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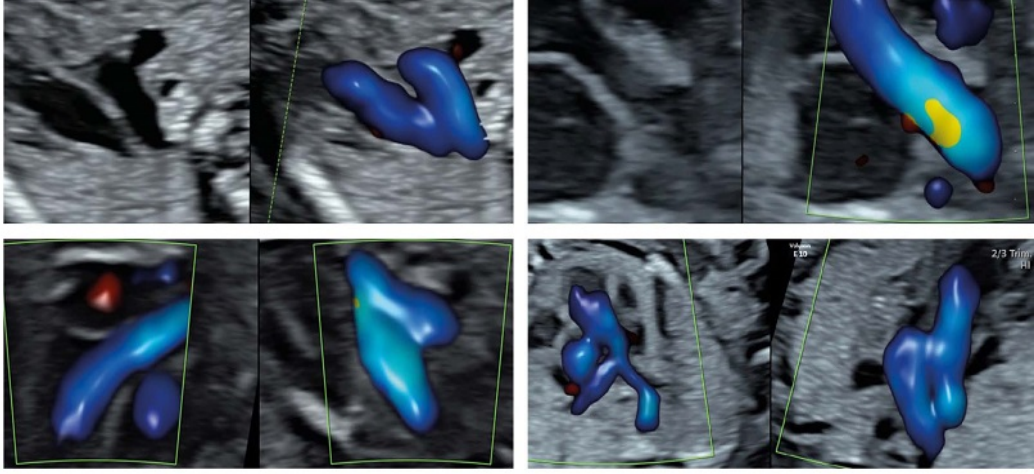

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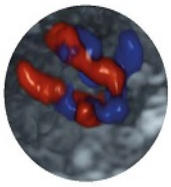

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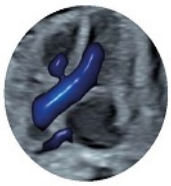

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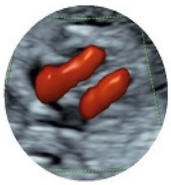

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Computerized fetal heart rate analysis in early preterm fetal growth restriction

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KEYWORDS: cardiotocography; fetal death; fetal growth restriction; preterm; short-term fetal heart rate variability

CONTRIBUTION

What are the novel findings of this work?
A highly abnormal computerized cardiotocography (cCTG) recording (short-term variability (STV) < 2.6 ms before 29 weeks' gestation and < 3.0 ms thereafter, and/or recurrent fetal heart rate decelerations), in combination with high umbilicocerebral ratio or umbilical absent or reversed end-diastolic flow, was associated with fetal death and neonatal asphyxia, but not with major neonatal morbidity and 2-year neurodevelopmental outcome. A strategy using a strict schedule of cCTG recordings and fetal arterial Doppler could detect all fetal deaths.

What are the clinical implications of this work?
In early preterm fetal growth restriction, application of a strict management strategy using computerized fetal heart rate analysis (STV) and fetal arterial Doppler with strict criteria for intervention could improve perinatal outcome.

ABSTRACT

Objective *To assess the value of computerized cardiotocography (cCTG) with calculation of fetal heart rate (FHR) short-term variability (STV) in early preterm fetal growth restriction (FGR) for prevention of fetal death and neonatal asphyxia, neonatal morbidity, and 2-year neurodevelopmental impairment.*

Methods *This was a retrospective cohort study of all women who were admitted to the Amsterdam University Medical Center-AMC between 2003 and 2015 due to FGR and/or pre-eclampsia, and who were delivered by prelabor Cesarean section, or had a fetal death, before 32 weeks' gestation. STV of all available cCTG registrations during the 5 days preceding fetal death or delivery was calculated retrospectively, and FHR decelerations were classified visually as absent, 1–2/h or recurrent (> 2/h). Adverse outcome endpoints were defined as fetal death, neonatal asphyxia at birth (including fetal death), neonatal death, major neonatal morbidity and 2-year neurodevelopmental outcome. A simulation analysis was performed to assess the incidence of adverse outcome using two thresholds for cCTG: (1) highly abnormal (STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or recurrent FHR decelerations); and (2) moderately abnormal (STV < 3.5 ms before 29 weeks and < 4.0 ms thereafter, and/or recurrent FHR decelerations). Three management strategies were assessed using a strict schedule for the frequency of cCTG recordings: (1) cCTG without use of fetal arterial Doppler; (2) cCTG with additional fetal arterial Doppler after 29 weeks; and (3) cCTG with additional fetal arterial Doppler after 27 weeks.*

Results *Included were 367 pregnancies (3295 cCTG recordings), of which 20 resulted in fetal death and 347 were delivered by Cesarean section before the onset of labor. Cesarean delivery was indicated by fetal condition in 94% of cases and by maternal condition in 6%. Median gestational age at delivery was 30 (interquartile range (IQR), 28–31) weeks and median birth weight was 900 (IQR, 740–1090) g. Six cases of fetal death were not anticipated by standard practice using visual assessment of CTG. A last highly abnormal cCTG was associated with fetal death and with neonatal asphyxia (including fetal death;* n = *99), but not with major neonatal morbidity and 2-year neurodevelopmental outcome. Moderately abnormal cCTG had no significant association with any endpoint. Simulation analysis showed that a strategy that*

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combined cCTG results with umbilicocerebral ratio or umbilical absent or reversed end-diastolic flow could detect all fetal deaths.

Conclusions *Computerized CTG in combination with fetal arterial Doppler, with a strict protocol for the frequency of recordings, is likely to be more effective than visual CTG assessment for preventing fetal death in early preterm FGR.*

INTRODUCTION

Fetal growth restriction (FGR) in the early preterm period is a rare but serious condition. It is associated with increased perinatal mortality and morbidity and an increased risk of later neurodevelopmental impairment. Management consists of fetal monitoring and timed delivery when it appears that the fetus no longer benefits from prolongation of intrauterine stay[1].

