ST ANALYSIS OF THE FETAL ECG

Towards evidence-based intrapartum surveillance

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ST ANALYSIS OF THE FETAL ECG

Towards evidence-based intrapartum surveillance

ST-analyse van het foetale ECG – naar evidence-based intrapartum bewaking
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 20 maart 2012 des middags te 4.15 uur

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te Sittard

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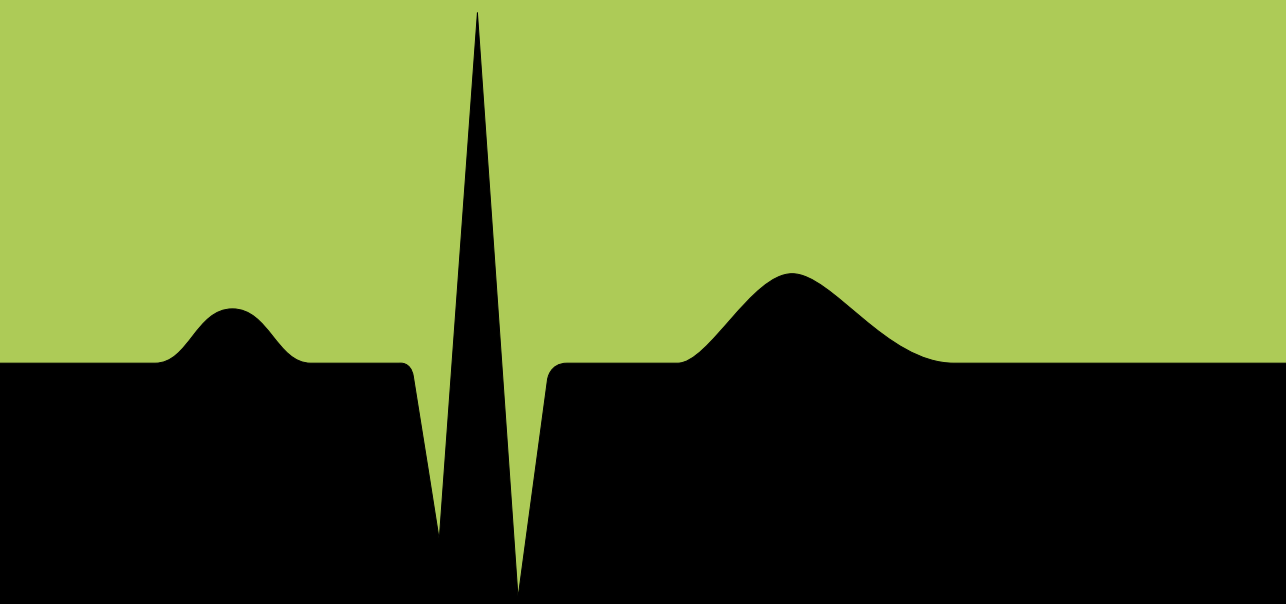
Introduction



Chapter 1

Introduction

Intrapartum fetal monitoring aims to identify the fetus at risk for asphyxia during delivery. Cardiotocography (CTG) was introduced in the 1970s and has been widely applied since. For an intervention so widely applied, it is striking how few trials have been performed to evaluate its efficacy. In 2006 the Cochrane Collaboration performed a meta-analysis on continuous cardiotocography as a form of electronic fetal monitoring, including only twelve trials, with the note that only two trials were of high quality.[1] This meta-analysis showed that continuous CTG during labor was associated with a reduction in neonatal seizures, but no significant differences in cerebral palsy, infant mortality or other standard measures of neonatal well-being, and comes at the costs of an increase in cesarean deliveries and instrumental vaginal births when compared to intermittent auscultation. The poor inter-observer agreement of the CTG classification and the high amount of abnormal CTG patterns during normal delivery are important reasons for the poor predictive ability of fetal monitoring using continuous CTG.[2,3] The CTG therefore seems to behave like a method of screening, and in case of abnormalities of the CTG trace, additional tests should be performed to check the fetal condition. Addition of fetal blood sampling (FBS) to the CTG does result in slightly better results at a lower intervention rate.[4] In view of the above, clinicians have been looking for alternative methods of intrapartum monitoring in search for a better specificity and sensitivity than the CTG could offer. In the 1990s, intrapartum analysis of the fetal ECG (FECG) in combination with conventional CTG was introduced. During labor, a scalp electrode is applied to the fetal head to record and analyze the fetal ECG signals.

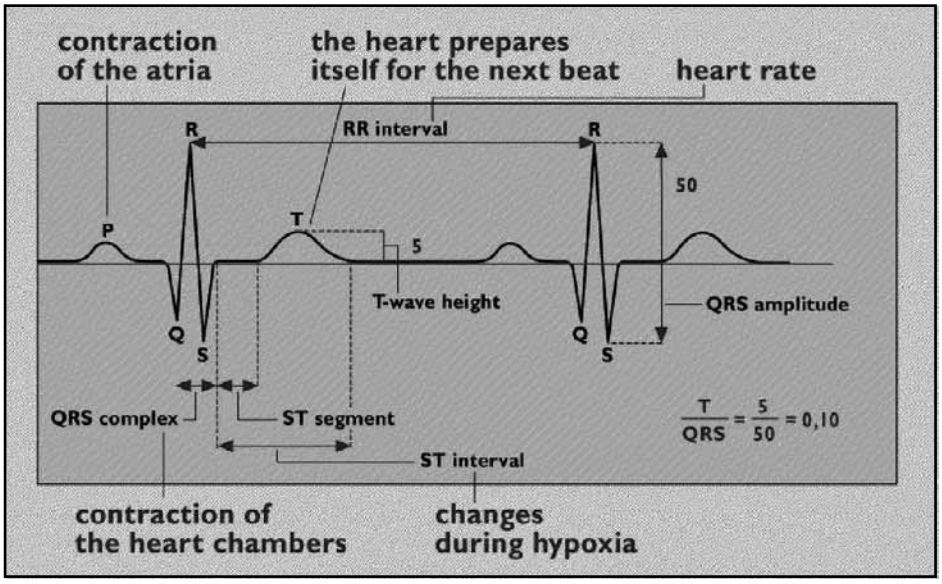


Figure 1: example of a normal ECG complex and calculation of the T-QRS ratio

In the ECG-complex (Figure 1), the P-wave represents the depolarization (pumping) of the upper heart chambers (atria). The QRS-complex represents the depolarization of the lower heart chambers (ventricles). The T-wave represents the repolarization (recovery) of the heart ventricles. When using the FECG during delivery, information is obtained on the amplitude of the T-wave in relation to the amplitude of the QRS complex (T-QRS ratio or T/QRS), and the shape of the ST segment. The ST-analysis (STAN®) concept is based on the association between changes of the ST-interval of the fetal ECG and the function of the fetal myocardium during hypoxia.

The changes in fetal ECG associated with fetal distress are either an increase in T-wave, quantified by the ratio T-wave to QRS-amplitude (T/QRS), or a biphasic ST-segment. An increase in T-wave and subsequently in T/QRS has been associated with a catecholamine surge, activation of ß-adrenoreceptors, myocardial glycogenolysis, and metabolic acidosis.[5] After positive results in animal studies on the identification of hypoxic sheep with this new method[5–7], randomized controlled trials in humans have been conducted to study if intrapartum fetal monitoring using the FECG in combination with conventional cardiotocography was more effective in the prevention of fetal asphyxia than the CTG alone.[8–13] In these studies, STAN clinical guidelines were introduced to help the clinician to interpret ST-waveform analysis. The STAN clinical guidelines link the specific types and heights of ST-events to CTG trace abnormalities and indicate when intervention in labor should be performed to prevent the fetus from being born with asphyxia (Appendix 1). Unfortunately, the results of these trials were not conclusive with regard to the prevention of fetal asphyxia (which was mostly defined as neonatal metabolic acidosis); whereas Amer-Wåhlin et al. found a significant reduction of metabolic acidosis when using STAN[8], this effect lacked significance in two of the other trials.[12,13] The trials of Ojala et al. and Vayssière et al. even found a non-significant opposite effect.[9,11] However, four of five trials found a reduction in operative vaginal deliveries when using STAN with no differences in cesarean delivery rates[8,11–13], and all trials found a reduction in the use of additional fetal blood sampling when using STAN.

After the first trial on the use of fetal ST-analysis during labor, guidelines were made how to use STAN in clinical practice and when ST-events should lead to an obstetric intervention. These guidelines were first used and published by Amer-Wåhlin in 2001.[8] and modified after the publication of three cases of metabolic acidosis despite the use of ST-waveform analysis.[14,15] Together with these modifications, recommendations were made which situations may require additional fetal information, such as additional fetal blood sampling (FBS), when using ST-waveform analysis in order to minimize the number of hypoxic fetuses not detected by ST-changes (Appendix 2). Although the experience with the STAN technology and it's guidelines is increasing year by year, the

guidelines and the recommendations on performing FBS that are currently being used are only partly based on empirical data, and partly based on expert opinion and case publications.

Aims of this thesis

It was the aim of this thesis to perform a meta-analysis of published trials on FECG monitoring during labor, to assess its effects on fetal outcome, on the use of FBS, and on instrumental and operative interventions (Chapter 2). Furthermore we conducted secondary studies of published data sets to address thus far unresolved issues, such as:

- Are the consensus-based recommendations for additional fetal information effective in preventing fetal acidosis (Chapter 4);
- What is the association between the baseline T/QRS of the FECG (i.e. the T/QRS at the beginning of a recording) and fetal outcome (Chapter 5);
- Are biphasic events of the FECG associated with adverse neonatal outcome (Chapter 6);
- What is the effect of maternal fever on the FECG complex (Chapter 7);
- What is the effect of maternal epidural analgesia on the FECG complex (Chapter 8).

To highlight the invasive character of FBS and the possible complications of this diagnostic procedure, we describe a case-report of a neonate born with a cerebrospinal leak due to the performance of fetal blood sampling together with a review of the literature on complications of FBS in Chapter 3.

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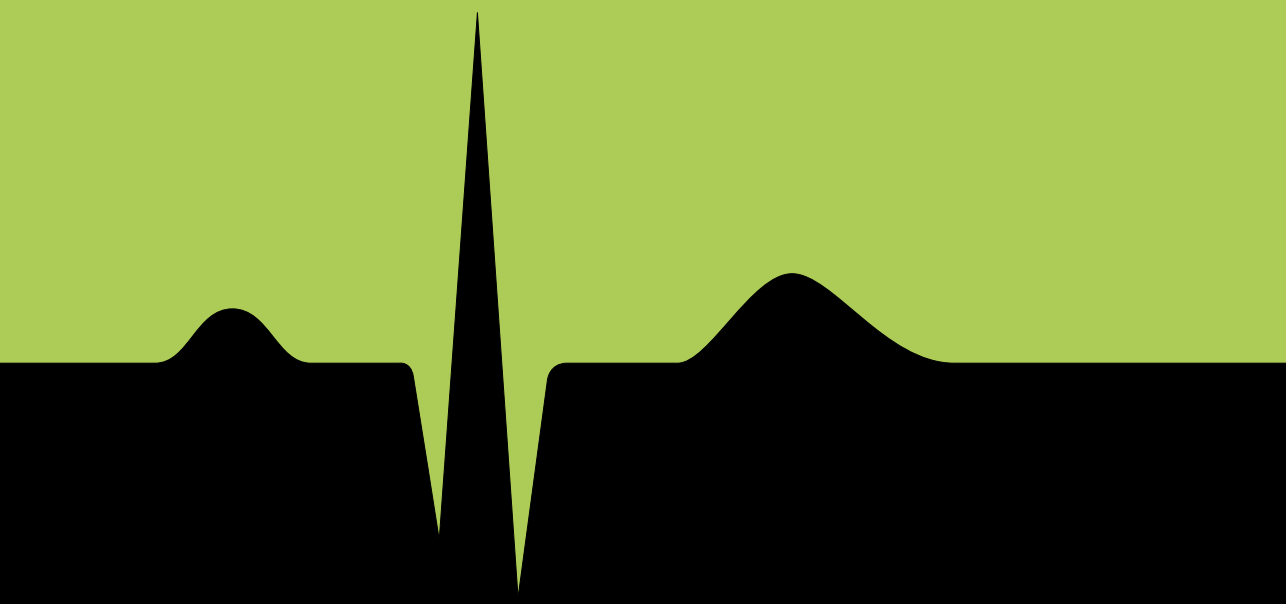
ST analysis of the fetal electrocardiogram in intrapartum fetal monitoring: a meta-analysis



Chapter 2

Jeroen H Becker, Leon Bax, Isis Amer-Wåhlin, Kati Ojala, Christophe Vayssière, Michelle EMH Westerhuis, Ben-Willem J Mol, Gerard HA Visser, Karel Maršál, Anneke Kwee, Karel GM Moons

Abstract

Objective

This study aimed to compare the effects of ST-waveform analysis in combination with cardiotocography (STAN) with conventional cardiotocography (CTG) for intrapartum fetal monitoring.

Data sources

We searched MedLine, Embase and PubMed for randomized controlled trials (RCTs) evaluating ST-waveform analysis for intrapartum fetal monitoring.

Methods of study selection

We identified RCTs that compared ST-waveform analysis and conventional CTG for intrapartum fetal monitoring of singleton pregnancies in cephalic presentation beyond 34 weeks of gestation and evaluating at least one of the following: metabolic acidosis, umbilical cord pH <7.15, umbilical cord pH <7.10, umbilical cord pH <7.05, umbilical cord pH <7.00, Apgar scores below 7 at 5 minutes, admittance to the neonatal intensive care unit, need for intubation, presence of hypoxic ischemic encephalopathy, perinatal death, operative delivery and number of fetal blood samplings. The primary outcomes assessed were metabolic acidosis, defined as umbilical cord pH <7.05 and base deficit >12mmol/L and all-cause operative delivery rate.

Tabulation, integration and results

Five RCTs, which included 15,352 patients, met the selection criteria. Random-effects models were used to estimate the combined risk ratios (RR) of STAN versus conventional CTG. Compared with conventional CTG, STAN showed a non-significant reduction in metabolic acidosis (RR 0.72, 95% CI 0.43-1.19; NNT 357). STAN significantly reduced the incidence of additional fetal blood sampling (RR 0.59, 95% CI 0.44-0.79; NNT 11), operative vaginal deliveries (RR 0.88, 95% CI 0.80-0.97; NNT 64), and total operative deliveries (RR 0.94, 95% CI 0.89-0.99; NNT 64). For other outcomes, no differences in effect were seen between STAN and conventional CTG, or data were not suitable for meta-analysis.

Conclusion

The additional use of ST-analysis for intrapartum monitoring significantly reduced the incidence of operative vaginal deliveries and the need for fetal blood sampling, but did not significantly reduce the incidence of metabolic acidosis at birth.

Introduction

Fetal monitoring during labor aims to identify fetuses at risk of neonatal and long-term injury due to asphyxia. Cardiotocography (CTG) was introduced in the 1960s and is widely applied, despite its poor specificity. The additional use of fetal blood sampling (FBS) improves the specificity to some extent,[1] but this is a time-consuming, invasive procedure, and is not routinely practiced in the majority of western countries. Furthermore, its addition to CTG does not decrease the rate of cesarean deliveries due to suspected fetal distress, nor does it improve long-term neonatal outcome.[1,2] Other tools for fetal surveillance, such as fetal pulse oximetry, have not been successful.[3]

The addition of the fetal electrocardiogram (ECG) to CTG could be helpful in preventing neonatal asphyxia. During labor, a scalp electrode is applied to the fetal head to record and analyze the fetal ECG signals. Information is obtained on the amplitude of the T-wave in relation to the amplitude of the QRS complex (T-QRS ratio), the shape of the ST segment and the length of the PR segment.

Extensive animal experimental research performed in the 1970s showed that changes in the ST interval of the fetal ECG with hypoxia precede the signs of failing cardiovascular function and are contemporaneous with serial changes in the somatosensory-evoked electroencephalogram.[4] In the 1990s, Westgate et al. were the first to design a randomized controlled trial (RCT) on the use of the fetal ECG in intrapartum monitoring.[5] Based on the absolute T/QRS value and CTG classification, the study protocol advised to continue monitoring, perform FBS, or initiate immediate delivery. This technology has been further developed, and more randomized trials have been published since. In one of the trials the PR interval instead of the T-QRS ratio was assessed, but no differences in neonatal outcome were found.[6] Later studies focused on T/QRS changes rather than on absolute values of T/QRS or the PR interval, and described an impact of CTG in combination with ST analysis (STAN) on both metabolic acidosis at birth and neonatal outcome.[7–10]

In 2009, the Cochrane Collaboration published a meta-analysis on fetal ECG for intrapartum fetal monitoring in which most of the abovementioned studies were included, except the recently published and the largest study in this domain by Westerhuis et al.[10,11] In light of this new evidence, we performed a meta-analysis of trials that compared continuous CTG with STAN. Our objective was to quantify the effect of STAN compared with conventional CTG in intrapartum fetal monitoring for a singleton fetus in cephalic position beyond 34 weeks of gestation on both neonatal and maternal outcomes.

Sources

All published randomized trials on STAN versus continuous CTG that included women in labor with a singleton pregnancy in cephalic presentation beyond 34 weeks of gestation were included in this meta-analysis. MedLine, Embase, and PubMed were searched for RCTs published from 1966 until January 2011. No language restrictions were applied. The key words 'fetus', 'electrocardiography', 'cardiotocography', 'fetal heart rate', 'cerebral palsy', 'acidosis', 'fetal hypoxia', 'fetal monitoring', 'blood gas analysis', 'asphyxia neonatorum', 'pregnancy', 'delivery', and 'obstetric' were used in combination with a Cochrane filter for the identification of randomized trials.[12] Appendix 3 provides details of the full search filter. The review protocol was not previously published.

Study selection

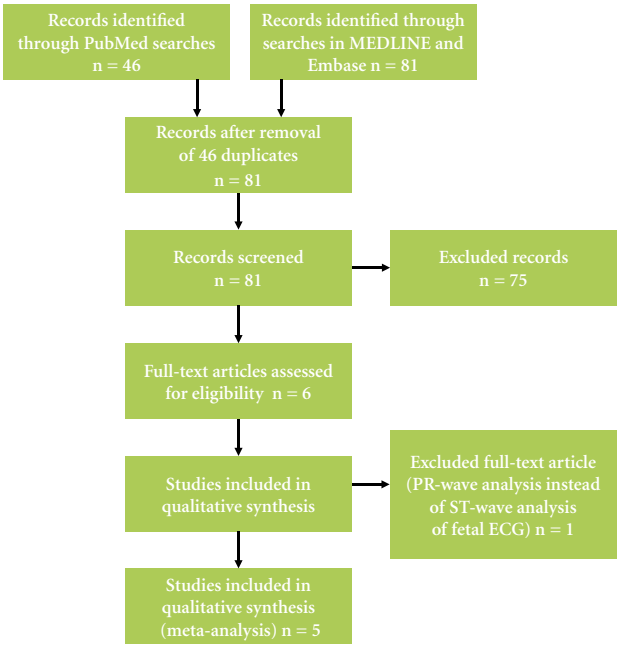
One reviewer (JB) performed the search and two reviewers (JB and LB) independently inspected the search results and reviewed citations for potentially eligible trials. Disagreements regarding inclusion of potentially eligible trials were resolved by discussion and, if necessary, arbitration by a third reviewer (AK). Each potentially eligible trial identified by the search strategy was obtained as a full-text article and was independently assessed for inclusion by three reviewers. Disagreements regarding eligibility for inclusion were resolved by discussion with all reviewers.

