turin, Italy; Christoph Brezinka, Department of Gynecological Endocrinology and Reproductive Medicine, Medical University of Innsbruck, Innsbruck, Austria; Sandra Calvert, Department of Obstetrics, St George's, University of London, London, UK; Rabih Chaoui, Center of Prenatal Diagnosis and Human Genetics, Berlin, Germany; Jerome M. J. Cornette, Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, The Netherlands; Thilo Diehl, Department of Obstetrics and Fetal Medicine, University Medical Center, Hamburg-Eppendorf, Germany; Jim van Eyck, Department of Perinatology, Isala Clinics, Zwolle, The Netherlands; Nicola Fratelli, Department of Obstetrics and Gynaecology, Spedali Civili di Brescia, Brescia, Italy; Inge-Lot van Haastert, Department of Neonatology, Division Woman and Baby, UMC Utrecht, Utrecht, The Netherlands; Samantha Johnson, Department of Health Sciences, University of Leicester, Leicester, UK; Silvia Lobmaier, Division of Perinatal Medicine, Department of Obstetrics and Gynecology, Technical University, Munich, Germany; Enrico Lopriore, Department of Neonatology, Leiden University Medical Center, Leiden, The Netherlands; Giuseppina Mansi, Department of Translational Medicine, University of Naples Federico II, Naples, Italy; Hannah Missfelder-Lobos, Addenbrooke's Hospital, Cambridge, UK; Paola Martelli, Department of Child Neuropsychiatry, Spedali Civili Brescia, Brescia, Italy; Gianpaolo Maso, Institute for Maternal and Child Health, IRCCS, Burlo Garofolo, Trieste, Italy; Ute Maurer-Fellbaum, Medical University of Graz, Graz, Austria; Nico Mensing van Charante, Department of Obstetrics and Gynecology, Academic Medical Centre, Amsterdam, The Netherlands; Susanne Mulder De Tollenaer, Neonatology, Isala Clinics, Zwolle, The Netherlands; Tamanna Moore, Institute of Womens Health, University College London, London, UK; Raffaele Napolitano, Department of Neuroscience, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy; Manuela Oberto, Department of Obstetrics and Gynaecology, University of Turin, Turin, Italy; Giovanna Ogge, Department of Obstetrics and Gynaecology, University of Turin, Turin, Italy; Joris van der Post, Department of Obstetrics and Gynecology, Academic Medical Centre, Amsterdam, The Netherlands; Lucy Preston, Addenbrooke's Hospital, Cambridge, UK; Francesco Raimondi, Department of Translational Medicine, University of Naples Federico II, Naples, Italy; Irwin K. M. Reiss, Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; Serena Rigano, Department of Woman, Mother and Neonate, Buzzi Children's Hospital, University of Milan, Milan, Italy; Ewoud Schuit, Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands, Stanford Prevention Research Center, Stanford University, Stanford, CA, USA and Julius Center for Health Sciences and Primary Care, Universitair Medisch Centrum, UMC Utrecht, Utrecht, The Netherlands; Aldo Skabar, Institute for Maternal and Child Health, IRCCS, Burlo Garofolo, Trieste, Italy; Marc Spaanderman, Department of Obstetrics, Maastricht University Medical Center, Maastricht, The Netherlands; Nynke Weisglas–Kuperus, Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; Andrea Zimmermann, Paediatrics, Technical University, Munich, Germany.

Study monitoring committee

Jim Thornton, Division of Child Health Obstetrics and Gynaecology, School of Medicine, University of Nottingham, Nottingham, UK; John Kingdom, University of Toronto and Mount Sinai Hospital, Toronto, Canada; Herbert Valensise, University of Rome Tor Vergata, Rome, Italy; Karel Marsal, Lund University, Lund, Sweden.

REFERENCES

1. Visser GH, Bekedam DJ, Ribbert LS. Changes in antepartum heart rate patterns with progressive deterioration of the fetal condition. *Int J Biomed Comput* 1990; **25**: 239–246.
2. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackeloer BJ, Kok HJ, Senat MV, Visser GH. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. *Ultrasound Obstet Gynecol* 2001; **18**: 564–570.
3. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015; **385**: 2162–2172.
4. Dawes GS, Moulden M, Redman CW. Short-term fetal heart rate variation, decelerations, and umbilical flow velocity waveforms before labor. *Obstet Gynecol* 1992; **80**: 673–678.
5. Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. *Ultrasound Obstet Gynecol* 1995; **6**: 168–174.
6. Mulder EJ, Derks JB, Zonneveld MF, Bruinse HW, Visser GH. Transient reduction in fetal activity and heart rate variation after maternal betamethasone administration. *Early Hum Dev* 1994; **36**: 49–60.
7. Verdurmen KM, Renckens J, van Laar JO, Oei SG. The influence of corticosteroids on fetal heart rate variability: a systematic review of the literature. *Obstet Gynecol Surv* 2013; **68**: 811–824.
8. Visser GH, Sadovsky G, Nicolaides KH. Antepartum heart rate patterns in small-for-gestational-age third-trimester fetuses: correlations with blood gas values obtained at cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 698–703.
9. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses. *Br J Obstet Gynaecol* 1991; **98**: 820–823.
10. Flynn AM, Kelly J, O'Conor M. Unstressed antepartum cardiotocography in the management of the fetus suspected of growth retardation. *Br J Obstet Gynaecol* 1979; **86**: 106–110.
11. Varma TR. Unstressed antepartum cardiotocography in the management of pregnancies complicated by intrauterine growth retardation. *Acta Obstet Gynecol Scand* 1984; **63**: 129–134.
12. Ribbert LS, Visser GH, Mulder EJ, Zonneveld MF, Morssink LP. Changes with time in fetal heart rate variation, movement incidences and haemodynamics in intrauterine growth retarded fetuses: a longitudinal approach to the assessment of fetal well being. *Early Hum Dev* 1993; **31**: 195–208.
13. Snijders RJ, Ribbert LS, Visser GH, Mulder EJ. Numeric analysis of heart rate variation in intrauterine growth-retarded fetuses: a longitudinal study. *Am J Obstet Gynecol* 1992; **166**: 22–27.