Fetal monitoring generally consists of measurement of fetal arterial and venous Doppler profile, ultrasound biometry and cardiotocography (CTG). There is no consensus on which modalities to use, at which cut-off levels delivery is indicated and if gestational age should be incorporated in a decision model. Some clinicians depend mostly on arterial Doppler and indicate delivery when umbilical end-diastolic flow is absent or reversed (ARED flow)[2]. Others recommend the use of computerized CTG (cCTG) analysis with calculation of fetal heart rate (FHR) short-term variability (STV), combined with ductus venosus (DV) pulsatility index (PI)[3].

A secondary, longitudinal analysis of cCTG recordings obtained in the Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) study showed that cCTG changes usually occurred unexpectedly within a short time. For each day of pregnancy prolongation, there was a 5% risk that the safety-net criteria for delivery (very low STV on cCTG and/or recurrent FHR decelerations) were surpassed in pregnancies with early FGR[3,4]. In this study, no association was found between cCTG and neonatal asphyxia at birth, morbidity or 2-year neurodevelopmental outcome.

We hypothesized that the main purpose of cCTG is to prevent fetal death by indicating timely delivery, and that a very low cut-off for cCTG (STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or the presence of recurrent FHR decelerations) appeared safe for clinical application in early preterm FGR, preferably in combination with DV-PI measurement. The objective of the current study was to test this hypothesis in an extended population of women with early preterm FGR.

METHODS

This retrospective study included all women who were admitted between 2003 and 2015 to the Amsterdam University Medical Centre-AMC, Amsterdam, The Netherlands because of early-onset FGR and/or pre-eclampsia and who were delivered by prelabor Cesarean section, or had fetal death, before 32 weeks of gestation.

FGR was defined as estimated fetal weight below the 10th centile and umbilical artery Doppler PI higher than the 95th centile, based on a recent consensus definition for early preterm FGR[5]. Percentiles and *Z*-scores for fetal weight, birth weight and Doppler parameters were calculated according to reference values from previous studies[6,7]. Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) consensus[8].

As long as fetal and maternal condition were deemed acceptable, management of pre-eclampsia generally followed a temporizing approach. Preferred antihypertensive drugs were methyldopa, nifedipine and labetalol. Magnesium sulfate was used in clinical pre-eclampsia only for the prevention of seizures. Administration of magnesium sulfate for neuroprophylaxis for the neonate was not standard practice during the study period. A single course of corticosteroids was generally given to improve fetal maturation. cCTGs were categorized according to whether they were recorded without exposure to corticosteroids, or < 2 days, 2–3 days or ≥ 4 days after administration of corticosteroids.

Fetal monitoring was by arterial Doppler assessment once or twice a week and CTG with visual assessment once or twice a day, depending on the fetal condition. In cases of abnormal CTG, assessment was often repeated after a short time to check consistency. Obstetric management was overseen by perinatologists, using visual assessment of CTG. cCTG and DV-PI were used only in women who participated in the TRUFFLE study[3]. We analyzed TRUFFLE participants separately.

CTGs were registered using Philips series 50A or M1350A (Philips Healthcare, Amsterdam, The Netherlands) machines. The files were stored digitally on a server, using Mosos CTG monitoring and archiving software (BMA Health Care Solutions, Houten, The Netherlands). For this study, all CTGs recorded during the last 5 days before fetal death or delivery, with a duration of at least 20 min, were analyzed *post hoc* using STVcalc[9]. STVcalc is locally developed software for FHR analysis, based on literature description of FetalCare (Huntleigh Healthcare, Cardiff, UK), with similar test performance[10–13]. The software code of STVcalc is available from GitHub (https://github.com/hwolf46), a repository for freeware and host for collaborating not-for-profit software developers. Because the software is not reliable for exact recognition of FHR decelerations, we classified decelerations visually as either absent, 1–2 decelerations/h or > 2 decelerations/h.

The following outcome parameters were used for analysis: antenatal death, neonatal asphyxia at birth, neonatal death, major neonatal morbidity and 2-year infant neurodevelopment.

Antenatal death could be unexpected, or anticipated in cases in which it was decided not to deliver the baby by Cesarean delivery when fetal condition was assessed as abnormal. This could be decided, after counseling and

discussion with the parents, if the likelihood of healthy survival was estimated to be low, based on poor fetal condition, gestational age and estimated fetal weight, or if the parents declined intervention.

Neonatal asphyxia was defined as 5-min Apgar score < 5 if delivery was before 29 weeks and < 7 if delivery was after 29 weeks, an arterial umbilical pH < 7.1 or a venous pH < 7.2, need for resuscitation after birth by intubation or cardiac compressions, or fetal death. The pH values are approximately 2 SDs below the mean in an average population[14,15]. All liveborn neonates were delivered by Cesarean section before the onset of labor. We assumed that, in this selected population, fetal death and neonatal asphyxia at birth were similarly caused by placental insufficiency and supply shortage, but only differed in severity of clinical expression. Therefore, for the purposes of this study, we evaluated asphyxia at birth in conjunction with fetal death.

Major neonatal morbidity was defined as intraventricular hemorrhage Grade 3 or 4[16], periventricular leukomalacia Grade 2 or 3[17], moderate or severe bronchopulmonary dysplasia[18], sepsis or meningitis with microbiological confirmation, or necrotizing enterocolitis Grade 2 or 3[19].

As part of the routine follow-up of early preterm-born infants, a physical examination was performed at the corrected age of 2 years and development was assessed using the Bayley II or Bayley III Scales of Infant and Toddler Development[20]. In cases that had a Bayley-II assessment, the scale was adjusted by adding 10 points to the mental development index (MDI) and the psychomotor development index (PDI)[21]. Motor behavior was assessed using the Touwen Infant Neurological Examination for the age of 2 years[22]. Infants had a formal neurological examination to establish the presence of cerebral palsy. The functional severity of cerebral palsy was scored using the Gross Motor Function Classification System (GMFCS)[23].