Inclusion criteria identified by the investigators included RCTs that evaluated singleton pregnancies in cephalic presentation of at least 34 weeks of gestation, assignment of participants to either intrapartum fetal monitoring using either ST-waveform analysis in combination with conventional CTG or conventional CTG alone, and clearly documented outcome data. Selected trials assessed at least one of the following outcomes: metabolic acidosis at birth (defined as umbilical cord pH <7.05 and base deficit in the extracellular compartment >12mmol/L), umbilical cord pH <7.15, umbilical cord pH <7.10, umbilical cord pH <7.05, umbilical cord pH <7.00, Apgar scores below 7 at 5 minutes, admittance to neonatal intensive care unit (NICU), need for intubation, presence of hypoxic ischemic encephalopathy (defined as Sarnat grade 2 or 3), perinatal death, number of FBS and operative delivery rates (all-cause and separate for suspected fetal distress (due to abnormal CTG, ST-events, or FBS with pH<7.20)).

Three reviewers (JB, LB, AK) independently assessed the risk of bias of all included trials using a risk of bias tool developed by the Cochrane collaboration.[13] The risk of bias tool contains specific items that assess adequate sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Three reviewers (JB, LB, AK) independently extracted data using predesigned data extraction forms. Study eligibility was verified again at the time of data abstraction or collection.

All meta-analyses were performed with MIX 2.0 (version 2.0.1.4, BiostatXL, Japan)[14] and Stata (release 10.0, Statacorp, College Station, TX). The risk-ratio (RR) and its

Figure 1: Flow diagram of study search and selection



corresponding 95% confidence intervals (95% CI) were calculated for each trial, where a risk-ratio below 1 indicates an effect in favor of STAN . The presence of inconsistency of outcomes across trials was assessed using the I^2 measure and the Paule-Mandel among-study variance estimate t^2.[2,15,16] Furthermore, this inconsistency or heterogeneity was graphically studied using forest plots, and Galbraith plots.[17] The latter is scatter plot to determine the amount of heterogeneity by plotting the 'z' statistic against 1/standard error such that larger studies with small standard errors aggregate away from the null value. When a clearly clinical and methodological variation was encountered for a particular outcome, a fixed-effect assumption would be unrealistic for those outcomes. Hence, we explicitly decided for random-effects models, while anticipating that they might default to the fixed-effect results the more the among-study variance t^2 is neared 0. When t^2 was estimated to be 0, the Mantel-Haenszel method was used for the syntheses of the risk ratios. We also assessed the impact of using fixed-effect models for analyses that were done with random effects models. When clinical heterogeneity or among-study variance between the included studies was substantial (substantial differences in inclusion criteria or I^2 >50%) and raised doubts about whether or not the studies should be combined in a single synthesis, sensitivity analyses that excluded these studies were performed. The presence of small study effects, indicative of biases related to selective dissemination of evidence,[18] was assessed with plots and Peters' regression test (i.e. an alternative to Egger's regression test, as it has lower type 1 error rates by using lnOR as the dependent variable and the

Table 1: Details of included studies

	Westgate 1993 United Kingdom	Amer-Wahlin 2001 Sweden	Ojala 2006 Finland	Vayssiere 2007 France	Westerhuis 2010 Netherlands
Type of study	RCT, N= 2334 Single-centre	RCT, N= 4966 Multi-centre	RCT, N= 1483 Single-centre	RCT, N= 799 Multi-centre	RCT, N= 5681 Multi-centre
Inclusion criteria	Laboring women ≥ 34 weeks of gestation	Laboring women ≥ 36 weeks of gestation Singleton fetus Cephalic presentation	Laboring women ≥ 36 weeks of gestation Singleton fetus Cephalic presentation	Laboring women ≥ 36 weeks of gestation Singleton fetus Cephalic presentation Meconium-stained amniotic fluid or abnormal CTG pattern	Laboring women ≥ 36 weeks of gestation Singleton fetus Cephalic presentation Age ≥ 18 years
Exclusion criteria	Gross fetal abnormality		Admittance during second stage of labour	Maternal infection Cardiac malformation	
Interventions	ST-waveform plus cardiotocography (S8801)	ST-waveform plus cardiotocography (S21)	ST-waveform plus cardiotocography (S21)	ST-waveform plus cardiotocography (S21)	ST-waveform plus cardiotocography (S21)
Controls	Cardiotocography	Cardiotocography	Cardiotocography	Cardiotocography	Cardiotocography
	Cord artery pH < 7.15 Cord artery pH < 7.05 Metabolic acidosis† 5' Apgar score ≤ 7 NICU admission Birth asphyxia‡	Metabolic acidosis 1' Apgar score < 4 5' Apger score < 7 NICU admission Neonatal encephalopathy Perinatal death	Cord artery pH < 7.10 Cord artery pH < 7.05 Metabolic acidosis 5' Apgar score < 7 Need for intubation NICU admission Seizures Encephalopathy	Cord artery pH < 7.05 Metabolic acidosis Abnormal neonatal outcome†† BD > 12 mmol/L 5' Apgar score < 7 NICU admission Seizures Neonatal death	Cord artery pH < 7.05 Cord artery pH < 7.00 Metabolic acidosis 1' Apgar score < 4 5' Apgar score < 7 NICU admission Neonatal encephalopathy Perinatal death
Maternal outcomes	Number of FBS Number of operative deliveries	Number of FBS Number of operative deliveries	Number of FBS Number of operative deliveries	Number of FBS Number of operative deliveries	Number of FBS Number of operative deliveries
Allocation concealment	Yes; adequate	Yes; adequate	Yes; adequate	Yes; adequate	Yes; adequate
Missing umbilical cord gasses	Not reported	728/4966 (14.7%)	36/1472 (2.4%)	Not reported	0/5667§

‡ Composite outcome defined as: metabolic acidosis, 5' Apgar score ≤ 7, active resuscitation for ≥ 4 minutes and one of the following problems in the postnatal period: hypoglycaemia (glucose < 1.6mmol/L) within the first 12 hours, neurological abnormalities, assisted ventilation in the first 48 hours or death. † pH<7.05 and BD>12 mmol/L
†† Composite outcome defined as: metabolic acidosis, 5' Apgar score < 7, NICU admission, seizures and neonatal death § Multiple imputation was used to handle missing umbilical cord gas data

inverse of the total sample size as the independent variable) and associated regression plots, although a small number of studies limits the applicability of these methods.[19] Meta-analysis was performed on outcomes that were reported in more than one trial. Numbers needed to treat (NNT) were calculated with control-group meta-analysis results as the typical expected event rate (TEER): NNT = 1/((1-RR) x TEER), or NNT = (1/(RR-1) x TEER), for cases where RR<1 and RR >1, respectively.

Results

We have identified 127 titles, of which 46 were duplicates. Of the 81 articles studied in detail, 75 did not satisfy the selection criteria (Figure 1). Full review was performed on six studies, of which five met all inclusion criteria. The study of Strachan et al. was excluded because in this study the PR waveform of the fetal ECG was analyzed rather than the ST segment.[6] The remaining five publications reported on a total of 15,352 patients: 7702 patients allocated to CTG plus ST analysis of the fetal ECG and 7650 patients allocated to CTG alone. Table 1 shows the characteristics of all studies.

For the outcome of metabolic acidosis (measured in the extracellular fluid compartment), data from four trials were available.[5,7,9,10] In the original paper of Ojala, base deficit (BD) was calculated in blood instead of extracellular fluid.[8] For us to include this study, converted data published by Norén and Rosén were used with permission of the author of the original article.[20] For the studies of Westerhuis and Amer-Wahlin, the corrected data after retrospective quality control were used.[21,22] In the Swedish trial, the corrections were related to present standards of intention-to-treat analysis which lead to renewed extraction from the original database and renewed quality control in relation to a more clinically relevant definition of metabolic acidosis. Furthermore, in the study of Ojala et al. analyses were performed according to the intention-to-treat principle for the delivery data (i.e. number of cesarean deliveries, number of vaginal operative deliveries and number of FBS).[8] However, patients with missing umbilical cord gas data were excluded from analyses concerning neonatal outcome (i.e., number of low Apgar scores, need for intubation, NICU admission, number of seizures, and number of neonatal encephalopathies). Upon request, the primary author of the Finnish trial sent us the data of the patients excluded from analysis for neonatal outcome and, consequently, meta-analysis could be performed on all data according to the intention-to-treat principle. FBS was performed in both study arms in all trials. The study of Westerhuis et al. was the only RCT with a strict protocol related to FBS use in the STAN arm. The total number of reported missing umbilical cord blood gasses was 764 of 15,338 (5.0%).
All trials employed adequate methods of allocation concealment and adequate generation of allocation sequences. Due to the nature of the intervention, blinding of participants and medical professionals was not possible. Blinding of outcome assessors was adequate

in all trials and incomplete data were assessed appropriately. We found no indications of selective outcome reporting or any other problems that could lead to bias.

Random-effects meta-analysis indicated that intrapartum ST-analysis of the fetal ECG is not associated with a reduced risk of metabolic acidosis in extracellular fluid: RR 0.72, 95% CI 0.43-1.19; NNT 357. Significant reductions in the risk of or need for operative deliveries (RR 0.94, 95% CI 0.89-0.99; NNT 64), vaginal operative deliveries (RR 0.88, 95% CI 0.80-0.97; NNT 64), and vaginal operative deliveries for suspected fetal distress (RR 0.86, 95% CI 0.76-0.97; NNT 74) were seen in analyses that estimated among-study variance as zero and applied the Mantel-Haenszel method. In a random-effects analysis, the need for additional fetal blood samples was significantly reduced by ST-analysis compared with CTG alone (RR 0.59, 95% CI 0.44-0.79; NNT 11). For the other outcomes no substantial differences were found between ST analysis and conventional CTG alone. Separate forest plots show the results for metabolic acidosis at birth, total operative deliveries, and 5 minute-Apgar scores <7 (Figures 2, 3 and 4), whereas a forest plot matrix shows the other outcomes (Figure 5). Tables 2 and 3 show detailed results for all studies.

Meta-analysis was performed on outcomes that were reported in more than one trial. The following outcomes were therefore excluded from analysis: fetal asphyxia[5], umbilical cord pH <7.15[5], umbilical cord pH <7.10[8], umbilical cord pH <7.00[10], need for intubation[8], metabolic acidosis measured in blood[8,10], seizures[8,9], abnormal neonatal outcome[9], BD >12 mmol/L[9], and 1 minute Apgar score <4[7,10.]

Although the reduction in metabolic acidosis in the main random effects analysis was not significant, fixed-effect analyses resulted in a significant risk reduction (RR 0.68, 95% CI 0.48-0.97). A fixed-effect alternative for the analysis of fetal blood samples did not have a large impact on the point estimate, although the confidence interval is substantially more narrow (RR 0.60, 95% CI 0.55-0.65). The study of Westgate et al.[5], performed in 1993, used the STAN 8801 recorder instead of the STAN S21 and S31 recorders that were used in the other four trials. The methodology of the STAN 8801 recorder included a visual analysis of the absolute T-QRS ratio instead of an automatic assessment of T-QRS ratio changes. Furthermore, biphasic ST changes were not yet part of this method of analysis. Therefore, we performed a sensitivity analysis of all outcomes by excluding the study of Westgate et al.. For most outcomes, the combined risk ratios were comparable with results of analyses with the study of Westgate et al. included. For the primary outcomes of metabolic acidosis and operative deliveries, the RRs were 0.81 (95% CI 0.47-1.42) and 0.95 (95% CI 0.89-1.00), respectively. Although the RR point estimate for operative deliveries is virtually unchanged, the RR for metabolic acidosis made a substantial shift towards indifference when the Westgate et al. study was excluded.

Table 2: Neonatal Outcome

Fetal outcomes	No. of analyzed studies	No. of analyzed participants	Statistical method	Effect size (95% CI)	Control group risk	Number needed to treat or harm
Metabolic acidosis	5	15338	Risk Ratio (PM, Random, 95% CI)	0.72 (0.43, 1.2)	0.01	NNT: 357
Cord artery pH < 7.05	5	15338	Risk Ratio (PM, Random, 95% CI)	0.97 (0.64, 1.5)	0.22	NNT: 152
Apgar score < 7	5	15338	Risk Ratio (PM, Random, 95% CI)*	0.95 (0.73, 1.2)	0.01	NNT: 2000
Admittance NICU	5	15338	Risk Ratio (PM, Random, 95% CI)*	0.90 (0.76, 1.1)	0.03	NNT: 333
Neonatal encephalopathy	3	12100	Risk Ratio (PM, Random, 95% CI)*	0.66 (0.19, 2.3)	0.001	NNT: 2941
Perinatal death	3	11432	Risk Ratio (PM, Random, 95% CI)*	1.17 (0.38, 3.6)	0.001	NNH: 420

* Because of the low among-study variance, random-effects analysis yielded the same results as fixed-effect analysis

Table 3: Maternal Outcome

Maternal outcomes	No. of analyzed studies	No. of analyzed participants	Statistical method	Effect size (95% CI)	Control group risk	Number needed to treat or harm
Total operative deliveries	5	15338	Risk Ratio (PM, Random 95% CI)*	0.94 (0.89, 0.99)	0.26	NNT: 64
Operative vaginal deliveries	3	12105	Risk Ratio (PM, Random 95% CI)*	0.88 (0.80, 0.97)	0.13	NNT: 64
Operative vaginal deliveries for SFD	5	15338	Risk Ratio (PM, Random 95% CI)	0.83 (0.67, 1.0)	0.08	NNT: 74
Caesarean section	3	12105	Risk Ratio (PM, Random, 95% CI)	1.03 (0.87, 1.2)	0.09	NNH: 370
Caesarean section for SFD	5	15338	Risk Ratio (PM, Random, 95% CI)	0.90 (0.67, 1.2)	0.05	NNT: 200
Fetal blood sampling	5	15338	Risk Ratio (PM, Random, 95% CI)	0.59 (0.44, 0.79)	0.22	NNT: 11

* Because of the low among-study variance, random-effects analysis yielded the same results as fixed-effect analysis

Figure 2: Forest plot for metabolic acidosis

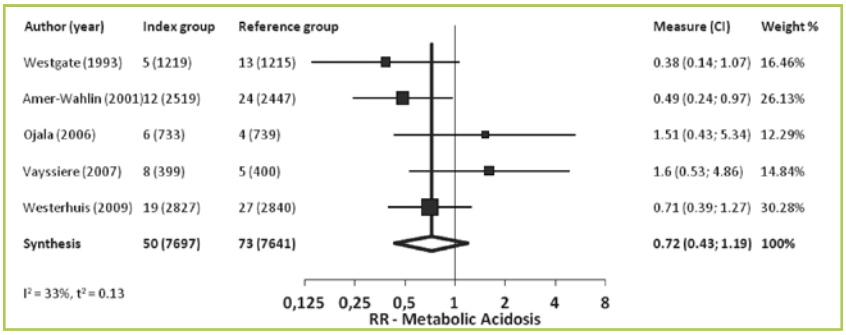


Figure 3: Forest plot for operative deliveries

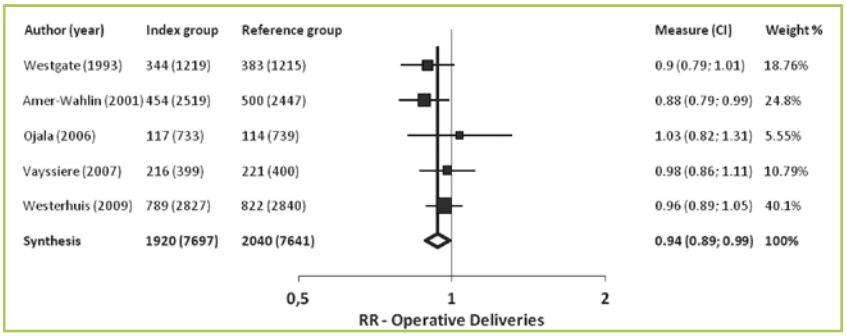


Figure 4: Forest plot for 5-minute Apgar Score <7

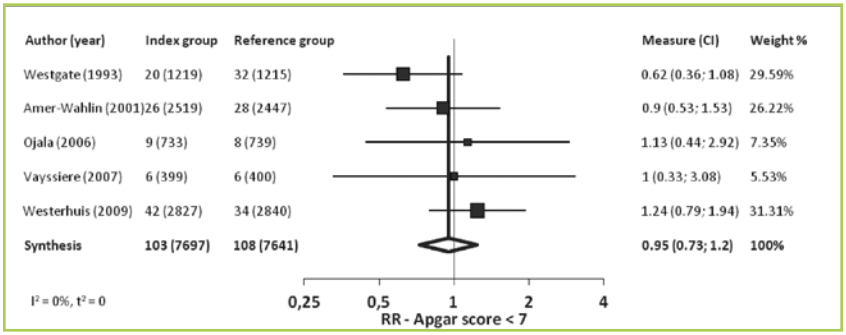
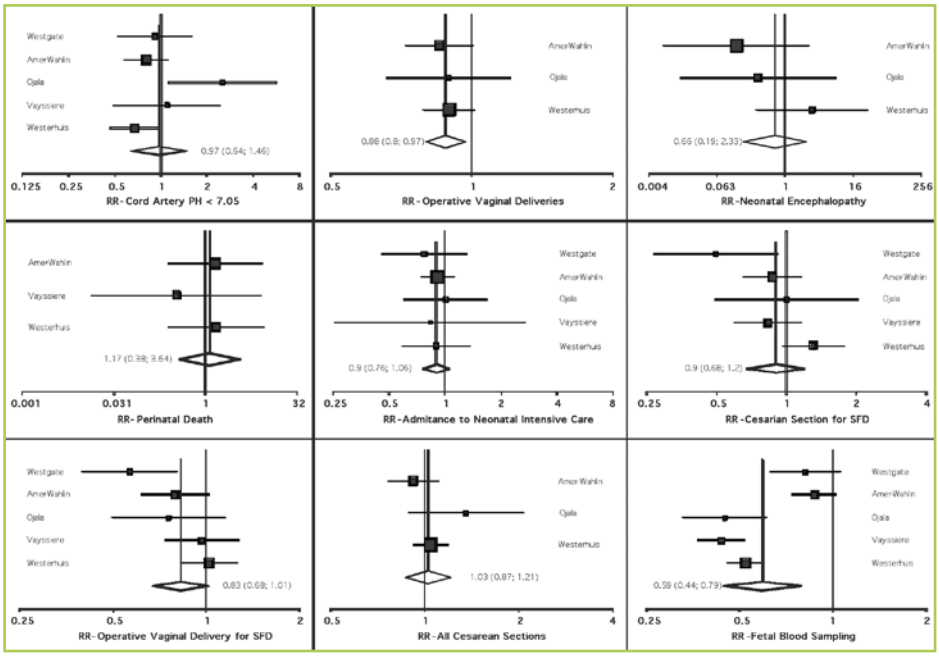


Figure 5: Forest plot matrix for secondary outcomes



Discussion

This meta-analysis shows that intrapartum monitoring with ST analysis of the fetal ECG is a safe method of intrapartum surveillance and that its implementation could lead to a reduction in operative deliveries as well as to a reduction in the need to perform additional FBS. Although the effect estimates of additional ST analysis show a reduced incidence in metabolic acidosis across a majority of randomized studies, this difference does not reach statistical significance.

Amer-Wahlin et al. were the first to find a significant reduction in metabolic acidosis (RR 0.49, 95% CI 0.24-0.97), with a significant reduction in operative deliveries for suspected fetal distress and a non-significant reduction in FBS.[7] This reduction in metabolic acidosis was not confirmed in the studies of Vayssiere et al. and Ojala et al..[8,9] In the latest and largest study, however, Westerhuis et al. found a non-significant reduction in metabolic acidosis.[10] The incidence of metabolic acidosis in their study population was no more than 0.8%, although a power analysis was performed with a hypothesized incidence of metabolic acidosis of 3.5%. This adversely affected the power of their analysis. The point estimates of metabolic acidosis of three of the five studies are consistent with the combined risk ratio of this meta-analysis; the studies of Ojala et al. and Vayssiere et al. both show an opposite effect.[8,9] The reason for these differences is unclear: while the study of Vayssiere et al. shows differences in inclusion criteria which might play a role in

the different effect on metabolic acidosis[9], the inclusion criteria of the study of Ojala et al. are very similar to those of the other studies[8]. Of note is that both these studies were relatively small and not powered to find a difference in metabolic acidosis. Furthermore, it is remarkable that the incidence of FBS in the two earliest studies showed no difference between the study arms, while these studies showed the largest effects on metabolic acidosis. The three most recent studies showed a large reduction of FBS in the ST arm, while the effect on metabolic acidosis was lower. As this finding seems to contradict what one might expect, we do not have a straightforward explanation for it.