Neurodevelopmental impairment was defined as a Bayley-III score or corrected Bayley-II MDI score or PDI score of < 85 or cerebral palsy, with a GMFCS of more than Grade 1, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted), or an abnormal Touwen score.

We performed a simulation analysis to determine if the use of cCTG could have improved perinatal or 2-year infant outcome in our population. For this assessment, two cCTG cut-offs were applied that had been used as thresholds for delivery in the TRUFFLE study[3]. The first threshold ('highly abnormal') was defined as a STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter. The second threshold ('moderately abnormal') was determined by a STV < 3.5 ms before 29 weeks and < 4.0 ms thereafter. Presence of recurrent FHR decelerations was also a safety-net criterion for delivery, irrespective of STV or gestational age. The frequency of recurrent decelerations was not defined in the TRUFFLE study. For the current analysis, we defined recurrent FHR decelerations as a frequency of more than two decelerations per hour.

We analyzed outcomes of both thresholds in women who never passed these thresholds for abnormality of cCTG, and in women who had a first abnormal cCTG < 24 h and in those with first abnormal cCTG ≥ 24 h before fetal death or delivery. Similarly, we analyzed women with an abnormal last cCTG and those with abnormal last two to three cCTGs before fetal death or delivery.

To test associations with fetal death, asphyxia, severe morbidity or neurodevelopmental impairment at 2 years, we performed a stepwise logistic regression analysis. Parameters were pre-eclampsia (yes/no), participation in the TRUFFLE study (yes/no), last cCTG highly abnormal (yes/no), STV on last cCTG, umbilical artery ARED flow on last Doppler assessment (yes/no), last umbilical artery PI /cerebral artery PI ratio (UCR) *Z*-score, gestational age at fetal death or delivery, and birth-weight *Z*-score.

In a simulation analysis, we evaluated three monitoring strategies to see if, in comparison with standard management during the study period, these might have changed perinatal or 2-year outcome. A requirement for all three strategies is that cCTG should be registered at least daily. If STV is moderately low (< 3.5 ms before 29 weeks and < 4.0 ms thereafter) the cCTG frequency should be increased to twice daily.

(1) Strategy A: cCTG only. Before 29 weeks' gestation, if highly abnormal cCTG (STV < 2.6 ms and/or recurrent FHR decelerations) is noted, the assessment should be repeated within 8 h. If cCTG is highly abnormal again, then delivery is indicated; otherwise cCTG should be repeated every 8 h. Recurrent highly abnormal cCTG indicates delivery. After 29 weeks' gestation, a highly abnormal cCTG (STV < 3.0 ms and/or recurrent FHR decelerations) at one timepoint indicates delivery.
(2) Strategy B: cCTG with additional Doppler after 29 weeks. Before 29 weeks' gestation, if highly abnormal cCTG (STV < 2.6 ms and/or recurrent FHR decelerations) is noted, the assessment should be repeated within 8 h. If cCTG is highly abnormal again, then delivery is indicated; otherwise cCTG should be repeated every 8 h. Recurrent highly abnormal cCTG indicates delivery. After 29 weeks' gestation, a highly abnormal cCTG (STV < 3.0 ms and/or recurrent FHR decelerations) at one timepoint *or* an abnormal cCTG (STV < 4.0) with a highly abnormal Doppler (ARED flow in the umbilical artery or UCR *Z*-score > 3) indicates delivery.
(3) Strategy C: cCTG with additional Doppler after 27 weeks. Before 29 weeks' gestation a highly abnormal cCTG (STV < 2.6 ms and/or recurrent FHR decelerations) *and* a highly abnormal Doppler (ARED flow in the umbilical artery or UCR *Z*-score > 3) indicates delivery. However, before 27 weeks' gestation both findings should be confirmed a second time within 8 h before intervention. If the findings are highly abnormal again, then delivery is indicated; otherwise cCTG should be repeated every 8 h. Recurrent highly abnormal cCTG indicates delivery. After 29 weeks' gestation, a highly abnormal cCTG (STV < 3.0 ms

and/or recurrent FHR decelerations) at one timepoint *or* an abnormal cCTG (STV < 4.0) with a highly abnormal Doppler (ARED flow in the umbilical artery or UCR *Z*-score > 3) indicates delivery.

We compared outcomes for these strategies between (1) women who never met the criteria; (2) women who met the criteria and were delivered within 8 h, or had follow-up measurement within the prescribed time interval; and (3) women who met the criteria and were delivered later than 8 h after the diagnostic criteria were below threshold, or did not have timely follow-up measurement.

To assess if short- and long-term outcomes changed over time, we divided the study period into four equal parts, each with a duration of 3 years 3 months, for outcome analysis.

Statistical analyses were performed using IBM SPSS statistics version 25 (IBM Corp., Armonk, NY, USA). Analysis was by Fisher's exact test, Mann Whitney *U*-test, or forward stepwise logistic regression analysis with a probability limit for entry set at 0.10.

Medical ethical approval was not required as this was an anonymous retrospective quality evaluation of data from women who had been treated in our center. All data were anonymized before analysis.

RESULTS

We included 367 women who had a total of 3295 cCTG recordings during the last 5 days before fetal death or delivery. Demographic and obstetric details of the study population are presented in Table 1. The number of cCTGs per woman during the last 5 days before fetal death or delivery varied between 1 and 20 (median, 10 (interquartile range (IQR), 6–13)). The median cCTG duration was 64 (IQR, 45–95) min and the median interval between cCTGs was 10 (IQR, 6–14) h.

The median STV of all cCTGs was 4.1 (IQR, 3.2–5.3) ms. One to two FHR decelerations per hour were noted in 1042 (32%) cCTGs and > 2 decelerations/h in 322 (10%), while prolonged deceleration (bradycardia) > 5 min was observed in 10 cCTGs and a sinusoid pattern (detected by STVcalc) in one. STV was below the very low cut-off (2.6 ms before 29 weeks and 3.0 ms thereafter) in 455 (14%) cCTGs and below the low cut-off (3.5 ms before 29 weeks and 4.0 ms thereafter) in 1311 (40%). We classified 693 (21%) cCTGs as 'highly abnormal' due to a STV below the very low cut-off and/or recurrent FHR decelerations (> 2/h) and 1311 (40%) as 'moderately abnormal' due to a STV below the low cut-off and/or recurrent FHR decelerations.

Fetal death

Fetal death occurred in 20 (5%) pregnancies. This was anticipated in 14 women who decided, after extensive multidisciplinary discussion, to abstain from intervention due to the anticipated low chance of intact infant survival.

Table 1 Demographic and perinatal characteristics of 367 pregnancies with early-onset fetal growth restriction and/or pre-eclampsia that had fetal death or prelabor Cesarean delivery before 32 weeks' gestation

Variable	*Value*
Nulliparous	232 (63)
GA at hospital admission (weeks)	27.9 (26.6–29.3)
Duration of antenatal hospitalization (days)	8 (4–16)
Pre-eclampsia	289 (79)
Antihypertensive medication	250 (68)
Corticosteroids for fetal maturation	
Started < 2 days before birth	58 (16)
Started 2–3 days before birth	95 (26)
Started ≥ 4 days before birth	200 (55)
None	14 (4)
Participation in TRUFFLE study	61 (17)
Last fetal assessment	
Umbilical artery ARED flow	153 (42)
UCR*	1.4 (1.1–2.1)
UCR *Z*-score*	3.2 (1.7–5.8)
FHR-STV (ms)	3.1 (2.4–3.9)
Highly abnormal cCTG†	241 (66)
Moderately abnormal cCTG‡	307 (84)
Male sex	169 (46)
Fetal death	20 (5)
Live birth	347 (95)
Indication for Cesarean delivery	
Fetal distress	325/347 (94)
Maternal condition	22/347 (6)
GA at delivery (weeks)	29.6 (28.3–30.7)
Birth weight (g)	900 (740–1090)
Birth weight < 10th percentile	358 (98)
Birth-weight *Z*-score	−3.5 (−4.2 to −2.8)
5-min Apgar score < 5 at < 29 weeks or < 7 at ≥ 29 weeks	19/347 (6)
Low pH (arterial < 7.1 or venous < 7.2)§	49/207 (24)
Asphyxia at birth¶	79/347 (23)
Major neonatal morbidity	149/347 (43)
Cerebral abnormality	17/347 (5)
Bronchopulmonary dysplasia	47/347 (14)
Necrotizing enterocolitis or sepsis/meningitis	127/347 (37)
Neonatal death ≤ 4 weeks of age	29/347 (8)
Late death (> 4 weeks and < 2 years of age)	11/347 (3)
Follow-up at 2 years of corrected age	240/307 (78)
Neurodevelopmental impairment	37/240 (15)

Data are given as *n* (%), median (interquartile range) or *n*/*N* (%). *Data available for 322 pregnancies (data on fetal middle cerebral artery pulsatility index missing in *n* = 45). †Highly abnormal cCTG considered as STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or recurrent (> 2/h) FHR decelerations. ‡Moderately abnormal cCTG considered as STV < 3.5 ms before 29 weeks and < 4.0 ms thereafter, and/or recurrent (> 2/h) FHR decelerations. §Data available for 207 infants. ¶Low 5-min Apgar score, low arterial or venous pH, or need for resuscitation after birth. ARED, absent or reversed end-diastolic; cCTG, computerized cardiotocography; FHR, fetal heart rate; GA, gestational age; STV, short-term variation; TRUFFLE, Trial of Randomized Umbilical and Fetal Flow in Europe[3]; UCR, umbilicocerebral ratio (umbilical artery pulsatility index/fetal middle cerebral artery pulsatility index).

In six women fetal death occurred unexpectedly notwithstanding regular monitoring. The details of all fetal deaths are presented in Table 2. Four of the six women with unexpected fetal death had a very low STV and/or recurrent FHR decelerations 13–24 h before confirmation of fetal death. One woman had a normal cCTG 26 h prior to fetal death, but did not have cCTG thereafter although four earlier cCTGs were highly abnormal. One woman had a normal cCTG 15 h before the diagnosis of fetal death, which was not repeated thereafter although UCR *Z*-score was very high (3.2). All pregnancies with anticipated fetal death had a highly abnormal cCTG between 1 and 83 h before fetal death, and 10 of them had a highly abnormal cCTG recurrently. Women with fetal death, compared with those with a liveborn infant, had a higher UCR *Z*-score, delivered at a lower gestational age and their babies had a lower birth weight (Table 3).

Three-hundred women (82%) had a highly abnormal cCTG at least once after inclusion (Table 3). In 238 (79%) of these, there was at least one earlier normal cCTG recorded before the first highly abnormal cCTG. The median time interval between a normal cCTG and a first highly abnormal cCTG was 10 (IQR, 7–15) h. In 114 (38%) pregnancies that were delivered within 8 h after the first highly abnormal cCTG, there was no fetal death and neonatal death occurred in 10%. However, in 55 (18%) women who were delivered between 8 and 24 h after the first highly abnormal cCTG, fetal death rate was 13% and the rate of neonatal mortality was 9%. In the 131 (44%) women who delivered more than 24 h after the first highly abnormal cCTG, fetal death rate was 9% and neonatal mortality occurred in 13%. The proportion of unexpected and anticipated fetal deaths was similar in both delayed time epochs. Overall, a first highly abnormal cCTG had a relative risk (RR) of 3.8 (95% CI, 0.5–28.3; $P = 0.14$; sensitivity, 95%; specificity, 18%) for fetal death and the risk of fetal death after 8 h was approximately 10%.

Two hundred and forty-one (66%) out of all pregnancies had a highly abnormal last cCTG (Table 3). The RR for fetal death after a last highly abnormal cCTG was 4.5 (95% CI, 1.1–19.0; $P = 0.02$; sensitivity, 90%; specificity, 35%).