Because of the among-study differences in the effect on metabolic acidosis, it is questionable whether metabolic acidosis is the right outcome to investigate. However, as the incidence of perinatal death and severe neonatal encephalopathies (defined as Sarnat stage 2 or 3) is extremely low, even in a high risk (near) term population, surrogate outcomes with a higher incidence are necessary for efficient evaluation of methods of intrapartum monitoring. Although the debate on which surrogate outcome is to be preferred is still ongoing, international consensus was reached in 1997 by the International Cerebral Palsy Task Force, which stated that an arterial umbilical cord pH <7.05 and BD ≥ 12 mmol/L are essential in defining an acute intrapartum hypoxic event.[23] Indeed, Malin et al. recently showed a strong association between umbilical cord pH and neonatal and long-term outcomes in a systematic review and meta-analysis.[24] Which of the calculations of BD, calculated in the extracellular compartment (BDecf) or calculated in blood (BDblood) better reflects adverse neonatal outcome is still uncertain.[25]

In 2006, Neilson performed a Cochrane review and meta-analysis on the fetal ECG for fetal monitoring during labor, which was updated in 2009.[11] With the publication of the study by Westerhuis et al. in 2010[10], the largest trial on this subject thus far, we re-performed this meta-analysis, focusing on ST-waveform analysis of the fetal ECG. When the present results are compared with the 2009 Cochrane review, this meta-analysis confirms the reduction in FBS, total operative deliveries, and vaginal operative deliveries when using ST analysis of the fetal ECG. Although fixed-effect models were used in the Cochrane review, in consideration of the clinical and methodological among-study variation, a fixed-effect assumption was considered unrealistic for a number of the outcomes. We therefore used random-effects models. Typical random-effects models use estimates of the within-study variances as well as an estimate of the among-study variance when calculating an overall meta-analysis result.[26] As such, they are generalizations of fixed-effect models, allowing the model to incorporate variation beyond the random error around the fixed-effect, if such variation is present. If there is no additional variation, the random-effects analysis yields results identical with those obtained using a typical inverse variance fixed-effect model. As the Cochrane review chose a fixed-effects model for all analyses, we have also provided the results of fixed-effect analyses for the outcomes that were analyzed with a random-effects model. In the case of metabolic acidosis, the

favorable effect of ST analysis of the fetal ECG then reaches statistical significance. Sensitivity analyses, excluding the older study of Westgate, show a substantial shift of the RR point estimate towards indifference and further indicate that the confidence interval of our random-effects model are realistic in the light of current evidence.

We found a reduction in operative deliveries for suspected fetal distress. The number of cesarean deliveries for suspected fetal distress was not significantly decreased, although the point estimate indicated a trend towards a lower intervention rate. The fact that ST analysis reduces not only the intervention rate for suspected fetal distress, but also the total intervention rate, indicates that there is a true effect of ST analysis on the number of interventions, and not a shift from interventions for suspected fetal distress to interventions for nonprogressive labor.

To appreciate the present results, a few limitations need to be addressed. Because of the low number of studies in this meta-analysis, the confidence intervals for the pooled effects are still considerably wide. As the different included studies were not completely homogeneous in the published outcomes, one or more studies were excluded from meta-analysis for some outcomes (i.e., incidence of cord artery pH<7.05; neonatal encephalopathy and operative vaginal deliveries), augmenting this effect.
Furthermore, all of the included studies were performed in countries where FBS is part of standard obstetric care. Therefore, these results might not be generalizable to countries where FBS is less common. In addition, the older studies showed a smaller impact of intrapartum ST analysis on the need for blood sampling. This could be explained by lower and more explicit decision thresholds for initiating the blood sampling in more recent studies, making blood sampling a more sensitive measure with time. Analyzing the more recent studies separately yields a homogeneous group of studies and shows an even larger effect than presented in the primary analysis (RR 0.48, 95% CI 0.43-0.54). The National Institutes of Health is currently conducting an RCT comparing intrapartum ST analysis of the fetal ECG in combination with CTG versus CTG alone as a multicenter trial across the United States (NCT01131260). It will be interesting to compare these results with the European trials conducted so far in the light of these transatlantic differences regarding the performance of FBS.

Implications for future research

As it was not possible to perform subgroup analysis or a proper meta-regression with the data provided by the individual trials, it would be worthwhile to perform an individual patient data meta-analysis to determine which patient groups can benefit most from the addition of ST analysis to conventional CTG.
To appreciate any new tool of intrapartum fetal surveillance, long-term follow-up is

essential. Thus far, studies investigating long-term follow-up of babies monitored by ST analysis of the fetal ECG are lacking. We would encourage any research on the effects of ST analysis of the fetal ECG on long-term neurological and behavioral outcome of these children. Furthermore, there is little information about the value of ST analysis of the fetal ECG in preterm fetuses as most trials included women from beyond 36 weeks of gestation and the study of Westgate included women from beyond 34 weeks of gestation. However, a Scandinavian multicenter study focusing on STAN in the preterm period was recently completed (STANPrem) and the data is being analyzed.

A last but important point is that implementation of the STAN-methodology should be carefully executed. The trial of Amer-Wahlin et al. showed that the favorable effect of STAN was mainly obtained in the second part of the trial.[27] An interim analysis showed several protocol violations among babies born with metabolic acidosis, after which training was repeated. Recently, observational studies have shown a decrease in incidence of metabolic acidosis after long-term use of STAN in Sweden, describing the changes in practice observed during 10 years of use.[28,29] The cases of adverse neonatal outcome described in the literature are mainly due to problems with the interpretation of the CTG or violation of guidelines.[30]

Since we found no clear evidence of neonatal benefit so far, cost-effectiveness analyses can provide the clinician with additional argumentation on whether or not ST-analysis should be used in everyday clinical practice. So far, two cost-effectiveness analyses have been published.[31,32] Although the two studies use different research methods and different time perspectives, both show that ST-analysis is a cost-effective method for intrapartum surveillance. However, the available studies are limited and the only available cost-effectiveness study focusing on lifelong outcomes uses a probabilistic decision model to calculate the cost-effectiveness.[31] Future studies on long-term behavioral and neurological outcomes will hopefully provide some information about long-term cost-effectiveness and can guide the clinicians' decision on whether or not fetal ST-analysis can add quality during labor in everyday clinical practice.
In conclusion, this meta-analysis shows that the additional use of ST analysis for intrapartum monitoring does not reduce the incidence of metabolic acidosis, but it does reduce the incidence of operative vaginal deliveries and the need for FBS. Cost-effectiveness studies are scarce but seem to provide some evidence that ST-analysis is a cost-effective method of intrapartum monitoring when compared with conventional CTG, when looking at both short- and long-term outcomes.

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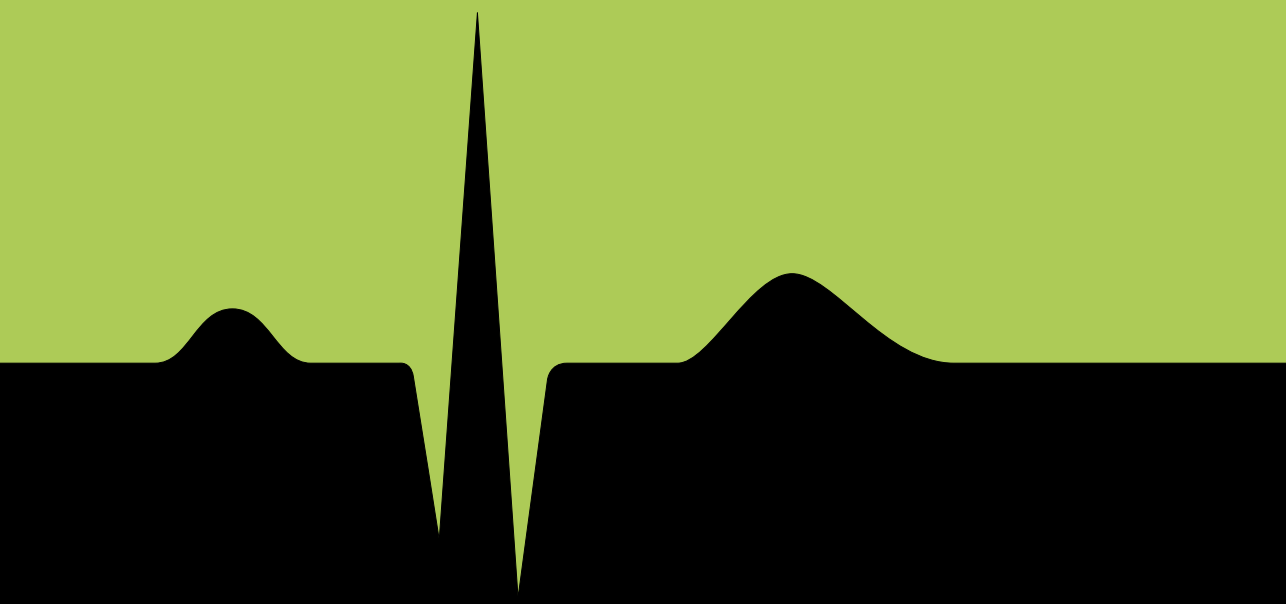
Cerebrospinal fluid leakage, an uncommon complication of fetal blood sampling: a case report and review of the literature



Chapter 3

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Abstract

In a recently published randomized clinical trial on intrapartum fetal monitoring, fetal blood samples were obtained in 879 women. One serious complication of fetal blood sampling (FBS) was reported, a case in which physical examination of the neonate after delivery revealed clear fluid loss from the incision site. Four layers of the scalp appeared to be incised. The subarachnoid space was closed with 2 sutures, and antibiotics were started due to the risk of meningitis. The patient was discharged in good clinical condition. In this article, the case is presented and the literature reviewed. We found 12 articles reporting 37 cases of a complication due to FBS, none concerning leakage of cerebrospinal fluid. In conclusion, complications of FBS are rare but can be serious. Excessive fetal bleeding is most frequently reported and often associated with an underlying coagulopathy in the neonate.

Introduction

Cardiotocography (CTG) for intrapartum fetal monitoring has been used to detect fetal distress and prevent neonatal and long-term injury due to asphyxia. Although this technique has been applied widely, it has been demonstrated to result in an increase in instrumental and operative deliveries with little or no benefit on neonatal outcome.[1] Fetal blood sampling (FBS) for pH determination as a method of fetal assessment was introduced in the 1960s by Bretscher and Saling.[2] It offers information on the acid-base status of the fetus and is regarded by some as the reference or "gold standard" to identify fetal distress during labor. Although FBS is more specific than CTG alone and thus can decrease the intervention rate, prevention of asphyxia is not guaranteed.[1] The technique is invasive and can be technically challenging, with a failure rate of at least 10%.[3] When CTG remains abnormal, the procedure may need to be repeated. In addition, complications of FBS have been described. Recently, the use of FBS to measure fetal lactate instead of pH to identify fetal acidosis has been introduced. Although outcomes such as metabolic academia and operative interventions were similar to FBS for fetal pH, a significantly lower failure rate was found, due to the smaller blood sample required.[4] It is therefore possible that this new strategy will lead to increased use of FBS, which is currently not used on a large scale worldwide.[5] Since the introduction of FBS, other techniques for fetal assessment in labor have been introduced, including ST analysis of the fetal electrocardiogram (STAN). We performed a multicenter randomized clinical trial to evaluate the effectiveness of intrapartum fetal monitoring by CTG plus STAN compared with usual care (CTG plus FBS when indicated).[6] There was a strict protocol for performance of FBS in the CTG + STAN arm of the trial. A series of 5667 pregnant women with a singleton fetus in vertex position and an indication for continuous CTG monitoring were included. In the trial, 1177 fetal blood samples were taken in 879 (15.5%) women. Among these, one (0.11% of all women who underwent FBS) uncommon, although serious, complication occurred. The purpose of this article is to report a patient with an uncommon complication of FBS and to present a review of the literature on this topic. After reading this article, physicians should be better able to assess the chance of possible complications due to FBS, select fetuses at risk for complications due to FBS, and evaluate certain technical precautions when performing this procedure.

Case reports

A 35-year-old primigravida with a gestational age of 40 weeks and 6 days was admitted to our delivery department in early labor at 4 centimeters of dilatation. She requested pain relief and received 150 mg of Pethidin. According to the guidelines of the International Federation of Gynecology and Obstetrics, the cardiotocogram (CTG) was classified as being intermediary, and FBS was performed using a standard 4-mm FBS blade. The

Table 1: case reports

Study	Cases	Incidence	Study design	Complication	Mode of delivery	Neonatal outcome	Coagulopathy
Roberts(20)	2	Unknown	Case series	Broken blade sample knife, retention in fetal scalp Broken blade sample knife, retention in fetal scalp	Unknown Unknown	Normal Normal	Unknown Unknown
Balfour (11)	6	6/678 (0,9%)	Case series	Scalp abscess Scalp abscess Scalp abscess Haemorrhage Haemorrhage Haemorrhage	Forceps Caesarean section Ventouse Caesarean section Caesarean section Spontaneous vaginal delivery	Forceps Normal Normal Died after 6 hours Normal Normal	Unknown - - + Unknown Unknown
Nelson(19)	1	Unknown	Case report	Broken blade sample knife, retention in fetal scalp	Unknown	Normal	Unknown
Hull (17)	1	Unknown	Case report	Haemorrhage, subaponeurotic haematoma postnatal	Spontaneous vaginal delivery	Normal	+
Modanlou(9)	6	6/250 (2.4%)	Case series	Haemorrhage Haemorrhage Broken blade sample knife, retention fetal scalp Broken blade sample knife Broken blade sample knife	Spontaneous vaginal delivery Spontaneous vaginal delivery Forceps Unknown Unknown	Died after 38 hours Normal Normal Unknown Unknown	+ + Unknown Unknown Unknown
Modanlou (10)	1	Unknown	Case report	Haemorrhage	Spontaneous vaginal delivery	Died after 26 hours	+ (DIC)
Reti(16)	1	Unknown	Case report	Haemorrhage	Spontaneous vaginal delivery	Normal	-
Young(18)	15	15/232 (6%)	Retrospective cohort study	Haemorrhage (11 cases) Scalp abscess (1 case) Other infections (3 cases)	Unknown Unknown Unknown	Unknown Unknown Unknown	Unknown Unknown Unknown
Chawla(15)	1	Unknown	Case report	Haemorrhage	Caesarean section	Normal	-
Jaiyesimi(14)	1	Unknown	Case report	Haemorrhage	Caesarean section	Normal	-
Pachydakis (13)	1	Unknown	Case report	Haemorrhage	Caesarean section	Normal	+
Sabir(12)	1	Unknown	Case report	Haemorrhage	Caesarean section	Normal	+
Present Case	1	1/1177 (0.08%)	Prospective cohort study (within RCT)	Cerebrospinal fluid leakage	Caesarean section	Normal	Unknown

procedure was uneventful. Blood gas analysis showed a pH of 7.31 and a base deficit (BD) of 5.7 mmol/L. One hour later she started active pushing, during which oxytocin was administered because of insufficient progress. Because of the development of an abnormal CTG, with a baseline tachycardia of 180 beats per minute, as well as failure to progress, an emergency cesarean delivery was performed. A male infant weighing 3140 g, with Apgar scores of 7, 9, and 9 after 1, 5, and 10 minutes, respectively, was delivered. Umbilical cord blood gas showed an arterial pH of 7.25 with a BD of 5.4 mmol/L and a venous pH of 7.32 with a BD of 5.5 mmol/L.

On physical examination of the newborn by a pediatrician, an incision of about 3 centimeters in length at the edge of the posterior fontanel was discovered. The incision perforated 4 layers of the scalp, including the dura and arachnoid meninges. Neurosurgical examination showed clear fluid loss from the incision site, suspicious for cerebrospinal fluid (CSF) leak. The subarachnoid space was closed with 2 sutures, and the newborn was admitted to the neonatal intensive care unit. The neonate received amoxicillin and cefotaxime prophylaxis for 48 hours due to the risk of meningitis. The clinical course was uneventful, laboratory results indicated no evidence of infection, and a culture from the incision site showed no pathogenic microorganisms. Two days after delivery, the newborn was discharged in good clinical condition.

Review of the literature

On September 1st, 2010, a MEDLINE search for "fetal scalp blood sampling" (Title/Abstract) AND "complications" (Title/Abstract) and their synonyms was performed, which yielded a total of 129 articles. After screening titles and abstracts and performing a reference check, 11 case reports and case series reporting a total of 22 cases were found. One retrospective cohort study on FBS was found, reporting 15 complications. Furthermore, the latest Cochrane review on intrapartum fetal monitoring was searched for complications of FBS.[1] Two additional clinical trials, each reporting one case of a complication due to electrode or scalp sampling, were mentioned.[1,7] However, detailed information on these 2 cases could not be retrieved, due to no full-text availability or inadequate reported information regarding the complication, and these 2 cases were therefore excluded. An overview of all other 37 cases is given in Table 1. Complications primarily consisted of excessive fetal bleeding and scalp abscesses.[8–18]In the early years of the procedure, broken blades of the knife used for FBS also occurred.[13,19] Although some cases of CSF leakage after the use of a scalp electrode were reported[20–22], no case reports concerning leakage of CSF as a complication of FBS were found in the literature.

Hemorrhage

The most frequently reported complication associated with FBS is excessive fetal bleeding, reported in 23 of 37 (62%) cases. In 6 cases (26%) hemorrhage was associated

with a coagulation disorder. Reported coagulopathies included hemophilia, vitamin K deficiency, and diffuse intravascular coagulation. In a recent review of bleeding disorders in neonates, Kenet et al. reported that about one-third of infants with hemophilia are diagnosed due to bleeding events in the first month of life; the other most common reasons for diagnosis are a positive family history and/or a known carrier mother.[23] FBS is the second most common antecedent for diagnostic workup leading to a diagnosis of hemophilia, preceded only by circumcision.[23] This emphasizes the necessity for inspection of the sample site in the newborn when FBS has been performed. In cases with sustained blood loss from the incision, the possibility of a coagulation disorder should be considered and testing for coagulopathies should be performed. In 2 of 3 cases in which neonatal death occurred following FBS, a coagulopathy was diagnosed. In one case, hemophilia A was diagnosed from coagulation studies. Hemorrhages in several organs were found on postmortem examinations, making the coagulation disorder the most likely cause of death.[8] A second neonate was diagnosed with disseminated intravascular coagulation and congenital syphilis.[9] In the third case, multiple abnormalities were present (dysmaturity, pulmonary hypoplasia, and hemorrhage of the liver) in addition to excessive bleeding of the scalp.[10] However, no coagulation studies were performed.

Scalp Abscesses

Four cases of scalp abscesses after FBS have been reported due to a variety of different organisms.[10,18] In one case, Escherichia coli was isolated from both the scalp abscess and the mother's cesarean section wound, presumably due to maternal-fetal transmission of the bacteria secondary to the FBS procedure. In 2 of the neonates with a scalp abscess, an assisted vaginal delivery was performed, either by forceps or vacuum extraction. It could be theorized that the instrumental delivery predisposed to a scalp infection, although the site on the fetal scalp for instrumental delivery does not typically correspond with the incision site for FBS. It is also possible that the instrumental delivery led to the development of a cephalohematoma, in which an infection may rarely develop.[24] Young et al. also presented 3 cases with other neonatal infections following FBS, consisting of cellulitis, herpes simplex virus, and erythema.[18] Given that no additional information on these cases was provided, such as the location of the infection and cultured organisms, it could be debated whether the latter should be interpreted as an actual infection caused by FBS.

Broken Blade

Six cases of broken blades in fetal sampling with retention in the fetal scalp have been described.[8,13,19] However, this complication has not been described since 1973, likely due to new and improved instruments.

Comment

Complications caused by FBS occur rarely, with an incidence ranging from 0.4% to 6%.[8,10,18] The highest incidence of 6% were reported by Young et al., with complications consisting of fetal bleeding and infection, in 15 of 232 cases. None of these complications resulted in serious consequences for the neonates, all of whom were discharged in good clinical condition.[18] In general, most complications due to FBS are minor, and they might even go unnoticed. Nonetheless, severe complications have been described, including cases resulting in neonatal death.[8–10] The complication we present, CSF leakage caused by FBS, has not been described before. Although a serious complication, including admission to the neonatal intensive care for 48 hours, management was relatively straightforward and the neonatal outcome was normal. However, this case indicates the necessity of caution during the procedure. Multiple punctures to obtain a sample, and puncture over the fontanels, should be avoided. Also, a careful physical examination of the neonate with attention to the incision site should always be performed after delivery. This review of the literature resulted in only 37 reported cases of complications following FBS, consisting primarily of excessive fetal bleeding, scalp abscesses, and broken sampling blades. Underreporting of cases is probable, but complications due to this procedure seem to be rare. Nevertheless, the technique is invasive and thought should be given to alternative, noninvasive means of assuring fetal well-being whenever possible. New results on STAN monitoring for decreasing the need for FBS seem promising.[6]

Conclusion

FBS for intrapartum fetal monitoring is not widely used, partly due to the potential risk of complications associated with the procedure. A review of the literature indicates that complications are relatively rare, the most frequent being excessive fetal bleeding commonly associated with an underlying coagulopathy. Analyzing data from our multicenter trial confirms the rareness of serious complications caused by FBS with an incidence of one of 1177 (0.08%) procedures.

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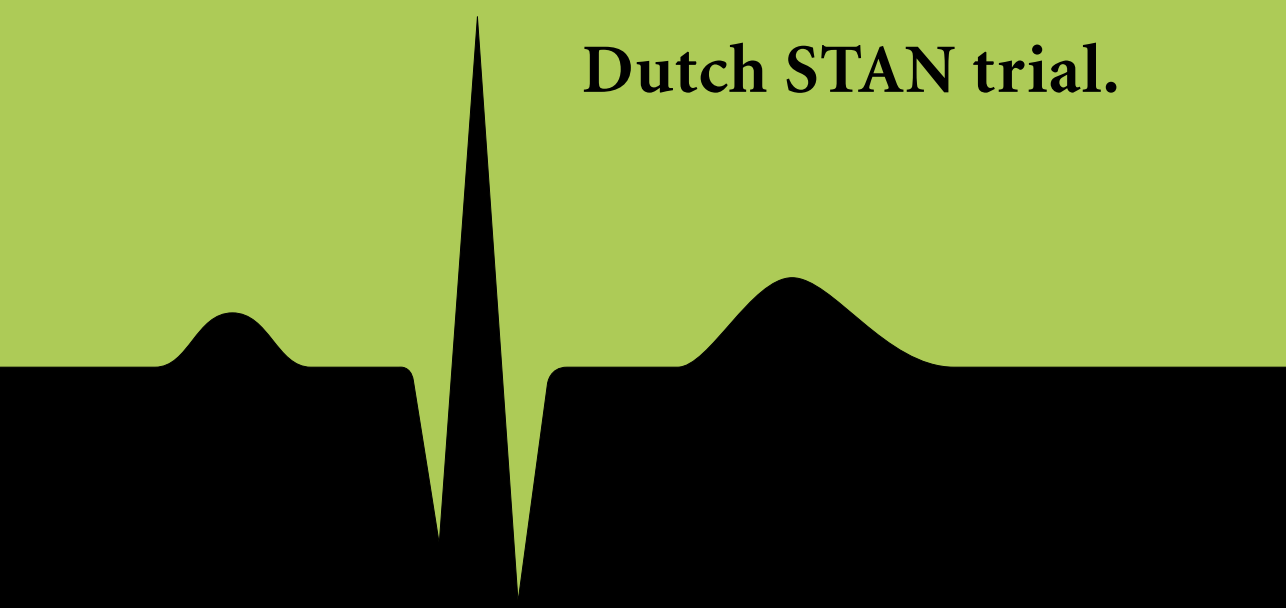
Fetal blood sampling in addition to intrapartum ST-analysis of the fetal electrocardiogram: evaluation of the recommendations in the Dutch STAN trial.



Chapter 4

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Abstract

Objective
To evaluate the recommendations for additional fetal blood sampling (FBS) when using ST-analysis of the fetal electrocardiogram.

Study design
Prospective cohort study

Setting
Three academic and six non-academic teaching hospitals in the Netherlands

Population
Laboring women with a high-risk singleton pregnancy in cephalic position beyond 36 weeks of gestation.

Methods
In laboring women allocated to the STAN arm of a previously published RCT who underwent one or more FBS during delivery, we assessed whether FBS was performed according to the trial protocol and how fetal acidosis, defined as a FBS pH<7.20, was related to ST-waveform analysis.

Main outcome measures
The number of FBS showing fetal acidosis, related to the different STAN-criteria where additional FBS is recommended.

Results
Among 2827 women monitored with STAN, 297 underwent FBS, of which 171 samples (57.6%) were performed according to the predefined criteria and 126 were performed in absence of these criteria. In the first group rates of fetal acidosis (pH<7.20) were 2/18, 0/9, 12/111 and 3/33 when FBS was taken for abnormal CTG at start, intermediary CTG at start, abnormal CTG >60 minutes, and poor FECG quality, respectively. When the predefined criteria were not met and ST-analysis showed no ST-events, only two cases of fetal acidosis were seen.

Conclusion
The performance of FBS is valuable in the advised STAN criteria. In situation were these criteria are not met, performance of FBS does not seem helpful in the detection of fetal acidosis.

Introduction

Intrapartum fetal monitoring aims to identify fetuses at risk for neonatal and long-term injury due to asphyxia. To serve this purpose, cardiotocography (CTG) has been introduced in the 1960s. Although CTG is widely applied, it is neither very sensitive nor specific for the detection of fetal acidosis, but comes at the cost of a significant increase of the operative delivery rate.[1–8] Addition of fetal blood sampling (FBS) to the CTG does result in slightly better results at a lower intervention rate.[6] However, performance of FBS is invasive, has to be repeated when CTG abnormalities persist and some studies report up to 21 per cent failures due to technical problems.[9] As with any other form of intrapartum surveillance, it still does not guarantee prevention of asphyxia.[10]

In recent years, ST-analysis of the fetal electrocardiogram (ECG; STAN) has been introduced, combining standard CTG with computerized ST-waveform analysis of the fetal ECG during labor. Several studies have identified changes in the ST-segment and T-wave of the fetal ECG in response to fetal hypoxia.[11–15] These changes are interpreted together with the CTG, according to the STAN clinical guidelines.

Five randomized trials have been performed to compare intrapartum fetal monitoring by CTG plus ST-analysis of the fetal ECG with CTG only.[16–20] Two large studies have shown that monitoring by CTG plus ST-analysis decreases the incidence of metabolic acidosis and the number of instrumental deliveries for fetal distress, as compared to CTG alone.[16,20] However, in both studies FBS was equally performed in the two study groups. In two smaller trials, the improvement in neonatal outcome as reported in the two largest trials could not be confirmed, but in both trials the incidence of FBS in the CTG plus ST-analysis group was significantly lower.[17,19] Recently, we reported that fetal monitoring by CTG plus ST-analysis of the fetal ECG as compared to CTG only, using a strict protocol for performance of FBS, reduced the number of newborns with (metabolic) acidosis, with a reduction of FBS from 20% to 10%.[18]

An important issue in intrapartum fetal monitoring concerns false-negative test results, leading to the birth of an infant with adverse outcome. In the use of the STAN technique, such false negative cases have also been reported.[21–23] Following these reports, in January 2007 European experts on ST-waveform analysis formulated consensus based criteria for CTG classification and ST-waveform interpretation. Existing STAN clinical guidelines were adjusted, now including recommendations for situations in which additional fetal information, such as by FBS, is needed to prevent false-negative results.[24]

As these STAN criteria are not based on empirical data, we evaluated all cases monitored by ST-analysis of the fetal ECG in the previously mentioned Dutch trial[18] in which at least one fetal blood sample had been performed. This study aims to evaluate the current recommendations for additional fetal blood sampling when using ST-analysis of the fetal electrocardiogram.

Materials and methods

Patients and Measurements

We used data of patients monitored in the STAN arm of a previously published multicentre randomized controlled trial[18] among laboring women with a high-risk singleton pregnancy in cephalic position at term (ISRCTN95732366). From January 2006 until July 2008 participants had been randomly assigned to monitoring by CTG combined with ST-analysis of the fetal ECG (index group) or CTG without ST-analysis (control group). The study was approved by the Institutional Review Board of the University Medical Centre Utrecht and had local approval from all other participating hospitals. The present study focussed on the women randomized to the index group in whom a FBS was taken.

In women in the index group, a scalp electrode was applied to the fetal head and connected to a STAN S21 or S31 fetal heart monitor (Neoventa Medical, Gothenburg, Sweden). Both monitors used the same ST analysis algorithms. Clinical management was guided by the STAN clinical guidelines (Appendix 1 and 2). In the study protocol FBS was advised in three situations: 1) start of STAN-registration with an intermediary or abnormal CTG trace; 2) abnormal CTG trace for more than 60 minutes without ST-events; and 3) poor ECG signal quality in the presence of an intermediary or abnormal CTG trace. Poor signal quality was defined as absence of ST-information for more than four minutes or less than one average ECG-complex per minute within a period of 10 minutes. Except for the advice to perform FBS in case a STAN recording started with an intermediary CTG, the study protocol was identical to the revised STAN guidelines of 2007.[24] Immediate delivery was recommended if FBS showed a pH below 7.20. If the pH was between 7.20 and 7.25 the advice was to repeat FBS after 30 minutes. If the pH was above 7.25, the fetal condition was considered well enough to continue labor. Apart from the FBS criteria, immediate delivery was also indicated if STAN abnormalities occurred as defined in the protocol.

Analysis of women undergoing fetal blood sampling

ECG recordings

For the present analysis, two observers (J.B. and K.S.) independently assessed all STAN recordings of women in the index group in which at least one FBS was performed. They examined whether or not additional FBS was performed according to the trial protocol. In case of discordant observations, the opinion of a third observer (M.W.) was decisive. The STAN recordings were presented digitally (STAN viewer software, Neoventa Medical AB, Sweden) to the observers using a paper speed of 2 cm/minute as this is the paper speed routinely used in the Netherlands. The observers were only provided with information on the timing of FBS, without knowledge of its result, other clinical parameters obtained during labor, and of the neonatal outcome.

For each FBS the following items had to be scored: 1) classification of the CTG as normal,

intermediary, abnormal or (pre)terminal within a 60-minute period before performance of FBS; 2) duration of an intermediary, abnormal or (pre)terminal CTG in minutes; 3) interpretation of any ST-events; and 4) judgement whether FBS was performed according to the RCT protocol. If so, the reason for FBS had to be defined based on one of the protocolized situations.

Evaluation of assessment by observers

For the fetal blood samples performed according to the trial protocol, the relation between pH result measured by FBS and the reason to perform FBS was described. In the samples that were not performed according to the RCT protocol (i.e. protocol violation), the relation between pH results of FBS and ST-waveform interpretation regarding fetal indications to intervene, was evaluated. Fetal acidosis was defined as a FBS pH below 7.20.

Patients were classified as being treated 'not according to trial protocol' if at least one of the FBS was not performed according to the trial protocol. This classification on patient level instead of FBS level allowed description of observer results in relation to neonatal outcome. For neonatal outcome, metabolic acidosis was defined as an umbilical cord artery pH below 7.05 and base deficit in extracellular fluid (BDecf) above 12 mmol/L.

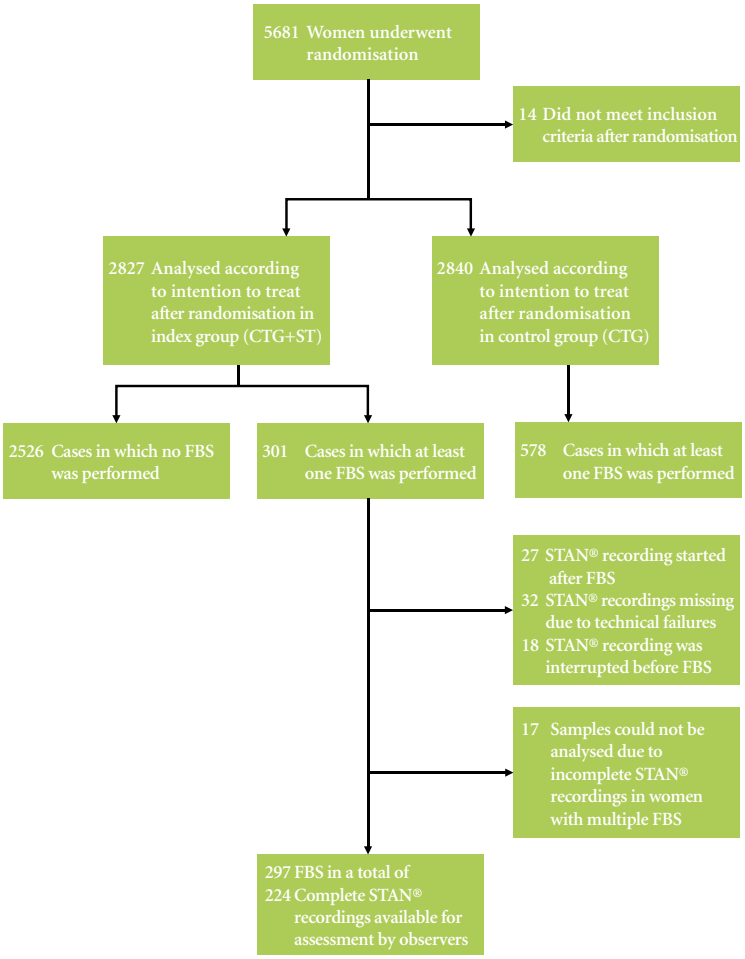
Results

In the trial, we randomized 5,681 women, 2,827 to the index and 2,840 to the control group, whereas 14 did not meet the inclusion criteria (Figure 1). Of 2,827 women allocated to the index group of the trial, at least one FBS was performed during 301 (10.6%) deliveries. STAN recordings for assessment by the observers were complete for 224 (74.4%) of these deliveries. The remaining 77 cases (25.6%) were excluded from analysis for the following reasons: FBS was performed before the start of a STAN recording (n=27), STAN recordings were missing or incomplete due to technical failures (n=32) or STAN recordings were interrupted before FBS was performed (n=18). Among the 77 cases excluded from analysis there were no cases of neonatal metabolic acidosis.

In the 224 available cases, 314 fetal blood samples were performed. Due to partly incomplete STAN recordings in women with multiple FBS, 17 (5.4%) samples could not be analysed. In total 297 fetal blood samples were available for analysis (Figure 1).

After protocol adherence was evaluated by two observers, 47 (15.8%) of 297 observations were discordant and therefore the opinion of a third observer was decisive. According to the observers, 171 (57.6%) FBS were performed according to the trial protocol; the remaining 126 (42.4%) samples were not performed according to protocol (i.e. protocol violation). We were not informed about the reasons of FBS performed not according to the trial protocol as this was not documented. Failed FBS procedures with missing pH results occurred in 4.7% (Table 1).

Figure 1: Flowchart



FBS according to trial protocol

In 17 of the 171 (9.9%) FBS performed according to the trial protocol, fetal acidosis was present (Table 1). This occurred in 12 of 111 (10.8%) samples performed because of an abnormal CTG beyond 60 minutes without ST-events, in 2 of 18 (11.1%) samples because of an abnormal CTG at the start of a STAN recording and in 3 of 33 (9.1%) samples because of poor ECG signal quality combined with an abnormal CTG (Table 2).

FBS not according to trial protocol

In 10 of the 126 scalp samples not performed according to the trial protocol fetal acidosis was found (7.9%) (Table 1). In 8 of these cases, intervention based on a significant ST-event was indicated before FBS was performed. In the remaining two cases FBS indicated

Table 1: FBS in deliveries monitored by ST-analysis of the fetal ECG related to the trial protocol.

Data are presented as absolute numbers (%)

	Total	According to trial protocol *	Not according to trial protocol**
Number of FBS	297	171	126
FBS result			
pH >7.25	208 (70.0)	112 (65.5)	96 (76.2)
pH 7.20-7.25	48 (16.2)	33 (19.3)	15 (11.9)
pH <7.20	27 (9.1)	17 (9.9)	10 (7.9)
Missing pH	14 (4.7)	9 (5.3)	5 (4.0)

* In the study protocol FBS was advised in three situations: 1) start of STAN-registration with an intermediary or abnormal CTG trace; 2) abnormal CTG trace for more than 60 minutes without ST-events; 3) poor ECG signal quality in the presence of an intermediary or abnormal CTG trace.
** FBS performed on indication of the clinician although the abovementioned conditions were not met (protocol violation).

Table 2. FBS in deliveries monitored by ST-analysis of the fetal ECG related to reasons according to the trial protocol.

Data are presented as absolute numbers (%).

Reason to perform FBS according to trial protocol					
	Total	Abnormal CTG at start	Intermediary CTG at start	Abnormal CTG>60 min without ST-event	Poor ECG signal quality
Number of FBS	171 (100)	18 (10.5)	9 (5.3)	111 (64.9)	33 (19.3)
FBS result					
pH >7.25	112 (65.5)	9 (50.0)	9 (100)	69 (62.2)	25 (75.8)
pH 7.20-7.25	33 (19.3)	5 (27.8)	0 (0.0)	24 (21.6)	4 (12.1)
pH <7.20	17 (9.9)	2 (11.1)	0 (0.0)	12 (10.8)	3 (9.1)
Missing pH	9 (5.3)	2 (11.1)	0 (0.0)	6 (5.4)	1 (3.0)

Table 3: Relation of presence or absence of significant ST-events and preterminal CTG with results of FBS not taken according to protocol (n=126)

	pH <7.20	pH 7.20-7.25	pH >7.25	Missing value	Total
Indication to intervene (≥1 significant ST-event)	8 (23.5%)	5 (14.7%)	19 (55.9%)	2 (5.9%)	34
No indication to intervene	2† (2.2%)	10 (10.9%)	77 (83.7%)	3 (3.2%)	92
Preterminal CTG	1 (100%)	0	0	0	1

† Although there was no indication to intervene at the time of FBS, a significant ST-event occurred 25 minutes after FBS.