Table 2 Computerized cardiotocography (cCTG) and Doppler findings in 20 pregnancies with early-onset fetal growth restriction and/or pre-eclampsia that resulted in fetal death

	Last cCTG			*Previous cCTG*			*Highly abnormal*	*Last Doppler*						
Case	*STV (ms)*	*Decel/ h*	*Interval to death (h)*	*STV (ms)*	*Decel/ h*	*Interval to death (h)*	*earlier cCTG* (n)	*UCR*	*UCR Z-score*	*UA ARED flow*	*GA at death (weeks)*	*Birth weight (g)*	*Birth-weight Z-score*	*Comment*
Unexpected fetal death														
1	4.1	1–2	***26***	3.5	0	41	***4***	0.64	0.1	No	29.6	1090	−2.7	Long delay after last cCTG
2	4.7	1–2	15	3.9	1–2	24	—	1.48	3.2	No	29.4	1045	−2.9	
3	***2.9***	1–2	24	3.6	1–2	42	—	2.3	6.5	Yes	29.1	780	−4.8	Long delay after last cCTG
4	***2.6***	***> 2***	13	4.6	***> 2***	24	—	3.5	10.8	Yes	29.1	880	−3.8	
5	3.2	***> 2***	16	—	—	—	—	2.1	5.8	Yes	29.1	690	−4.7	First cCTG performed shortly after admission
6	—	***Long***	0	***2.7***	0	17	***1***	1.1	1.8	No	31.3	910	−4.5	Persistent bradycardia on last cCTG; emergency Cesarean section; stillbirth
Anticipated fetal death (no intervention)														
7	3.3	***> 2***	1	***1.8***	***> 2***	23	***1***	1.1	1.9	No	26.5	700	−3.6	
8	***2.4***	1–2	10	***2.2***	1–2	38	—	0.7	0.2	No	25.9	665	−2.9	
9	***1.3***	1–2	14	***2.0***	1–2	34	—	4.7	15.4	Yes	26.6	580	−4.3	
10	8.3	***> 2***	14	5.6	0	22	—	—	—	—	29.4	1400	−0.5	Abruption
11	5.8	***> 2***	33	5.9	***> 2***	39	***1***	1.2	2.1	No	30.0	645	−5.7	Abruption
12	5.5	***Sinus***	14	4.9	***> 2***	17	—	—	—	—	27.5	1000	−1.1	Abruption, cCTG sinusoid pattern
13	***1.9***	1–2	12	***2.1***	***> 2***	15	—	3.8	12.2	Yes	27.3	755	−3.4	
14	***2.0***	0	14	***1.7***	0	63	***2***	1.7	4.0	No	27.9	660	−4.4	
15	***2.3***	***> 2***	16	***1.7***	***> 2***	63	—	5.1	17.1	Yes	27.0	665	−3.9	
16	***2.5***	***> 2***	15	4.3	1–2	131	—	7.7	26.6	Yes	26.7	555	−4.8	
17	2.9	***> 2***	12	***2.2***	***> 2***	30	***1***	6.7	22.7	Yes	28.0	535	−5.7	
18	***1.5***	0	23	***2.4***	0	49	–	4.8	15.8	Yes	26.8	560	−4.6	
19	***1.2***	1–2	83	2.8	1–2	207	***1***	3.0	9.2	Yes	28.1	620	−5.0	
20	***1.7***	***> 2***	12	—	—	—	—	4.0	12.7	Yes	25.9	530	−4.7	

cCTG results are indicated in bold italic if highly abnormal (i.e. STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or > 2 Decel/h). ARED, absent or reversed end-diastolic; Decel, fetal heart rate decelerations; GA, gestational age; STV, short-term variation; UA, umbilical artery; UCR, umbilicocerebral ratio (umbilical artery pulsatility index/fetal middle cerebral artery pulsatility index).

Nearly all women (344/367; 94%) had a moderately abnormal cCTG at least once after inclusion, or a moderately abnormal last cCTG (84%) (Table 3). Moderately abnormal cCTG had no predictive value for fetal death.

Asphyxia

Ninety-nine (27%) neonates were asphyxiated at birth or stillborn. These pregnancies had more often a (recurrent) highly abnormal cCTG, and had lower gestational age at delivery/death than babies born in normal condition (Table 3). The RR of a highly abnormal last cCTG for fetal death or asphyxia at birth was 2.1 (95% CI, 1.3–3.2) and that of a moderately abnormal last cCTG was 4.8 (95% CI, 1.6–14.6).

Morbidity and long-term outcome

Major neonatal morbidity occurred in 149 (41%) infants. No differences were observed between cCTGs of infants with and those without major morbidity (Table 3). However, in infants with major morbidity, compared with those without, umbilical artery ARED flow was observed more often, UCR *Z*-score on last Doppler examination was higher, and gestational age at delivery, birth weight and birth-weight *Z*-score were lower. In neonates who died ($n = 40$; 11%) these parameters were more abnormal in comparison with surviving neonates. Follow-up at the corrected age of 2 years was available in 240 infants (78% of surviving infants). In 37 of the 240 examined infants (15%), development was classified as abnormal. Infants with abnormal neurodevelopmental outcome at 2 years had similar cCTG classification but had more often umbilical ARED flow, a lower gestational age at delivery, and lower birth weight and birth-weight *Z*-score compared with infants with normal 2-year neurodevelopmental outcome (Table 3).