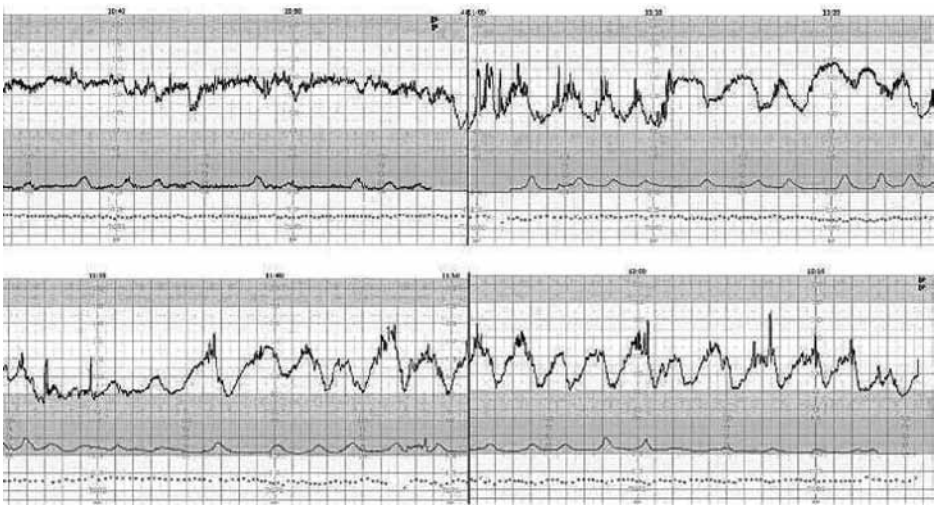
fetal acidosis in the absence of a significant ST-event. In both cases an abnormal CTG for less than 60 minutes with rapid deterioration of fetal heart rate variability had been present. As a secondary finding, we found that in one of these two cases a significant ST-event occurred 25 minutes after FBS showed a pH of 7.13 during first stage of labor. In the other case, there were no ST-events and FBS was performed in the second stage of labor, and showed a pH of 7.18; part of that recording during second stage of labor is shown in Figure 2. For both cases neonatal outcome was favorable. For the FBS that were taken not according to the protocol, the relation of the presence of significant ST-events or a preterminal CTG pattern within 60 minutes prior to the FBS with the result of the FBS (i.e. normal, intermediate or abnormal) is shown in table 3.

Neonatal outcome

Of 224 deliveries available for analysis, 123 (54.9%) were treated according to the trial protocol and 101 (45.1%) were not. Among the women where FBS was taken according to the trial protocol, three delivered a neonate with metabolic acidosis at birth. In one of these cases the CTG had been abnormal for only 36 minutes in combination with poor ECG signal quality before FBS with pH 7.19 was performed. In the other two cases FBS was performed because of CTG abnormalities >60 minutes and these were normal, but CTG abnormalities persisted between this normal FBS and birth. In one case the time between FBS and birth was only 20 minutes with poor signal quality (result FBS 7.24, umbilical cord artery pH 7.00), while in the other case the time between FBS and birth was 9 hours with an abnormal CTG for the last 115 minutes (FBS 7.32, umbilical cord artery pH 6.93).

In the group where FBS was performed not according to the trial protocol, metabolic acidosis at birth was found in three infants as well. In all three cases earlier intervention was recommended based on significant ST-events. In one of these cases multiple FBS

Figure 2: Recording of a case with rapid deterioration of the fetal heart rate variability without ST-events



were performed because of an abnormal CTG-pattern (pH 7.38, 7.33, 7.31, 7.28 and 7.28). The final two FBS were both preceded by a significant ST-event. CTG abnormalities persisted hereafter and ST-analysis showed one more significant ST-event 76 minutes after the last FBS, during second stage of labor. Time between the last FBS and delivery was 114 minutes. After a failed vacuum extraction, the baby was born by a cesarean delivery which showed a uterine rupture. The baby was born with an umbilical cord pH of 6.96 and BDecf 15 mmol/L and died of severe asphyxia and encephalopathy.

Discussion

This study provides empirical data with respect to intrapartum situations that require additional assessments in patients monitored by ST-analysis of the fetal ECG. When additional FBS was applied according to the criteria it revealed acidosis in almost 10% of cases (17/171). FBS performed both in absence of these criteria and significant ST-events, detected only two cases of acidosis. These results largely support the recently adjusted STAN guidelines.[24] This is also illustrated by table 3 which shows that in FBS taken not according to the protocol and where ST-analysis showed no significant events, acidosis was seen in just 2.2% (2/92), whereas acidosis was seen in as much as 23.5% (8/34) in presence of significant ST-events.

However, table 3 also shows that the majority of FBS, taken in the presence of significant ST-events, show a pH >7.25. As a consequence, the question arises if performance of FBS may prevent the clinician conducting delivery unnecessarily when significant ST-events are

present during first stage of labor and when there are no possible causes of fetal hypoxia which could be alleviated . However, because the performance of FBS in this situation was not recommended, it is likely that there was bias in the clinicians' decision to perform FBS in these situations, therefore this finding has to be interpreted with caution.

There are some limitations of this study that need to be addressed. First we had to exclude a relatively large number of cases in which at least one FBS was performed (25%) due to different reasons. However, there were no cases of metabolic acidosis among these exclusions. Secondly, we only analyzed cases in which FBS was performed. It is therefore unknown to what extent criteria with respect to performing FBS were indeed followed in cases without FBS. Although we speculate that the need to perform FBS in addition to ST-analysis could be further reduced when criteria are followed more strictly, this cannot be thoroughly concluded without analyzing all deliveries in which no FBS was performed. Furthermore, we defined a threshold for fetal acidosis to occur at a scalp pH below 7.20. Although this cut-off represents the lower limit of normal fetal intrapartum capillary blood values as described by Beard in the late 1960's[25], it is questionable whether this can be correlated to ST-analysis of the fetal ECG. Since the latter informs us about the ability of the fetal myocardium to respond to hypoxia, and FBS informs us about acidosis, results of both techniques are not completely comparable. However, although a scalp pH is not a gold standard, in clinical practice it is used as a reference test with pH of 7.20 as the lowest acceptable value for continuation of expectant management. In addition, as mentioned in the methods section, when STAN recordings were evaluated the observers were only provided with information on the timing of FBS, without knowledge of its result, other clinical parameters obtained during labor, and of neonatal outcome. However, the observers might be indirectly informed of the result of the FBS since a low pH would probably have led to delivery (and therefore the end of the registration) and an intermediate pH would probably have led to another FBS. Due to the nature of this study this was unavoidable and we don't believe this has led to significant bias. Lastly, we would like to stress the fact that the evaluation was performed from data of a RCT. Although unavoidable for solid research purposes, it is a situation far from everyday practice conditions and the results should be judged appropriately.

The addition of the category 'abnormal CTG for more than 60 minutes with normal ST', which was added to the latest STAN guidelines as a criterion that may require additional fetal information, seems valuable, since 12 cases with fetal acidosis were detected this way. However, 62.2% of scalp samples performed because of an abnormal CTG trace for more than 60 minutes without ST-events, showed a pH above 7.25. One may wonder whether, in cases of an abnormal CTG without ST-events, the threshold for assessment of fetal well-being in addition to ST-analysis might be raised to 90 minutes. Expectant management for 90 instead of 60 minutes of abnormal CTG without ST-changes would,

in our study, have led to four missed cases with fetal acidosis (equals an additional 1.8%), assuming that no ST-events would have appeared in the additional 30 minutes (data not shown). Consequently, we feel that a period of 60 minutes of abnormal CTG without ST-events is the maximal period.

In our trial protocol the category 'intermediary CTG at the start of registration' for assessment of fetal condition at the start of a STAN recording was incorporated, to evaluate whether in these cases ST-waveform analysis would be reliable. This extension of the STAN criteria has not been proven to be useful in detecting fetal hypoxia. Although based on only nine cases, we do not advise addition of this category to the STAN clinical criteria as a recommended situation for assessment of fetal well-being.

The results of our study showed that in the group of FBS that was not performed according to the trial protocol, in 8% fetal acidosis was present, of which eight out of ten cases were detected by significant ST-events before FBS was taken and one shortly after. The remaining case without ST-events may be considered as 'false-negative'. In this case, an abnormal CTG for less than 60 minutes with rapid deterioration of fetal heart rate variability had occurred.
Although the existing criteria do mention rapid deterioration of fetal heart rate pattern in combination with an abnormal CTG and normal ST as an indication to perform FBS, heart rate variability is not mentioned. It is not entirely clear which criterion would fulfil the definition of 'rapid deterioration of the fetal heart rate pattern'. Although the interpretation of a CTG will always be prone for subjectivity and debate amongst clinicians, we feel that the fetal heart rate variability is a more objective parameter to assess a deterioration of the CTG. Therefore, we would encourage addition of the category 'abnormal CTG <60 minutes with rapid deterioration of fetal heart rate variability with normal ST-waveform analysis' to the STAN clinical guidelines as a required situation for qualified assessment and checking for non-deteriorating fetal condition. This may achieve STAN users to be more alert to the assessment of fetal heart rate variability and further reduce the false negative rate.

Overall, in 10% of cases in the index group of our large randomized trial FBS was performed.[18] Given the fact that in more than 40% FBS was not performed according to the STAN criteria, we speculate that this incidence may be further reduced when STAN clinical criteria are followed more strictly. The reason of this large proportion of FBS performed not according to protocol could not be studied, but lack of trust in a new method of fetal surveillance might have played a role. Of all 224 cases with FBS analysed in this study, only six had metabolic acidosis at birth, of which three had been identified by ST-waveform analysis before the moment of FBS. In previous studies, evaluating the relation between scalp pH and ST-waveform analysis, it was also found that a substantial

part of FBS was preceded by ST-events and thus performed to verify the significance of CTG plus ST abnormalities.[26,27] Since FBS may be a time consuming procedure, hampered by technical and logistic problems and failed attempts, this may cause a serious delay in delivery, especially during the second stage of labor and thus should not be performed anymore in case of significant ST-events during second stage of labor.

Whereas in most western European countries the performance of FBS is incorporated in daily obstetric practice, in the USA it is not. The abovementioned drawbacks of FBS could well be the explanation for this major transatlantic difference. At the moment the National Institute of Health (NIH) is conducting a randomized controlled trial comparing intrapartum ST-analysis of the fetal ECG in combination with CTG to CTG alone as a multicentre trial across the USA (NCT01131260). It will be very interesting to compare these results with the European trials conducted so far in the light of these transatlantic differences regarding the performance of FBS. Finally, to increase the external validity of these results, we encourage a comparable analysis in other trials.

Conclusion

In our study the consensus based recommendation in the STAN criteria to additionally check fetal condition by FBS in case of an abnormal CTG beyond 60 minutes without ST-changes, has been effective for early identification of fetal acidosis. Consequent adherence to the STAN criteria may further decrease the necessity for FBS in addition to ST-analysis of the fetal ECG.

Acknowledgements

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Conflicts of interest

All authors declare that they had no potential conflicts of interest relevant to this article.

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Ethics approval statement

The original study was approved by the Institutional Review Board of the University Medical Centre Utrecht on the 5th of August 2005, approval number: 05-157 and had local approval from all other participating hospitals.

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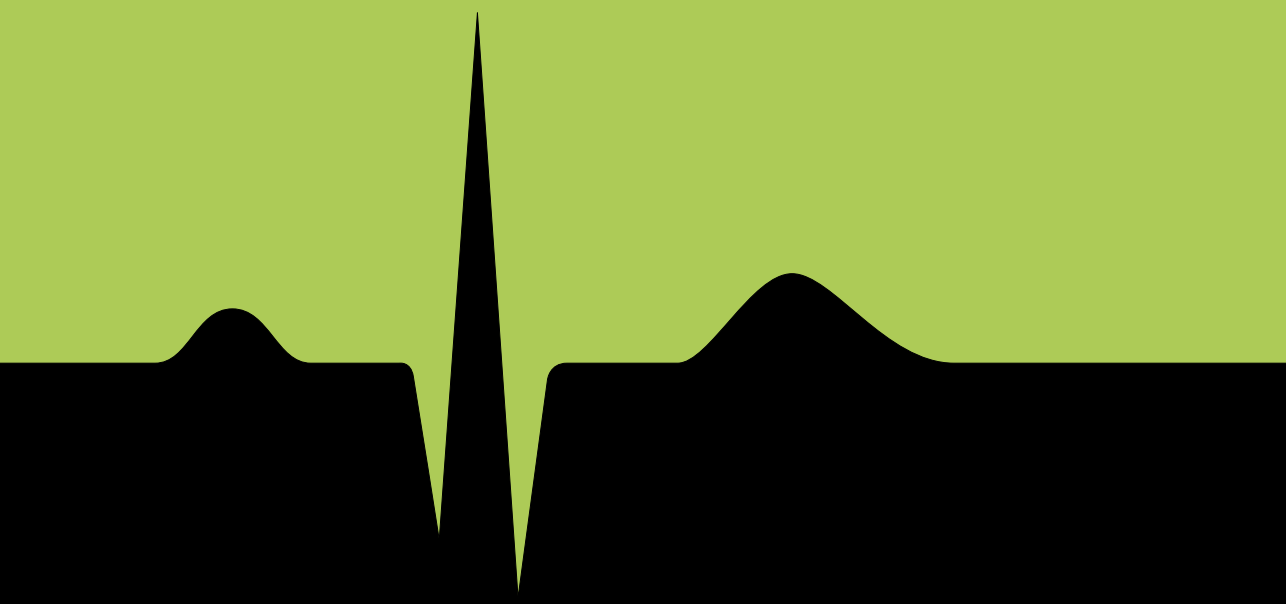
Predictive value of the baseline T-QRS ratio of the fetal electrocardiogram in intrapartum fetal monitoring: a prospective cohort study



Chapter 5

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Abstract

Objective
To evaluate the added value of the baseline T-QRS ratio to other known risk factors in predicting adverse outcome and interventions for suspected fetal distress.

Design
Prospective cohort study.

Setting
Three academic and six non-academic teaching hospitals in the Netherlands.

Population
Laboring women with a high-risk cephalic singleton pregnancy beyond 36 weeks of gestation.

Methods
We obtained STAN-recordings (ST-analysis, Neoventa, Sweden) from two previous studies. Three patient groups were defined: cases with adverse outcome, cases with emergency delivery because of suspected fetal distress without adverse outcome and a reference group of uncomplicated cases. Baseline T-QRS ratios among the adverse outcome and intervention for suspected fetal distress cases were compared to the uncomplicated cases. The ability for the baseline T/QRS to predict adverse outcome and suspected fetal distress was determined using a multivariable logistic model.

Main outcome measures
The added value of the baseline T/QRS to other known risk factors in the prediction of adverse outcome and interventions for suspected fetal distress.

Results
From 3,462 recordings 2,459 were available for analysis. Median baseline T/QRS for uncomplicated cases, adverse outcome and interventions for suspected fetal distress were 0.12 (range 0.00-0.52), 0.12 (0.00-0.42) and 0.13 (0.00-0.39), respectively. There was no statistical difference between these groups. Multivariable analysis showed no added value of baseline T/QRS in the prediction of adverse outcome or in the prediction of interventions for suspected fetal distress.

Conclusion
Baseline T/QRS has no added value in the prediction of adverse neonatal outcome or interventions for suspected fetal distress.

Introduction

ST-analysis of the fetal electrocardiogram (STAN; ECG) is an additional method for intrapartum fetal monitoring. Changes in the ST-segment of the fetal ECG are an indicator of myocardial stress. The T-wave represents the depolarization of myocardial cells. An increase in the T-wave indicates a threatened energy balance and glycogenolysis, whereas an ST-depression occurs in case of ischemia. When the energy balance of the heart is threatened, other central organs may be at risk for hypoxia as well. Therefore, ST-changes may serve as an indirect measurement of the condition of the fetal brain during labor[1–3]. Several parameters of the fetal ECG have been studied in the past, such as PR interval, QRS wave duration, T-QRS amplitude ratio, and ST slope[4–8]. In these studies, the T-QRS ratio (T/QRS) appeared to have the highest clinical value in predicting neonatal metabolic acidosis. Therefore, more recent randomized trials have focused on this[9–13].

The first trial used the absolute value of the T/QRS as an indication for intervention, with a cut-off point of T/QRS ≥ 0.25[13]. However, van Wijngaarden et al argued against the use of absolute T/QRS thresholds and recommended the use of individualized T/QRS over time to discriminate between compromised and non-compromised fetuses[14]. Recommendations for expedite delivery based on ST-changes were set in STAN clinical guidelines (Appendix 1). Subsequent studies used these changes in T/QRS over time, rather than an absolute threshold for the T/QRS as an indication for intervention[9–13]. In these studies, a baseline T/QRS was determined at start of registration and significant changes in T/QRS over time were indicated as a so-called *ST-event*. ST-events are interpreted together with the CTG to determine whether or not intervention is indicated.

In the current use of fetal ECG, the baseline T/QRS (i.e. the absolute value of the T-QRS ratio at the start of registration) is only used for comparison with later changes. In European STAN expert meetings held in 2007 and 2009 question marks were set regarding the interpretation of a high baseline T/QRS at the start of a registration, since several cases had been encountered in which neonates born with metabolic acidosis appeared to have high baseline T/QRS. This suggests that high baseline T/QRS could be predictive for intrapartum asphyxia.

Newbold et al showed great variation in baseline T/QRS recorded during labor in normal women[15], and Yli et al showed a frequent occurrence of ST-depression in fetuses from mothers with diabetes mellitus[16]. This study first aimed to quantify the predictive ability of baseline T/QRS for adverse neonatal outcome and interventions for suspicion of fetal distress. Our second aim was to evaluate which variables might influence the height of the baseline T/QRS.

Material and methods

For this study, we used STAN-tracings from a large observational cohort study and from a large randomized trial, including a total of 3,462 patients. Materials and methods of these studies have been described elsewhere[12,17].

The first study was the Dutch part of the European Implementation cohort study[17]. This study was executed between September 2000 and November 2002 at University Medical Centre, Utrecht. During the study period 637 women were monitored with STAN. The second study was a multicenter randomized trial comparing STAN-monitoring to CTG only[12]. In this trial 5,667 women participated, of which 2,827 were allocated to the STAN arm and were included in the present analysis. For this analysis, all singleton pregnancies in cephalic position beyond 36 weeks of gestation were studied.

Fetal ECG was automatically determined by the STAN S21 and S31 monitors (Neoventa Medical AB, Mölndal, Sweden). Each T/QRS was calculated from an average of 30 subsequent ECG-complexes. As soon as there was a 20 minutes window containing 20 T-QRS ratios, the baseline T/QRS was then calculated as the median value of these T-QRS ratios. Baseline T/QRS were automatically extracted from all STAN-tracings by Neoventa Medical AB. No patient information or information on neonatal outcome was provided to Neoventa Medical.

To address the first aim, the study population was divided into three outcome groups: uncomplicated cases, cases with adverse neonatal outcome (AO) and cases with a cesarean delivery or vaginal instrumental delivery because of suspected fetal distress (IFD). If a baby with adverse neonatal outcome was born by operative delivery it was classified in the AO group.

Uncomplicated cases were all cases in which labor was uneventful, leading to a delivery with normal neonatal outcome. Cases with vacuum extraction, forceps extraction or cesarean delivery for suspected fetal distress were included in the IFD group. Adverse neonatal outcome was defined as the presence of perinatal death, metabolic acidosis (defined as umbilical cord artery pH <7.05 and BDecf >12), umbilical cord artery pH <7.00, 5 min. Apgar score <7, neonatal intensive care unit (NICU) admittance or signs of moderate or severe hypoxic ischemic encephalopathy (HIE) at neonatal discharge. For the second aim, the outcome was the baseline T-QRS ratio itself.

Data analysis

In the analyses of the first aim, we used logarithmic transformation of the baseline T/QRS values because of a partly skewed distribution of baseline T/QRS in all three outcome groups. We then first estimated the difference in mean baseline ln(T/QRS) between uncomplicated cases, AO cases and cases with IFD, using one-way ANOVA.