Corticosteroids

Fourteen women did not receive corticosteroids; in six, this was due to anticipated fetal death and in eight because, shortly after arrival, an abnormal cCTG

Table 3 Incidence of fetal or neonatal short- and long-term outcomes according to recording of highly abnormal computerized cardiotocography (cCTG) (short-term variation (STV) < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or recurrent (> 2/h) fetal heart rate (FHR) decelerations), moderately abnormal cCTG (STV < 3.5 ms before 29 weeks and < 4.0 ms thereafter, and/or recurrent (> 2/h) FHR decelerations), Doppler indices, inclusion in Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study, gestational age at birth and birth weight, in pregnancies with early-onset fetal growth restriction and/or pre-eclampsia

Parameter	*Antenatal death* (n = *20*)	*Asphyxia at birth (incl. antenatal death)* (n = *99*)	*Major neonatal morbidity* (n = *149*)	*Neonatal death* (n = *40*)	*Neurodevelopmental impairment at 2 years* (n = *37*)	*All* (n = *367*)
Highly abnormal cCTG						
Never	1 (5)	12 (12)	28 (19)	6 (15)	8 (22)	67 (18)
First > 24 h before delivery/death	12 (60)*	36 (36)	53 (36)	17 (43)	13 (35)	131 (36)
First < 24 h before delivery/death	7 (35)*	51 (52)*	68 (46)	17 (43)	16 (43)	169 (46)
Last cCTG	18 (90)*	79 (80)*	99 (66)	30 (75)	23 (62)	241 (66)
Last 2–3 cCTGs	12 (60)*	49 (50)*	60 (40)	18 (45)	18 (49)	135 (37)
Moderately abnormal cCTG						
Never	0 (0)	3 (3)	9 (6)	1 (3)	5 (14)	23 (6)
First > 24 h before delivery/death	13 (65)	57 (58)	99 (66)	29 (73)	22 (60)	237 (65)
First < 24 h before delivery/death	7 (35)	39 (39)	41 (28)	10 (25)	10 (27)	107 (29)
Last cCTG	19 (95)	96 (97)*	130 (87)	38 (95)	31 (84)	307 (84)
Last 2–3 cCTGs	14 (70)	73 (74)	103 (69)	34 (85)*	27 (73)	243 (66)
Doppler data						
Last UA ARED flow	11 (55)	37 (37)	80 (54)*	31 (76)*	19 (51)*	153 (42)
Last UCR *Z*-score‡	6.1 (2.1–13.3)*	2.9 (1.6–5.3)	3.8 (1.9–6.9)*	4.8 (3.1–7.5)*	3.5 (2.3–5.3)	3.2 (1.7–5.8)
TRUFFLE participant	2 (10)	14 (14)	23 (15)	3 (8)	5 (14)	61 (17)
Delivery data						
GA at delivery or death (weeks)	27.9 (26.7–29.3)†	29.1 (27.9–30.2)†	28.8 (28.0–29.8)†	28.1 (27.2–28.7)†	29.3 (28.1–30.5)†	29.4 (28.3–30.7)
Birth weight (g)	678 (590–903)†	860 (665–1070)	790 (668–965)†	660 (564–746)†	835 (723–940)†	900 (740–1090)
Birth-weight *Z*-score	−4.3 (−4.7 to −3.0)†	−3.5 (−4.4 to −2.7)	−3.7 (−4.4 to −3.1)†	−4.2 (−4.9 to −3.6)†	−3.9 (−4.6 to −3.3)†	−3.5 (−4.2 to −2.8)

Data are *n* (%) or median (interquartile range). $P < 0.05$ (Pearson chi-square test or Mann–Whitney *U*-test) compared with: *women with normal cCTG/Doppler findings in same column; †women who did not have outcome reported in same column. ‡Data available for 322 pregnancies (data on fetal middle cerebral artery pulsatility index missing in $n = 45$). ARED, absent or reversed end-diastolic; GA, gestational age; incl., including; TRUFFLE, Trial of Randomized Umbilical and Fetal Flow in Europe[3]; UA, umbilical artery; UCR, umbilicocerebral ratio (umbilical artery pulsatility index/fetal middle cerebral artery pulsatility index).

necessitated Cesarean delivery. cCTGs that were recorded 2–3 days after corticosteroid administration ($n = 592$; 18% of all cCTGs) had a median STV of 3.5 (IQR, 2.9–4.5) ms, which was significantly lower than the STV recorded before corticosteroid administration, or the STV recorded during the first 2 days or ≥ 4 days after corticosteroids. STV was similar in these three epochs (before corticosteroids, < 2 days after or ≥ 4 days after) and the overall median was 4.3 (IQR, 3.4–5.4) ms. In the epoch of 2–3 days after corticosteroid administration, STV was more often below the very low threshold (< 2.6 ms before 29 weeks and < 3.0 ms thereafter) than in the other epochs (23% *vs* 11%; chi-square $P < 0.0001$). However, there was no difference between the epochs in the frequency of recurrent FHR decelerations, or in perinatal mortality, neonatal morbidity or infant 2-year neurodevelopmental outcome.

Multivariable analysis

Odds ratios for antenatal death, asphyxia at birth, severe neonatal morbidity, infant death and long-term infant neurodevelopmental outcome were calculated in a logistic regression analysis using the diagnostic parameters (last highly abnormal cCTG, last STV, last UCR *Z*-score, umbilical ARED flow on last Doppler examination), gestational age at fetal death or delivery, birth-weight *Z*-score, pre-eclampsia and TRUFFLE study participation (Table 4). A last highly abnormal cCTG (STV < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or recurrent FHR decelerations) was associated with antenatal death and asphyxia at birth, but not with severe neonatal morbidity, neonatal death, or 2-year neurodevelopment. The likelihood of fetal death was increased when an abnormal UCR *Z*-score was recorded at the last assessment. Gestational age at fetal death or delivery and umbilical artery ARED flow on the last Doppler examination were significantly associated with asphyxia at birth, major neonatal morbidity and neonatal death. A higher birth-weight *Z*-score reduced the risk of neonatal death and 2-year neurodevelopmental abnormality. TRUFFLE study participation was associated with a lower neonatal mortality and a better 2-year neurodevelopmental outcome.

Monitoring-intervention strategies

Evaluation of the three proposed monitoring strategies is shown in Table 5. For all three strategies, no fetal death occurred if the woman was delivered within 8 h after the criteria for delivery were met, or had a timely next cCTG. However, using Strategy A (cCTG only) one fetal death occurred in the group that was treated according to this strategy, but never met the criteria for delivery. Women managed according to the criteria of Strategy B (cCTG with additional Doppler after 29 weeks) and Strategy C (cCTG with additional Doppler after 27 weeks), or who did not pass the criteria for intervention did not have fetal death. Women who were not delivered within 8 h after meeting the criteria for Strategy A, Strategy B and Strategy C were delivered within a median of 37 (IQR, 14–69), 41 (IQR, 16–76) and 43 (IQR, 16–79) h, respectively. The indication for delivery in women who were delivered

Table 4 Multivariable logistic regression analysis for fetal or neonatal short- and long-term outcomes in pregnancies with early-onset fetal growth restriction and/or pre-eclampsia, using parameters pre-eclampsia, Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study participation, last computerized cardiotocography (cCTG) classification, last short-term variation, last umbilicocerebral ratio (UCR) *Z*-score, absent or reversed end-diastolic (ARED) flow in the umbilical artery (UA) on last Doppler examination, gestational age at fetal death or delivery, and birth-weight *Z*-score

Endpoint	P	*Odds ratio (95% CI)*	*AUC (95% CI)*
Antenatal death ($n = 20$)			
Last UCR *Z*-score (per SD)	0.06	1.2 (1.0–1.3)	0.80 (0.67–0.92)
Last cCTG highly abnormal* (yes/no)	0.09	3.7 (0.8–16.5)	
GA at fetal death or delivery (per week)	< 0.0001	0.5 (0.3–0.7)	
Asphyxia at birth (incl. antenatal death) ($n = 99$)			
UA ARED flow on last Doppler (yes/no)	0.07	1.6 (1.0–2.6)	0.65 (0.59–0.72)
Last cCTG highly abnormal* (yes/no)	< 0.0001	2.5 (1.4–4.3)	
GA at fetal death or delivery (per week)	< 0.0001	0.8 (0.7–0.9)	
Major neonatal morbidity ($n = 149$)			
UA ARED flow on last Doppler (yes/no)	0.01	2.0 (1.2–3.2)	0.75 (0.70–0.80)
GA at delivery (per week)	< 0.0001	0.5 (0.4–0.6)	
Neonatal death ($n = 40$)			
UA ARED flow on last Doppler (yes/no)	< 0.0001	3.6 (1.5–8.5)	0.88 (0.82–0.93)
TRUFFLE study participation (yes/no)	0.07	0.3 (0.1–1.1)	
GA at delivery (per week)	< 0.0001	0.4 (0.3–0.6)	
Birth-weight *Z*-score (per SD)	0.01	0.6 (0.4–0.9)	
Neurodevelopmental impairment at 2 years ($n = 37$)			
TRUFFLE study participation (yes/no)	0.09	0.4 (0.1–1.2)	0.70 (0.61–0.79)
GA at delivery (per week)	0.07	0.8 (0.6–1.0)	
Birth-weight *Z*-score (per SD)	< 0.0001	0.5 (0.3–0.8)	

Regression analysis was performed by forward procedure with probability limit for entry set at 0.10. *Highly abnormal cCTG considered as short-term variation < 2.6 ms before 29 weeks and < 3.0 ms thereafter, and/or recurrent (> 2/h) fetal heart rate decelerations. AUC, area under the receiver-operating-characteristics curve; GA, gestational age; incl., including.

Table 5 Simulation analysis of short- and long-term outcome of pregnancies with early-onset fetal growth restriction and/or pre-eclampsia managed according to three monitoring strategies, for women who did not meet the criteria for delivery (criteria not passed), women who met the criteria and were managed in accordance with the strategy indication for a next computerized cardiotocography (cCTG) or delivery within 8 h (in accordance), and those who met the criteria but were not managed in accordance with the strategy (not in accordance)

Strategy	*Time to delivery (h)*	*Antenatal death (n = 20)*	*Asphyxia at birth (incl. antenatal death) (n = 99)*	*Major neonatal morbidity (n = 149)*	*Neonatal death (n = 40)*	*Neurodevelopmental impairment at 2 years (n = 37)*	*All (n = 367)*
Strategy A: cCTG only							
Criteria not passed	—	1 (5)*	12 (12)	28 (19)	6 (15)	8 (22)	67 (18)
In accordance	3 (2–4)	0 (0)*	39 (39)	63 (42)	18 (45)	13 (35)	142 (39)
Not in accordance	37 (14–69)	19 (95)*	48 (49)	58 (39)	16 (40)	16 (43)	158 (43)
Strategy B: cCTG with Doppler after 29 weeks							
Criteria not passed	—	0 (0)*	10 (10)	24 (16)	5 (13)	7 (19)	55 (14)
In accordance	3 (2–4)	0 (0)*	37 (37)	55 (37)	16 (40)	9 (24)	121 (33)
Not in accordance	41 (16–76)	20 (100)*	52 (53)	70 (47)	19 (48)	21 (57)	191 (52)
Strategy C: cCTG with Doppler after 27 weeks							
Criteria not passed	—	0 (0)*	10 (10)	24 (16)	5 (13)	7 (19)	55 (14)
In accordance	3 (2–4)	0 (0)*	32 (32)	45 (30)	13 (33)	4 (11)	106 (29)
Not in accordance	43 (16–79)	20 (100)*	57 (58)	80 (54)	22 (55)	26 (70)	206 (56)

Data are given as median (interquartile range) or *n* (%). *Significant difference between three groups within same strategy ($P < 0.05$, Fisher's exact, Pearson chi-square or Mann–Whitney *U*-test). incl., including.

> 8 h after meeting the criteria was most often fetal condition (89%) and rarely maternal condition (6%), and, in the remaining, induction was due to fetal death (5%). There were no differences in gestational age at delivery or birth-weight *Z*-score between the strategy subgroups (Mann–Whitney *U*-test, data not shown). There were no differences between the three strategies with respect to the other short- and long-term outcomes evaluated.

Outcome change over time

Nearly all anticipated deaths occurred in the first two quarters of the study period (12 of 14; 86%), showing a change in attitude in this respect during the study period. Perinatal mortality remained the same during the study period, varying between 12% and 22% per each quarter of the study period. There were no significant changes in the incidence of asphyxia at birth (without fetal death), major neonatal morbidity or 2-year neurodevelopmental outcome during the study period.