To assess the predictive association of baseline T/QRS on the occurrence of adverse outcome and interventions for suspected fetal distress, first a univariable polytomous logistic regression analysis was performed. Polytomous (instead of dichotomous or

binary) logistic regression allows for simultaneous estimation of the probability of more than two different outcomes [18]. This method fits simultaneous logistic regression models to compare each of the outcomes (AO and IFD) with the reference category (uncomplicated cases). Subsequently, the independent predictive value of baseline T/QRS to known risk factors of adverse outcome and intervention for suspected fetal distress was assessed using multivariable logistic regression analysis. Based on the literature, the following risk factors for adverse outcome and interventions for suspected fetal distress were included: prolonged gestational age (defined as a gestational age beyond 41 weeks), nulliparity, previous cesarean delivery, maternal diabetes, intra-uterine growth restriction (IUGR) and meconium-stained amniotic fluid[19–22]. Besides adding the logarithm (ln) (T/QRS) as a continuous variable to the model, we also performed multivariable logistic regression with 'high baseline T/QRS' as a dichotomous variable. High baseline T/QRS was defined as a baseline T/QRS more than two standard deviations elevated from the mean T/QRS in the group of uncomplicated cases after logarithmic transformation. Because Westgate et al. used a threshold of T/QRS ≥ 0.25 to be classified as being rised[13], we repeated the logistic regression analysis with high baseline T/QRS being defined as T/QRS ≥0.25 to identify possible differences in sensitivity in the prediction of AO or IFD between these two thresholds of high baseline T/QRS. The ability of the models without and with (high) baseline T/QRS to discriminate between women with and without a child with AO or IFD was studied with the likelihood ratio test (using a p-value of 0.15) and the area under the Receiver Operating Characteristic (ROC) curve (c-statistic).

Furthermore, in the subgroup of cases with high baseline T/QRS (≥0.25 or ≥2SD from the mean) the CTG during the first 60 minutes of the registration was classified as being normal, intermediate, abnormal or preterminal according to the FIGO guidelines[23] (Appendix 1). The different outcome groups were compared between the CTG classifications.

For the second aim, the following variables were hypothesized to have a possible association with the height of the baseline T/QRS value: gestational age, birthweight, fetal gender and maternal diabetes. To address this, we analyzed the group of uncomplicated cases only, using both univariable and multivariable linear regression analysis with baseline T/QRS as the dependent variable. Variables showing a p-value <0.20 in univariable analysis were included in the multivariable linear regression model. Statistical analysis was performed using SPSS 15.0 for Windows.

The original study was approved by the Institutional Review Board of the University Medical Centre Utrecht on the 5th of August 2005, approval number: 05-157 and had local approval from all other participating hospitals.

Results

There were 3,451 women eligible for inclusion (Figure 1). For 757 women (22%) STAN-

tracings were not available. For 234 (9%) of the remaining women umbilical cord data were incomplete and they were therefore excluded from the analyses. A total of 2 459 women with complete data on all study variables were available for analysis. Baseline characteristics of the completely observed study population and the excluded patients are shown in Table 1. There were no major differences between the two groups, indicating that there were no selectively missing data (largely missing at random). Hence, analyses of the completely observed women would yield valid results.

Among 2,459 neonates, 68 (2.8%) with an adverse neonatal outcome were identified. In 220 cases (8.9%) operative delivery was performed because of suspected fetal distress, of which 89 were by cesarean delivery and 131 by vaginal instrumental delivery. In all 2,171 (88.3%) women had an uncomplicated delivery. Table 2 shows the baseline characteristics for all uncomplicated, AO and IFD cases.

Median baseline T/QRS for the uncomplicated, AO and IFD cases was 0.12 (range 0.00-0.52), 0.12 (0.00-0.42) and 0.13 (0.00-0.39), respectively (Table 3). Univariable polytomous logistic regression analysis showed no statistically significant relation between ln(T/QRS) and AO (OR 1.09, 95% CI 0.69-1.75) or between ln(T/QRS) and IFD (OR 1.27, 95% CI 0.97-1.66). In the multivariable analysis, three conventional risk factors were identified to independently predict AO (Table 4): nulliparity (OR 2.68, 95% CI 1.38-5.20), history of cesarean section (OR 2.35, 95% CI 0.99-5.60), and maternal diabetes (OR 2.12, 95% CI 0.75-6.01). After adding ln(T/QRS) to this model (OR 1.08, 95% CI 0.67-1.75; p-value=0.75) the area under the ROC curve changed marginally from 0.607 to 0.614.

The following risk factors were identified to predict IFD (Table 4): prolonged pregnancy (OR 1.43, 95% CI 1.07-1.89), nulliparity (OR 3.51, 95% CI 2.34-5.27) and history of cesarean section (OR 2.45, 95% CI 1.43-4.20). After adding ln(T/QRS) to this model (OR 1.22, 95% CI 0.92-1.60 the area under the ROC curve again changed marginally from 0.629 to 0.638. ROC curves are shown in Figures 2A and 2B.

In the log normal distribution the mean ln(T/QRS) was -2.1581 with 0.52458 standard deviation. After transformation the threshold for high baseline T/QRS was set on 0.33 (i.e. $e^{-1.1089} = 0.3299$). Multivariable analysis with high baseline T/QRS included as a dichotomous variable defined as T/QRS ≥0.33 or as T/QRS ≥0.25 again showed marginally, non-significant, improve in predictive ability for AO and IFD (Table 5).

There were 140 fetuses (5.7%) with T/QRS ≥0.25 of which 99 had a normal CTG pattern at the start of the registration, 17 an intermediate CTG pattern and 34 an abnormal CTG pattern. There were 44 fetuses (1.8%) with T/QRS ≥0.33 of which 28 had a normal CTG pattern at the start of the registration, six an intermediate CTG pattern and 10 an abnormal CTG pattern. Both for T/QRS ≥0.25 and for T/QRS ≥0.33 there were no differences in CTG classification between these groups (Table 6).

All of the selected variables showed a significant association with the baseline T/QRS in univariable analyses: increasing gestational age in days, increasing birthweight and male fetal gender were associated with higher levels of baseline T/QRS, while presence

Figure 1: Flowchart of the study population

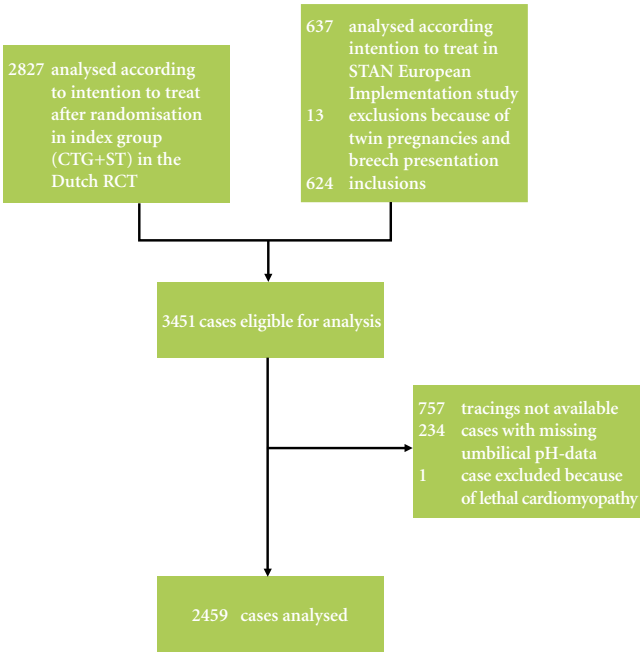

Table 1: Baseline characteristics of included and excluded patients

Characteristic n(%) or Mean	Study population (n = 2459)	Excluded patients (n = 992)
Mean patient age at delivery - years	31.7	32.3
Mean gestational age at delivery - weeks	40.2	40.1
Nulliparous	1452 (59)	563 (56.8)
Previous cesarean delivery	283 (11.5)	104 (10.5)
Prolonged pregnancy (>41 weeks)	852 (34.6)	316 (31.9)
Induction of labor	982 (39.9)	397 (40)
Meconium-stained amniotic fluid	662 (26.9)	248 (25)
Epidural analgesia	893 (36.3)	394 (39.7)
Mean birthweight - gram	3548	3528
Birthweight <2500 g	48 (2)	22 (2.2)*
Neonatal male sex	1319 (53.6)	517 (52.1)

* Data available of 987 women

of maternal diabetes was associated with lower levels of baseline T/QRS (Table 7). For example, for gestational age we found that beyond a gestational age of 36 weeks (which was the inclusion criterion), per extra day of pregnancy, the ln(T/QRS) increased by 0.009 (95% CI 0.007-0.011), which was a significant association.

In the multivariable linear regression analysis, only presence of maternal diabetes, gestational age (days) and fetal sex remained associated with ln(T/QRS). Although all of these variables showed highly significant associations with baseline ln(T/QRS), effect sizes were small and accounted for very little of the overall variation in baseline ln(T/QRS) expressed by an adjusted R^2 of 0.054, which means that only 5.4 per cent of the total variance in ln(T/QRS) was explained by these variables.

Table 2: Baseline characteristics of the study population, comparison of the different outcome groups

Characteristics N(%) or Mean (SD)	All cases n = 2459	Uncomplicated n = 2171	AO n = 68	IFD n = 220
Mean Maternal age – years	31.7 (4.9)	31.7 (4.9)	31.8 (4.7)	31.9 (5.0)
Nulliparous		1231 (56.7)	50 (73.5)	171 (77.7)
Mean gestational age at delivery – weeks	40.2 (1.5)	40.2 (1.5)	40.2 (1.6)	40.5 (1.3)
Prolonged pregnancy (≥41 weeks)	852 (34.6)	733 (33.8)	25 (36.8)	94 (42.7)
Maternal diabetes	81 (3.3)	71 (3.3)	4 (5.9)	6 (2.7)
Induction of labor	982 (39.9)	877 (40.4)	28 (41.2)	77 (35.0)
Meconiumstained amniotic fluid	662 (26.9)	580 (26.7)	18 (26.5)	64 (29.1)
Epidural analgesia	893 (36.3)	759 (35.0)	32 (47.1)	102 (46.4)
Mean birthweight – gram	3548 (520)	3562 (517)	3433 (618)	3436 (491)
Birthweight <2500 g	48 (2.0)	37 (1.7)	5 (7.4)	6 (2.7)
Neonatal male gender	1319 (53.6)	1145 (52.7)	42 (61.8)	132 (60.0)
Mean Umbilical cord blood pH	7.21 (0.08)	7.22 (0.07)	7.08 (0.13)	7.18 (0.08)

Uncomplicated = uncomplicated cases, AO = cases with adverse outcome, IFD = cases with intervention because of suspected fetal distress, SD = standard deviation

Table 3: Median values of Baseline T/QRS in the different outcome groups

Baseline T-QRS ratio	Uncomplicated n = 2171	AO n = 68	IFD n = 220
Median (IQR)	0.12 (0.08)	0.12 (0.09)	0.13 (0.09)
Geometric mean†	0.12	0.12	0.12
p-value*	0.223		

Uncomplicated = uncomplicated cases, AO = cases with adverse outcome, IFD = cases with intervention because of suspected fetal distress, IQR = interquartile range † geometric mean = Exp (mean ln(T/QRS))
* p-value was calculated using one-way ANOVA of the logarithmically transformed baseline T/QRS

Table 4: Multivariable models for the prediction of adverse neonatal outcome and interventions for suspected fetal distress with and without ln(T/QRS)* as a predictive variable. Adjusted odds ratios and area under receiver operator characteristics (ROC) curve.

Prediction of adverse neonatal outcome			
Model	**Variables included**	**OR (95% CI)**	**Area under ROC curve**
Model 1	Nulliparity History of caesarean section Maternal diabetes	2.68 (1.38-5.20) 2.35 (0.99-5.60) 2.12 (0.75-6.01)	0.607
Model 2	Nulliparity History of caesarean section Maternal diabetes Ln(T/QRS)*	2.88 (1.44-5.75) 2.55 (1.05-6.17) 2.21 (0.78-6.30) 1.08 (0.67-1.75)	0.614
Prediction of interventions for suspected fetal distress			
Model	**Variables included**	**OR (95% CI)**	**Area under ROC curve**
Model 1	Prolonged pregnancy Nulliparity History of cesarean section	1.43 (1.07-1.89) 3.51 (2.34-5.27) 2.45 (1.43-4.20)	0.629
Model 2	Prolonged pregnancy Nulliparity History of cesarean section Ln(T/QRS)*	1.36 (1.02-1.82) 3.47 (2.31-5.21) 2.40 (1.40-4.12) 1.22 (0.92-1.60)	0.638

Ln(T/QRS) = logarithmic transformation of the T-QRS ratio

Figure 2A: ROC-curves for the prediction of adverse outcome with and without ln(T/QRS) in the predictive model

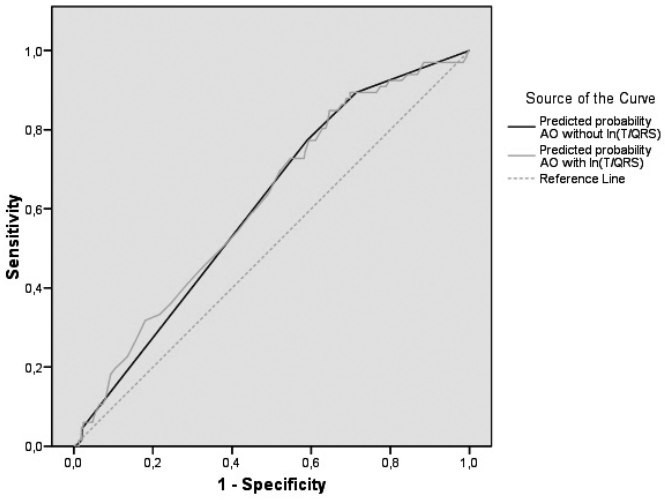

Figure 2B: ROC-curves for the prediction of interventions for suspected fetal distress with and without ln(T/QRS) in the predictive model

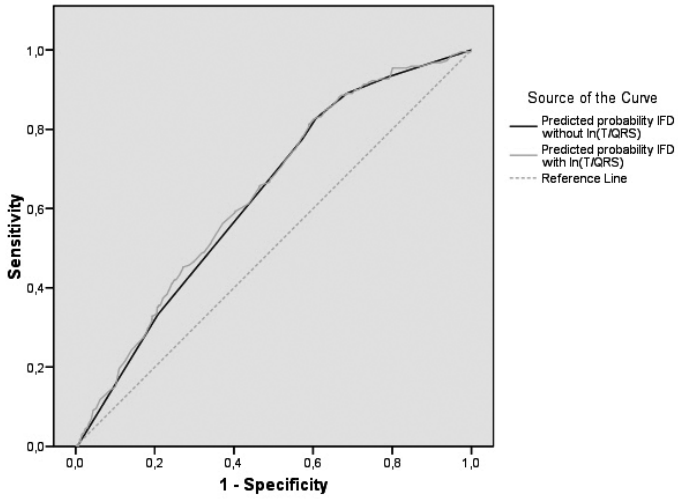

Table 5: Multivariable models for the prediction of adverse neonatal outcome and interventions for suspected fetal distress with and without high baseline T/QRS (T/QRS ≥ 0.25 and T/QRS ≥ 0.33) as a dichotomous predictive variable. Adjusted odds ratios and area under receiver operator characteristics (ROC) curve.

Prediction of adverse neonatal outcome			
Model	**Variables included**	**OR (95% CI)**	**Area under ROC curve**
Model 1	Nulliparity History of caesarean section Maternal diabetes	2.68 (1.38-5.20) 2.35 (0.99-5.60) 2.12 (0.75-6.01)	0.603
High baseline T/QRS defined as ≥ 0.33			
Model 2	Nulliparity History of caesarean section Maternal diabetes T/QRS ≥ 0.33	2.68 (1.38-5.20) 2.35 (0.99-5.60) 2.11 (0.74-6.00) 0.79 (0.11-5.86)	0.603
High baseline T/QRS defined as ≥ 0.25			
Model 3	Nulliparity History of cesarean section Maternal diabetes T/QRS ≥ 0.25	2.67 (1.38-5.19) 2.35 (0.99-5.61) 2.10 (0.74-5.95) 0.71 (0.22-2.29)	0.604
Prediction of interventions for suspected fetal distress			
Model	**Variables included**	**OR (95% CI)**	**Area under ROC curve**
Model 1	Prolonged pregnancy Nulliparity History of cesarean section	1.43 (1.07-1.89) 3.51 (2.34-5.27) 2.45 (1.43-4.20)	0.631
High baseline T/QRS defined as ≥ 0.33			
Model 2	Prolonged pregnancy Nulliparity History of cesarean section T/QRS ≥ 0.33	1.42 (1.07-1.89) 3.51 (2.34-5.27) 2.45 (1.42-4.20) 1.16 (0.45-3.00)	0.632
High baseline T/QRS defined as ≥ 0.25			
Model 3	Prolonged pregnancy Nulliparity History of cesarean section T/QRS ≥ 0.35	1.41 (1.06-1.88) 3.52 (2.34-5.28) 2.44 (1.42-4.19) 1.36 (0.81-2.29)	0.634

Ln(T/QRS) = logarithmic transformation of the T-QRS ratio

Table 6: CTG classification at the start of the registration for cases with high baseline T/QRS (T/QRS ≥ 0.25 and T/QRS ≥ 0.33)

		CTG classification				
Outcome	Baseline T/QRS	Normal n(%)	Intermediate n(%)	Abnormal n(%)	Preterminal n(%)	Total n
Uncomplicated	≥ 0.25 ≥ 0.33	86 (66.2) 25 (64.1)	15 (11.5) 5 (12.8)	28 (21.5) 9 (23.1)	0 0	129 39
AO	≥ 0.25 ≥ 0.33	2 (66.7) 1 (100.0)	0 0	1 (33.3) 0	0 0	3 0
IFD	≥ 0.25 ≥ 0.33	11 (61.1) 3 (60.0)	2 (11.1) 1 (20.0)	5 (27.8) 1 (20.0)	0 0	18 5

Table 7: Influences of the baseline T/QRS: univariable and multivariable linear association with ln(T/QRS) as the dependent variable

Univariable association with ln(T/QRS)			
Variable	Regression coefficient	95% CI	P-value
Gestational age (days)	0,009	0,007-0,011	<0.001
Birthweight (grams)	0.0000668	0.00-0.00	0.002
Male fetal gender	0,153	0,108-0,197	<0.001
Maternal diabetes	-0.198	-0.322- -0.075	0.002
Multivariable model for the prediction of ln(T/QRS)			
Variables included	Regression coefficient	95% CI	P-value
Gestational age (days)	0.009	(0.007-0.011)	<0.001
Sex	0.155	(0.111-0.199)	<0.001
Maternal diabetes	-0.11	(-0.236-0.010)	0.072
Adjusted R2 = 0.054			

Discussion

This study aimed to offer a scientific ground for the assumption of a clinical value of baseline T/QRS for predicting adverse outcome. We did not find any arguments for the use of a high baseline T/QRS at the start of the recording in the prediction of adverse neonatal outcome or intervention for fetal distress. We have performed multivariable regression analyses with both baseline T/QRS as a continuous variable and high baseline T/QRS as a dichotomous variable. These variables showed no significant association with adverse outcome and interventions for suspected fetal distress and the AUC for both ROC-curves showed only marginal improvement after adding these variables to a predictive model, also indicating that these variables showed no additional value in the prediction of adverse outcome or interventions for suspected fetal distress. We did not find any association with adverse outcomes when the CTG-patterns at the start of the registration of cases with a high baseline T/QRS were analyzed separately.

When STAN was first introduced, general clinical guidelines were composed, which were used in the Plymouth trial[13]. These guidelines were adjusted with the development and introduction of the STAN S21 device and extended with recommendations during a STAN consensus meeting in 2007[24]. Both the STAN guidelines and its accompanying recommendations have previously been published elsewhere[25]. During the most recent STAN expert meeting, held in 2009, it appeared that some groups had extended the original STAN-guidelines, based on the experience of several cases with adverse neonatal outcome which had high baseline T/QRS. In this study we have demonstrated that the baseline T/QRS has no predictive value for adverse neonatal outcome or interventions for suspected fetal distress.