DISCUSSION

This retrospective simulation analysis showed that the use of cCTG with a strict management protocol might prevent most fetal deaths in a population with early preterm FGR. Four unanticipated fetal deaths in this cohort could potentially have been prevented by the use of cCTG analysis and two more might have benefitted from more frequent cCTG assessment. Using UCR or umbilical ARED flow to determine cCTG cut-off levels, as proposed in Strategies B and C, could be even more effective for the prevention of fetal death.

Application of these monitoring strategies would consequently result in earlier delivery with potentially higher preterm-related neonatal morbidity. However, this effect seems negligible, as there was only 1–2 days' difference between the moment that the strategies indicated delivery and the moment of actual delivery in women who were not delivered within 8 h after meeting the strategy criteria. Gestational age at delivery and birth-weight *Z*-score were comparable between women delivered in accordance with a strategy and those who were not.

A further argument to support the use of a strict management protocol with cCTG analysis is that the women who participated in the TRUFFLE study had better outcome than the women managed outside of this trial, using visual assessment of CTG. The TRUFFLE study is the only trial in which women were randomized to monitoring strategies for early preterm FGR with strict criteria for intervention. The study's main outcome was that the risk of neurodevelopmental impairment at 2 years' corrected age in surviving infants was lower when using a management strategy that combines cCTG and DV-PI[3]. It remains uncertain if this improvement was due to the lower cCTG cut-off criteria in the DV-PI groups or the addition of the DV-PI measurement, or a combination of the two.

The most important parameter associated with all outcomes was gestational age at fetal death or delivery (Table 4). This seems to support prolongation of pregnancy; however, such a conclusion would be seriously biased. Gestational age in this study is not an independent parameter, but is determined by the limits of placental supply to the fetus, either resulting in fetal death or causing signs of abnormal fetal condition indicating delivery. Gestational age at fetal death or delivery could be interpreted as a measure of the severity of placental

insufficiency, i.e. the earlier signs of a deterioration of fetal condition occurred, necessitating delivery, the more severe the underlying nutritional supply deficit. Only a few women (6%) were delivered for maternal condition, and in these, gestational age at delivery could also be considered a measure of severity of the disease.

On multivariable logistic regression analysis, a last highly abnormal cCTG was associated with an increased risk for fetal death and also, to a lesser extent, with asphyxia at birth, but not with neonatal morbidity, neonatal death, or long-term neurodevelopmental outcome. This lack of association might be due to the fact that most fetuses ultimately had a highly abnormal cCTG or indicate that a highly abnormal cCTG is not a sign of irreparable fetal damage. A secondary longitudinal analysis of cCTG data from the TRUFFLE study similarly observed no association of low STV and/or recurrent decelerations with short-term or long-term outcome, which supports the second hypothesis[4].

Corticosteroids are suggested to affect FHR variability during the first 3–4 days after administration[24]. A recent study observed that slight decrease in FHR variation after 48–71 h is possible, but concluded that abnormally low values should be considered as a sign of fetal distress[25]. Our findings further support this conclusion. The history of one woman with unexpected fetal death can serve as an example. The patient received corticosteroids at 31 weeks, 3 days before the last cCTG, which in retrospect showed a STV of 2.7 ms without FHR decelerations. The cCTG was accepted as normal based on visual interpretation but 17 h later, at the next cCTG, a terminal bradycardia was registered.

Literature comparing STV with neonatal outcome in FGR is limited. All studies are restricted to short-term outcome, with the exception of a secondary analysis of the TRUFFLE study[3,4]. This study observed no association of cCTG with neonatal asphyxia at birth, morbidity or 2-year neurodevelopmental outcome. One review analyzed seven studies, including 780 women with a STV registration shortly before delivery (mostly by Cesarean section before the onset of labor), using 2×2 tables to calculate test characteristics[26]. A low STV (definition varied from 2.5 to 5.1 ms) had a RR for acidosis (definition varied from 7.0 to 7.25) of 3.3 (95% CI, 2.5–4.2). The wide range of the definitions for STV and pH in this review impedes clinical usefulness. A recent systematic review from our group, targeted on early preterm FGR, included five studies with a total of 387 women who had STV registration shortly before birth[27]. The pooled RR for acidosis (pH < 7.2) after a low STV (< 3.5 ms) was 1.41 (95% CI, 0.63–3.16). These two reviews demonstrate that STV shortly before delivery does not allow a clinically useful prediction of acidosis at birth, which is similar to the findings of the current study.

Most previous studies evaluating the clinical application of cCTG used FetalCare (Huntleigh Healthcare). However, for research purposes FetalCare software has some disadvantages: the analysis time is restricted to 1 h, batch processing is not available, and it works only with its own data acquisition and storage system. STVcalc was previously compared with FetalCare (version 2) and was shown to give similar STV values[9]. STVcalc allows automated assessment of cCTGs and thereby facilitates the processing of a large number of cCTGs as required in this study. When we compared STVcalc with Fetalcare in women with early preterm FGR, in whom FHR decelerations are frequent, it appeared that both programs were not sufficiently reliable for the assessment of decelerations. Therefore, in this study, we classified FHR decelerations visually.

As with all observational studies of diagnostic methods, the results of our study are strongly influenced by clinical management, which is always aimed at improving outcome parameters. Prospective randomized studies are needed to determine how effective the proposed strategies are for prevention of fetal death in early preterm FGR. Randomizing monitoring strategies within one clinic may cause confusion for participating women and staff, and result in protocol violation or failure to randomize. The most realistic approach is a cluster analysis in which centers are randomized. Preferably cCTG should be combined with fetal arterial and venous Doppler.

In conclusion, cCTG in combination with fetal arterial Doppler, with a strict protocol for the frequency of recordings, is likely to be more effective than visual assessment of CTG for preventing fetal death in early preterm FGR.

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