In the past, several studies have been published about the variation in baseline T/QRS of fetal ECG-recordings during labor in normal subjects[15,26,27]. In all these studies reference values were only based on small numbers of measurements. In our study reliable reference values could be assessed by using a large number of patients. Furthermore, we demonstrated that fetal gender, presence of maternal diabetes and gestational age have an independent association with the baseline T/QRS, although the effect sizes were small and accounted for very little of the overall variation in baseline T/QRS. Although we found no literature on the effect of fetal gender and birthweight on the *amplitude* of the QRS complex and ST-segment, several studies can be found on the effect of these variables on the *conduction times* of the fetal ECG. Rijnbeek et al. showed a longer QRS duration in the male compared to the female fetus[28], and Morgan et al. found positive correlation between QRS width and birthweight [29]. Interestingly, van Leeuwen et al. not only showed shortening of conduction times in the growth-restricted fetus, but also that these changes were different between the male and female fetus which might be caused by hormonal differences[30].

Yli et al. showed a higher incidence of ST depression during labor in fetuses of mothers with diabetes mellitus[16], but no information is present on the T-QRS ratio. This might

indicate that diabetes might predominantly influence the ST-segment of the fetal ECG, while fetal gender and birthweight seems to have a more dominant influence on the QRS-complex.

A last interesting point is the hypothesis that baseline T-QRS ratio is influenced by fetal arousal, which is physiologic during labor[31]. Other studies also showed that ST-events occur frequent during normal CTG-patterns[32]. When the baseline T/QRS is being determined during such physiological periods of T/QRS elevation, it might be possible that pathological T/QRS rises later on in labor are not shown by the STAN monitor as these will not reach the threshold which has been set at the start of the registration during the period of physiological arousal.

To appreciate the present results, some limitations have to be taken into account. Although the variables used for the multivariable regression analysis for the prediction of AO and IFD were based on existing literature on risk factors for AO and IFD, to our knowledge there is no study that computed a well-fitted prediction model for these outcomes. The model we computed was made to act as a reference model to investigate the added value of baseline T/QRS and was not computed for an accurate prediction of adverse outcome or interventions for suspected fetal distress in the general population. To serve this goal, a computed model should first be validated internally and corrections for optimism should be made, where after the model has to be validated in a different population. This outreached the goal for the present study.

Furthermore, the large number of missing registrations and baseline T-QRS ratios due to technical failures might influence the results. However, we still compared more than 2,100 laboring women for our analyses and the missing registrations seem to be missing completely at random, thus not introducing bias.

Finally, we did not assess all recordings of cases with interventions for suspected fetal distress regarding the indication of suspected asphyxia. Although we are aware that this might bias the results as it could lead to an underestimation of the predictive value of the baseline T-QRS ratio, this kind of assessment is difficult since the researchers were only informed about some aspects of the delivery and not all information that has led to the clinician's decision to intervene was present. However, since the mean arterial pH of the cases with an intervention for fetal distress was substantially lower than that in the normal outcome cases and since we showed that baseline T-QRS ratio has no predictive value in the prediction of adverse outcome, we believe that it is not a major issue for our study and results.

Conclusion

This is the first study to address the role of baseline T/QRS in respect to adverse neonatal outcome and interventions for suspected fetal distress. This study showed that baseline T/QRS is not discriminating in the prediction of adverse neonatal outcome or interventions for suspected fetal distress. Therefore, the current European guidelines are still suitable (and local STAN guidelines should be (re)adjusted if appropriate). Fetal sex, presence of maternal diabetes and gestational age influence the height of the baseline T/QRS, but account for little of the total variation of baseline T/QRS.

Acknowledgements

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Conflicts of interest

All authors declare that they had no potential conflicts of interest relevant to this article.

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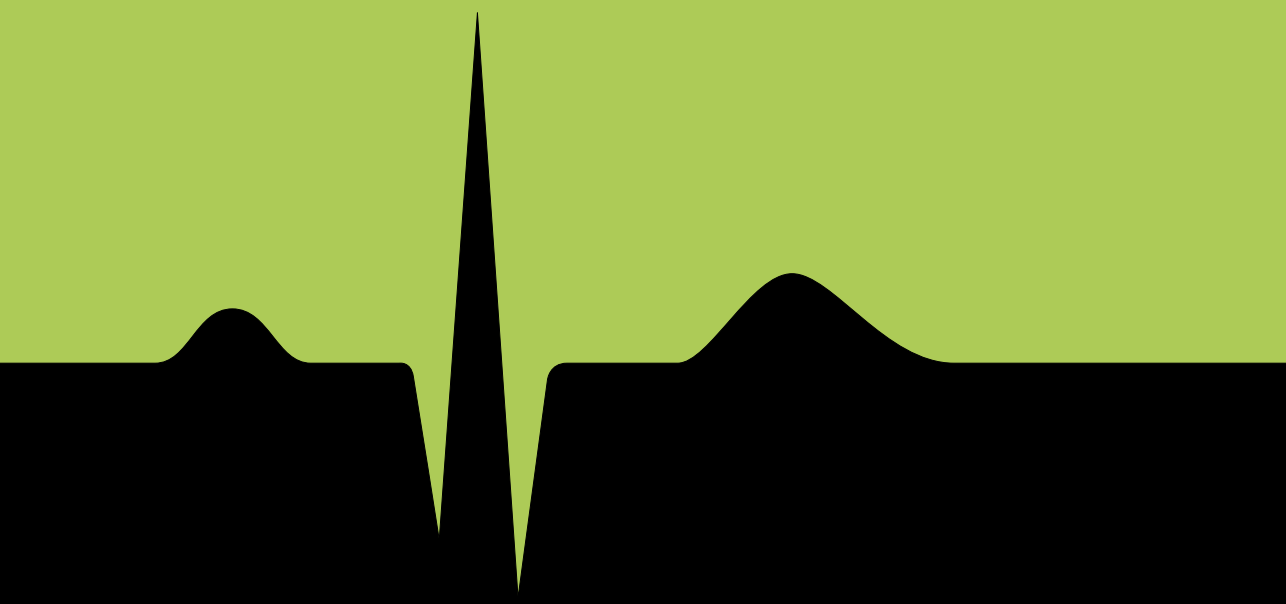
The predictive value of biphasic events in ST analysis of the fetal electrocardiogram for intrapartum fetal monitoring



Chapter 6

Jeroen H Becker, Anniek Krikhaar, Ewoud Schuit, Annika Mårtendal, Karel Maršál, Anneke Kwee, Gerard HA Visser, Isis Amer-Wåhlin

Abstract

Objective

To study the predictive value of biphasic ST-events for interventions for suspected fetal distress (IFD), and adverse neonatal outcome (AO), when using ST analysis of the fetal electrocardiogram (ECG) for intrapartum fetal monitoring

Study design

Prospective cohort study

Setting

Three academic hospitals in Sweden

Population

Laboring women with a high-risk singleton fetus in cephalic position beyond 36 weeks of gestation

Methods

In laboring women who were monitored with conventional cardiotocography (CTG), ST-waveform analysis was recorded and concealed. Fetuses with biphasic ST-events of the fetal electrocardiogram (FECG) (index) were compared with fetuses without biphasic events of the FECG concerning the presence of IFD and AO. Multivariable logistic regression was used to assess the added value of biphasic events in the prediction of IFD and AO.

Main outcome measures

Interventions for suspected fetal distress, and adverse neonatal outcome (defined as presence of either metabolic acidosis (i.e. umbilical cord pH <7.05 and BDecf >12mmol), umbilical cord pH <7.00, five-minute Apgar score <7, admittance to neonatal intensive care unit (NICU), or perinatal death), related to the presence of biphasic events.

Results

Although women with presence of biphasic events of the FECG monitored during labor, had more IFD and an increased risk of giving birth to neonates with AO, compared with women without biphasic events, presence of *significant* (i.e. intervention advised) biphasic events showed no independent association with IFD (OR 1.71, 95% CI: 0.65-4.50) or AO (OR 1.96, 95% CI: 0.74-5.24), and significant biphasic events showed no added value in the prediction of IFD or AO.

Conclusion

This study suggests that the presence of significant biphasic events is not discriminating in the prediction of IFD or AO. Therefore, the justification of biphasic events in the current STAN guidelines is questionable and might lead to an unnecessary increase in operative deliveries without improving neonatal outcome.

Introduction

ST analysis of the fetal electrocardiogram (ECG) in combination with conventional cardiotocograpghy (CTG; STAN) was introduced in the 1990s to help the obstetric clinician to identify the fetus at risk for asphyxia. Changes in the ST-segment of the fetal ECG are an indicator of myocardial stress. The T-wave represents the depolarization of myocardial cell. An increase in the T-wave indicates a threatened energy balance and glycogenolysis, whereas an ST-depression occurs in case of ischemia. When the energy balance of the heart is threatened, other central organs may be at risk for hypoxia as well. Therefore, ST-changes may serve as indirect indicators of the condition of the fetal brain during labor.[1–3] Whether or not STAN improves fetal outcome in comparison to conventional CTG has been evaluated in several randomized trials since.[4–8] The current STAN clinical guidelines defines three different types of ST-changes: (1) baseline ST-events, which reflect a rise in the T-QRS ratio (T/QRS) that lasts longer than 10 minutes; (2) episodic baseline events, which reflect a rise in T/QRS that returns to normal limits within 10 minutes; and (3) biphasic ST-events, which reflects a decrease of the T/QRS. The biphasic events can be divided into three subclasses: a class 1 biphasic event reflects a negative ST-slope, but with the entire ST-segment above the baseline of the fetal ECG (FECG). A class 2 biphasic event has a negative ST-slope and the ST-segment crosses the FECG baseline, while a class 3 biphasic event has a negative ST-slope and lies entirely below the FECG baseline.

Although in the first randomized trial on ST-waveform analysis, obstetric management was influenced only by T/QRS rises[8], the addition of biphasic ST-events in the STAN guidelines results from several observations in animal studies: Widmark et al. showed that, in contrast to guinea-pigs of normal growth who showed a rise in T/QRS, the growth retarded guinea-pigs showed a decrease in T/QRS, when hypoxia was induced by umbilical cord occlusion.[9] In addition, Westgate et al. found that near-term sheep, in reaction to umbilical cord occlusion, showed an initial rise of the T/QRS, followed by a decrease in T/QRS.[2] They hypothesized that biphasic ST waveforms might reflect severe cardiac decompensation. In human studies, Yli et al. demonstrated that biphasic events are more common in fetuses of mothers with diabetes mellitus.[10] However, the presence of biphasic events was not correlated with hypoxia, but was thought to result from an altered ability of the fetal myocardium to response to the stress of labor. This finding was confirmed in a later study by the same group, again showing that the increased prevalence of biphasic events in fetuses from mothers with diabetes didn't correlate to moderate acidemia.[11] The uncertain ability of biphasic events to predict asphyxia was also shown in a secondary analysis of the Swedish RCT, in which Norén et al. found biphasic events in 5.6% of laboring women, not primarily associated with acidemia.[12] Finally, Kwee et al. surprisingly found a reduced incidence of biphasic events in deliveries complicated by meconium-stained amniotic fluid and maternal hypertension, in which one could expect a higher rate of fetal hypoxia.[13]

The performance of fetal monitoring depends on the ability of the staff to interpret the recordings and to manage the cases according to specific guidelines. Although the current STAN guidelines are pretty straightforward in the interpretation of baseline T/QRS rises and episodic T/QRS rises, the interpretation of biphasic events is more complex. Whether or not the occurrence of biphasic events reflect fetal hypoxia depends not only on the classification of the CTG pattern, but also on the number and class of biphasic messages, the time span between the biphasic messages and the clinical situation.
Because of the difficulties in interpreting biphasic ST-events, and the uncertain ability of biphasic events to predict asphyxia, we aimed to evaluate the added value of biphasic events in the prediction of adverse neonatal outcome.

Materials and methods

Data was used from a previously published Swedish trial that compared STAN with conventional CTG alone.[4,14] In this trial, 5,049 laboring women with a singleton fetus in cephalic position were randomly assigned to intrapartum fetal monitoring using CTG plus ST-analysis (CTG+ST group, n=2,565), or intrapartum fetal monitoring using conventional CTG alone (CTG group, n=2,484). In the CTG group, ST analysis was recorded but not shown, and clinical management was guided by CTG interpretation according to the FIGO guidelines[15] (Appendix 1) with the option of fetal blood sampling at the discretion of the clinician. In the CTG+ST group, ST-analysis of the fetal ECG was shown and clinical management was guided by CTG interpretation and supported by computerized ST-waveform assessment (ST log) according to the trial protocol. In the present study, only the concealed registrations of the CTG group were used. Of this cohort, all registrations which showed biphasic events at any given time were extracted and CTG patterns were classified according to the FIGO guidelines[16] by two independent reviewers (AKr and AM). CTG patterns at the start of the registration, and when ST-events occurred, were classified as being normal, intermediate, abnormal, or preterminal. In discordant cases, the opinion of three other independent reviewers (JB, AKw, and IAW) was decisive. During CTG interpretation, clinical information was not available for the reviewers. Depending on the number and type of biphasic event (i.e. class 1,2 or 3), the events were classified as being *significant* (i.e. intervention advised) or not. To be classified as being significant according to the STAN clinical guidelines, two or three biphasic messages of class 2 or 3 must be accompanied with an intermediary or abnormal CTG pattern.[15] The maximal time interval between different biphasic events to be linked together was set at 60 minutes.
Registrations with poor signal quality >25% of the final 120 minutes of registration and registrations with a total registration time <20 minutes were excluded from analysis. Although the originally published Swedish RCT was performed according to a modified intention-to-treat principle[4], a new analysis was published recently according to the

standard intention-to-treat principle.[14] In the latest analysis all randomized women were where included, however we decided to exclude all cases with malformation, breech presentation, premature labor, and with a change in monitoring mode during delivery since these factors might influence the incidence of biphasic events (i.e. malformation, breech presentation, and prematurity) or could have influenced the concealing of ST-waveform analysis during the delivery (i.e. change of monitoring mode).

Adverse neonatal outcome (AO) was defined as presence of either metabolic acidosis (i.e. umbilical cord pH <7.05 and BDecf >12mmol), umbilical cord pH <7.00, five-minute Apgar score <7, admittance to neonatal intensive care unit (NICU), or perinatal death.

In addition to study the predictive value of significant biphasic events for adverse neonatal outcome, we also decided to assess if significant biphasic events have an independent association with interventions for suspected fetal distress, since, if such an association exists, this might have influenced the incidence of adverse neonatal outcome. All women with operative vaginal deliveries and cesarean deliveries because of CTG abnormalities or low fetal scalp pH were classified as having an intervention for suspected fetal distress (IFD).

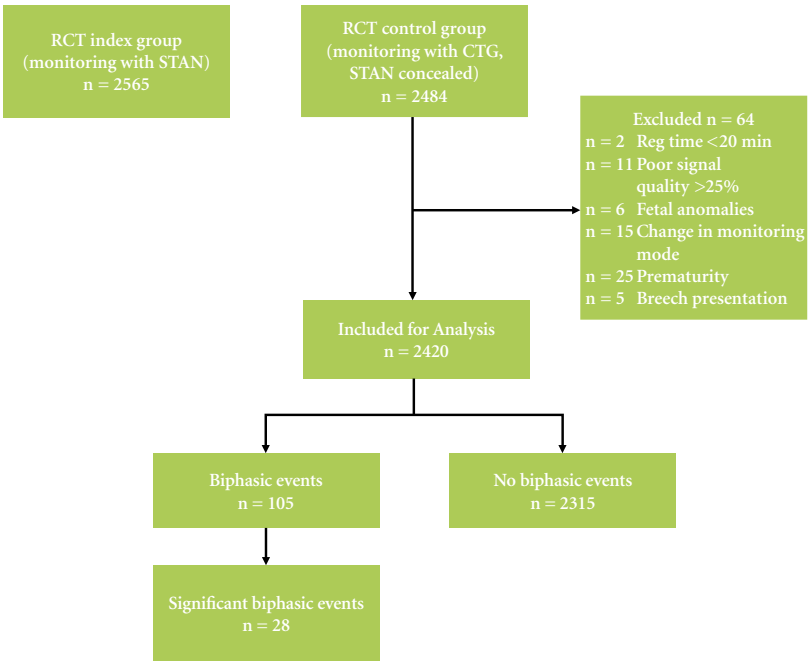
To study the association of biphasic events with IFD and AO, in the cohort of women with concealed recordings of ST-waveform analysis, women in labor with a fetus that showed biphasic events of the FECG (index) were compared with women with a fetus without biphasic events of the FECG (controls) concerning the presence of IFD and AO. The ability of biphasic events to predict IFD and AO was assessed using multivariable logistic regression with the presence of IFD and AO as the dependent, and presence of *significant* (i.e. intervention advised) biphasic events as one of the independent variables. Based on the literature, the following risk factors for IFD and AO were also included in the multivariable logistic regression analysis: prolonged gestational age (defined as a gestational age beyond 41 weeks), nulliparity, birthweight <2500 gram, maternal diabetes and meconium-stained amniotic fluid.[17–20]

Statistical analysis was performed using SPSS 15.0 for Windows. Descriptive information is given in absolute numbers (%), median and/or mean (±SD). For continuous variables, Mann-Whitney test was be used to test if cases differed significantly from controls. Categorical data was compared using the x^2 test or Fisher's exact test. P-values <0.05 were considered significant.

Results

Of 5,049 women included in the previously published trial, 2484 were allocated to fetal monitoring using only conventional CTG.[14] Although intrapartum treatment was solely based on conventional CTG, ST-waveforms were registered by the computer and concealed for both patient and clinician. Of these, 64 cases were excluded because of a

Figure 1: flowchart



registration time <20 minutes (n=2), poor signal quality >25% (n=11), fetal anomalies (n=6), change in monitoring mode during delivery (n=15), premature delivery (n=25), and breech presentation (n=5). A total of 2,420 women were included for analysis. In this group, 105 FECG registrations showed biphasic events, of which 28 registrations showed *significant* biphasic events (i.e. intervention advised) (Figure 1).

The baseline characteristics of women with biphasic events of the FECG, with significant biphasic events of the FECG, and without biphasic events of the FECG registration are shown in Table 1. Women with (any type of) biphasic were more often nulliparous than women without biphasic events, and had more often induction of labor, epidural analgesia, and oxytocin augmentation than women without biphasic events. Remarkably, meconium-stained amniotic fluid was more often present in women with *significant* biphasic events, and less often in women with any type of biphasic events when compared with women without biphasic events. The incidence of male fetal gender was much higher in women without biphasic events than in women with biphasic events. Furthermore, there were more operative vaginal deliveries and cesarean deliveries among women with (any type of) biphasic events of the FECG compared with women without biphasic events. Neonates with (any type of) biphasic events showed more adverse neonatal outcome compared with neonates without biphasic events, and a higher incidence of birthweight <2500 gram (Table 2). Cord artery pH data was missing

of 18 neonates with biphasic events, 5 neonates with significant biphasic events, and 317 neonates without biphasic events. Of the women with significant biphasic events and missing arterial cord-pH (n=5), venous cord pH was available in all cases and showed a pH of 7.19, 7.26, 7.37, and 7,44; indicating that, most likely, neonatal outcome was uncomplicated in these cases.

Logistic regression analysis showed no independent association of presence of *significant* (i.e. intervention advised) biphasic events with interventions for suspected fetal distress (OR 1.71, 95% CI: 0.65-4.50) (Table 3). Because of the differences in baseline characteristics of women with and without biphasic events of the FECG registration, next to the earlier described risk factors for IFD and AO, other variables have been included in the multivariable analysis to adjust for these baseline differences. The area under the ROC curve (AUC) increased only marginally when presence of significant biphasic events was added to the multivariable logistic model (AUC: 0.660 to 0.661), showing that presence of significant biphasic events has no added value in the prediction of interventions for suspected fetal distress (Figure 2).

In addition, presence of significant biphasic events showed no independent association with adverse neonatal outcome (OR 1.96, 95% CI: 0.74-5.24) (Table 4). The area under the ROC curve again only marginally increased when presence of significant biphasic events was added to the multivariable logistic model (AUC: 0.658 to 0.659) (Figure 3), again showing that presence of significant biphasic events had no added value in the prediction of adverse neonatal outcome in the studied cohort (Figure 3).

Discussion

This is the first study on the predictive value of biphasic events of the FECG for interventions for suspected fetal distress and adverse neonatal outcome. In this cohort, presence of *significant* biphasic events (i.e. intervention advised) has no added value in the prediction of interventions for suspected fetal distress or adverse neonatal outcome.

Although animal studies have shown that the ST segment of hypoxia-induced sheep can show a biphasic pattern[2,9], the association of biphasic events with adverse outcome in humans has been a subject of debate.[10–13,21] Since the development of STAN, clinical guidelines has been expert- rather than evidence-based, and since the same guidelines are rather complex concerning the need for intervention when biphasic events are present, we studied the added predictive value of significant biphasic events in a cohort of women with concealed STAN recordings. Although ST-waveform analysis of the FECG was registered in these women, it was concealed to the clinician and management was guided by interpretation of the CTG pattern alone. Since obstetric management was not influenced by the possible presence of ST-events, this gave us the unique opportunity to evaluate the predictive value of biphasic ST-events. The results show that,

Table 1: Baseline characteristics of women with biphasic events, women with significant biphasic events, and women without biphasic events of the FECG registration.

Characteristic n (%)	Biphasic events (n = 105)	Significant biphasic events (n = 28)	No biphasic events (n = 2315)
Nulliparity	77 (73.3)	25 (89.3)	1412 (61.0)
Prolonged pregnancy (>41 weeks)	29 (27.6)	8 (28.6)	682 (29.5)
Maternal diabetes	1 (1.0)	1 (3.6)	9 (0.4)
Induction of labor	26 (24.8)	9 (32.1)	371 (16.0)
Epidural analgesia	60 (57.1)	20 (71.4)	918 (39.7)
Meconium-stained amniotic fluid	17 (16.2)	9 (32.1)	539 (23.3)
Oxytocin augmentation	80 (76.2)	25 (89.3)	1422 (61.4)
Male neonatal gender	41 (39.0)	11 (39.3)	1227 (53.0)

Table 2: Neonatal and maternal outcomes of women with biphasic events, significant biphasic events, and women without biphasic event in the FECG registration.

Characteristic n (%) or Mean (SD)	Biphasic events (n = 105)	Significant biphasic events (n = 28)	No biphasic events (n = 2315)
Adverse neonatal outcome†	16 (15.2)	6 (21.4)	189 (8.2)
Metabolic acidosis†	3 (2.9)	0 (0.0)	25 (1.1)
pH <7.00†	2 (1.9)	1 (3.6)	20 (1.0)
Five-minute Apgar <7	0 (0.0)	0 (0.0)	26 (1.1)
NICU admittance	13 (12.4)	6 (21.4)	160 (6.9)
Birthweight <2500gram	3 (2.9)	2 (7.1)	36 (1.6)
Interventions for fetal distress	13 (12.4)	6 (21.4)	210 (9.1)
Cesarean delivery	14 (13.3)	4 (14.3)	206 (8.9)
Vaginal operative delivery	20 (19.0)	7 (25.0)	262 (11.3)

† Cord artery pH data was missing of 18 neonates with biphasic events, 5 neonates with significant biphasic events, and 317 neonates without biphasic events

although women with presence of biphasic ST-events of the FECG significantly differed from women without biphasic events of the FECG, and although both interventions for suspected fetal distress and adverse neonatal outcome were more often present in

presence of biphasic events, significant biphasic events in itself have no added value in the prediction of interventions for suspected fetal distress (OR 1.71, 95% CI: 0.65-4.50) or in the prediction of adverse neonatal outcome (OR 1.96, 95% CI: 0.74-5.24). This is also illustrated by the areas under the ROC curve, which increased only marginally when presence of significant biphasic events was added to the multivariable models that predict interventions for suspected fetal distress and adverse neonatal outcome.
Although this study showed no independent association of significant biphasic events with interventions for suspected fetal distress or adverse neonatal outcome, some interesting differences in baseline characteristics can be seen between women with and women without biphasic events of the fetal ECG concerning parity, presence of maternal diabetes, induction of labor, epidural analgesia, oxytocin augmentation, and fetal gender. The higher incidence of biphasic events in women with diabetes has already been illustrated by Yli et al.[10] The authors suggest that this finding might represent a marker for the presence of a hypertrophic myocardial wall, which is commonly present in fetuses and neonates of women with diabetes. Kwee et al. showed that laboring women with a gestational age between 36 and 37 weeks showed more biphasic events than laboring women at later gestation, and that biphasic events were less common in presence of maternal hypertension, meconium-stained amniotic fluid, and female sex.[13] Although we can confirm the lower incidence of biphasic events in presence of meconium-stained amniotic fluid, surprisingly, in our population, biphasic events were more often present in female fetuses. These contradictory findings suggest a multifactorial pathway behind these differences. Only in the presence of maternal diabetes, studies consistently show a higher incidence of biphasic events, and the altered response of the myocardial wall to the stress of labor provides a reasonable pathofysiological pathway that might explain this.

To appreciate the present results, some limitations have to be addressed. Although the variables used for the multivariable regression analysis for the prediction of IFD and AO were based on the existing literature, to our knowledge there is no study that computed a well-fitted prediction model for these outcomes. The model we computed was made to act as a reference model to investigate the added value of significant biphasic events and was not computed for an accurate prediction of IFD or AO in the general population. To serve this goal, a computed model should first be validated internally and corrections for optimism should be made, where after the model has to be validated in a different population. This outreached the goal for the present study.
Furthermore, since the presence of adverse neonatal outcome is relatively rare, performing multivariable regression analysis could lead to a bias of the regression coefficient. However, since we included only ten variables in the analysis, the number of events per variable is well over ten, which has been shown to be the limit under which the validity of the regression model can be negatively influenced.[22] Finally, since the original trial was not conducted to evaluate the predictive value of biphasic events, due to the low numbers of biphasic events,

Table 3: multivariable model for the prediction of interventions for suspected fetal distress: adjusted odds ratios (OR)

Variables included	OR	95% CI
Presence of *significant* biphasic event	1.71	0.65-4.50
Prolonged gestational age (>41 weeks)	1.36	1.00-1.85
Nulliparity	1.76	1.27-2.45
Birtweight <2500 gram	4.93	2.38-10.22
Maternal diabetes	2.30	0.46-11.40
Meconium-stained amniotic fluid	1.88	1.38-2.55
Induction of labor	1.75	1.23-2.49
Epidural analgesia	1.24	0.91-1.69
Oxytocin augmentation	1.00	0.72-1.40
Neonatal sex	1.05	0.79-1.40

Table 4: multivariable model for the prediction of adverse neonatal outcome: adjusted odds ratios (OR)

Variables included	OR	95% CI
Presence of *significant* biphasic event	1.96	0.74-5.24
Prolonged gestational age (>41 weeks)	1.05	0.75-1.45
Nulliparity	1.60	1.14-2.24
Birtweight <2500 gram	5.19	2.46-10.96
Maternal diabetes	2.18	0.42-11.22
Meconium-stained amniotic fluid	1.88	1.36-2.60
Induction of labor	1.97	1.38-2.81
Epidural analgesia	1.18	0.86-1.62
Oxytocin augmentation	0.82	0.58-1.17
Neonatal sex	0.76	0.56-1.03

the power to detect significant differences is limited. This is further enhanced by the low numbers of adverse neonatal outcomes. However, we were able to analyze 2,420 women with concealed ST waveform recordings, and it is questionable if an even larger cohort with concealed ST waveform analysis will become available in the future.

Conclusion

This study showed that the presence of significant biphasic events is not discriminating in the prediction of interventions for suspected fetal distress or adverse neonatal outcome. Therefore, the justification of biphasic events in the current STAN guidelines is questionable and might lead to an unnecessary increase in operative deliveries without improving neonatal outcome. The results of this study should be validated in a different (ideally even larger) population, and if confirmed, STAN clinical guidelines should be adjusted appropriately.

Acknowledgements

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Disclosure of interest

There are no known financial, personal, political, intellectual or religious interests of any of the authors.

Figure 2: Receiver operator characteristics curve for the prediction of interventions for suspected fetal distress: predicted probability with and without significant biphasic events as independent variable.

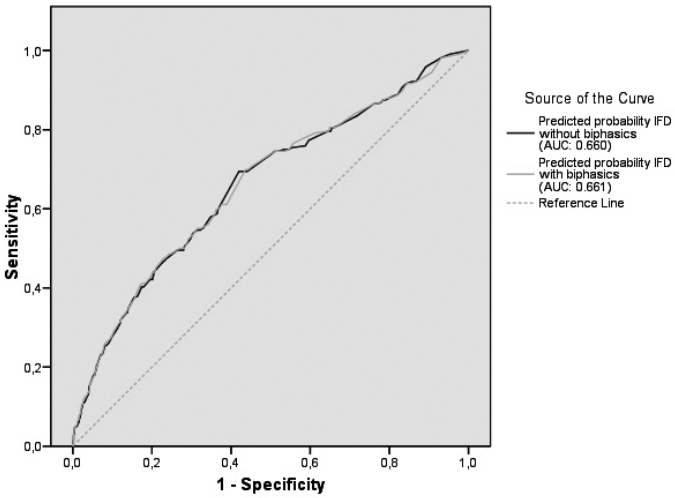
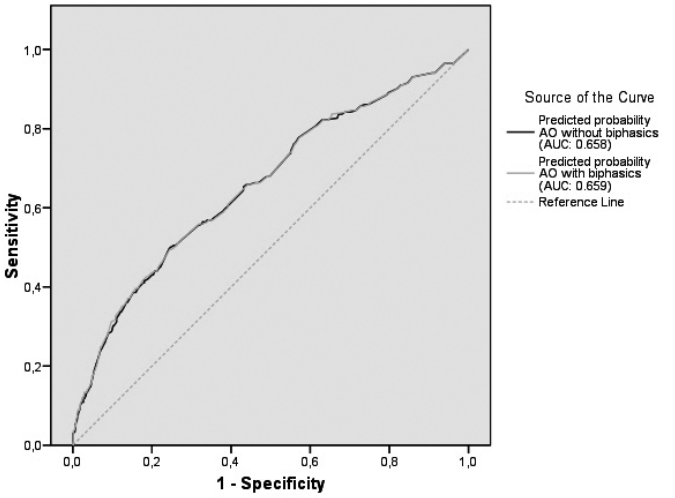


Figure 3: Receiver operator characteristics curve for the prediction of adverse neonatal outcome: predicted probability with and without significant biphasic events as independent variable.



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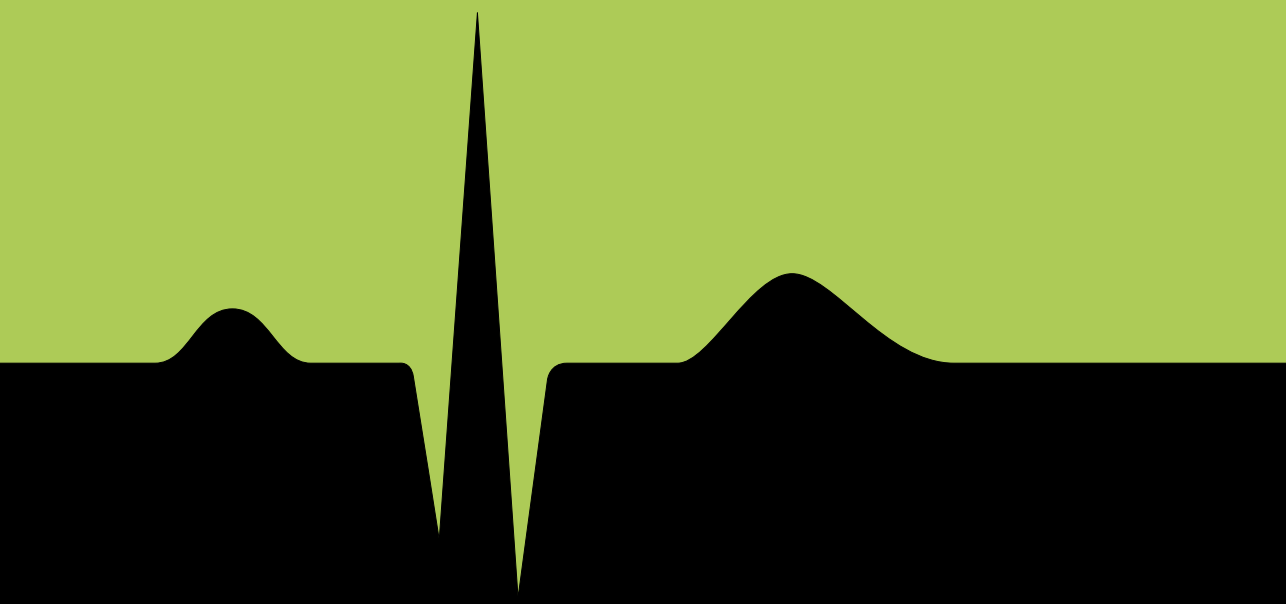
Is intra-partum fever associated with ST-waveform changes of the fetal electrocardiogram? A prospective cohort study



Chapter 7

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Abstract

Objective
Maternal intra-partum fever is a frequent complication during labor and is associated with adverse maternal and neonatal outcome. It is presently not known if intrapartum fever is associated with ST-waveform changes in term fetuses. The purpose of this study was to investigate the association between maternal intra-partum fever and ST-waveform changes of the fetal ECG.

Design
Prospective cohort study

Setting
Three academic and six non-academic teaching hospitals in the Netherlands

Population
Laboring women with a high-risk singleton pregnancy in cephalic position beyond 36 weeks of gestation.

Methods
We studied 142 women with fever (maternal temperature ≥38.0 °C) during labor and 141 women with normal temperature who had been included in two previous studies. In both groups, we counted the number and type of ST-events and classified them as significant (intervention needed) or not significant, based on STAN clinical guidelines.

Main Outcome Measures
Number and type of ST-events.

Results
Both univariable and multivariable regression analysis showed no association between the presence of maternal intrapartum fever and the number or type of ST-events.

Conclusions
Maternal intra-partum fever is not associated with ST-segment changes of the fetal ECG. Interpretation of ST changes in laboring women with fever should therefore not differ from other situations.

Introduction

Maternal intra-partum fever is a frequent complication during labor, occurring in up to 15% of term labors.[1,2] It has been identified as a risk factor for cerebral palsy. Even fever in absence of infection may be a cause for concern, since both in primates and in human studies hyperthermia has been associated directly with the development of fetal hypoxia and metabolic acidosis. [3–9]

Both maternal fever and acidosis are risk factors for encephalopathy. It is of utmost importance to identify the fetus at risk for hypoxia in case of maternal fever since many publications have assigned a synergistic effect of inflammatory responses and hypoxia, resulting in neonatal encephalopathy in up to 12.5% of cases.[8,10–12]

Fetal surveillance with cardiotocography (CTG) during labor is standard care in high risk pregnancies. A relatively new method for continuous fetal monitoring is the STAN methodology (Neoventa Medical, Gothenburg, Sweden) in which (classification of) the CTG is combined with ST analysis of the fetal electrocardiogram (ECG). Abnormalities in the ST segment of the fetal ECG are related to fetal metabolic acidosis, both in primate studies[13–15] and in randomized controlled trials in humans.[16–19]

The STAN concept is based on the association between changes of the ST-interval of the fetal ECG and the function of the fetal myocardium during hypoxia. The changes in fetal ECG associated with fetal distress are either an increase in T-wave, quantified by the ratio T-wave to QRS-amplitude (T-QRS ratio), or a biphasic ST-segment. An increase in T-wave and subsequently in T-QRS-ratio has been associated with a catecholamine surge, activation of ß-adrenoreceptors, myocardial glycogenolysis, and metabolic acidosis.[15] A biphasic shape of the ST-segment is related to two situations. First, it may occur when the fetal heart is exposed to acute hypoxic stress whereby it has had no time to respond to hypoxia or second, when the fetal heart has a reduced capacity to respond due to (chronic) stress situations and lack of or already utilized resources. Biphasic ST-changes of the fetal ECG have been associated with disturbances in heart muscle function, infection or malformations.[14]

Very little is known about the fetal ECG response to hyperthermia and infection. We hypothesized that intrapartum fever may affect the ST segment, either by an increased occurrence of hypoxia or by direct effects on the myocardium, and thus may result in a higher incidence of ST-events. As a consequence, STAN guidelines might not be applicable for the prediction of fetal hypoxia when fever is present. We therefore studied the association of maternal intra-partum fever at term with the presence of ST-segment changes of the fetal ECG.

Methods

Study population

The study population of this study was extracted from two previous prospective cohort studies performed on ST-analysis of the fetal ECG during labor in nine teaching hospitals in the Netherlands.[17,19] STAN monitoring was used in both studies in women with a gestational age beyond 36 weeks and a singleton fetus in cephalic position.

For the present study all women with an intra-partum rectal temperature ≥ 38 degrees Celsius were included as the index group. For the control group we randomly sampled women among those without fever who matched parity and gestational age (±7 days).

Maternal temperature was measured routinely at entry in the delivery room, every 2 hours after rupturing of the membranes and every hour in case of epidural analgesia and presence of fever. The first intra-partum body temperature ≥38 degrees Celcius was defined as T0. In the control-group, T0 was defined as the moment that the woman had the same dilatation in centimetres (± 1cm) as the matched woman had at the moment of the first fever measurement.

ST changes

Fetal heart rate was recorded with a STAN-21® or STAN-31® fetal heart rate monitor (Neoventa Medical, Gothenburg, Sweden), using a scalp electrode. The STAN monitor automatically detects elevation or depression of the ST segment, which is displayed on the screen as a baseline ST event (rise in T/QRS >10 min) or an episodic ST event (rise in T/QRS <10 min), which correspond to ST segment elevations and biphasic ST events, which correspond to a ST segment depression.

Digital versions of the CTG and fetal ECG (FECG) traces were viewed using specific software (STAN viewer, Neoventa Medical). STAN-recordings were evaluated by two of the authors for the first two hours after T0, without them having knowledge about presence of maternal fever or neonatal outcome. CTG recordings were classified as normal, intermediary, abnormal or pre-terminal. Number and type of ST-events (i.e. baseline rises, episodic rises, and biphasic ST-events) were counted and classified as significant (intervention needed) or not significant based on the STAN clinical guidelines[24] (Appendix 1).

Data collection

Charts of all women were reviewed for parity, gestational age, onset of labor, duration of first and second stage, augmentation with oxytocin, meconium stained amniotic fluid, epidural analgesia, duration of rupture of membranes (ROM), mode of delivery and neonatal outcome (i.e. five-minute Apgar score <7, umbilical artery pH, admission to neonatal intensive care unit (NICU) and medium care unit (MC).

Metabolic acidosis was defined as umbilical artery pH <7.05 and BD >12 mmol/l. Neonatal infection was defined as a positive blood culture or clinical signs of infection in

combination with positive infection parameters (CRP> 10 mg/l). Because information on histological analysis of placenta and cord was not systematically reviewed, it was not included in the analysis.

Statistical methods

Statistical analysis was performed using SPSS 17.0 for Windows. We compared the baseline characteristics and neonatal outcomes of women who had fever and women who had not. We then quantified the association between fever and ST segment changes using the odds ratio with 95% CI.

Then, to quantify whether the association between fever and the occurrence of ST-events was independent of other differences found between women without and with fever, we performed a multivariable logistic regression analyses with the presence of (any kind of) ST-events within two hours after T0 as the dependent variable and the following variables as independent variables: presence of fever, oxytocin augmentation, duration of ruptured membranes before birth (less or more than 24 hours) , onset of labor (induction versus spontaneous), history of caesarean section, presence of meconium-stained amniotic fluid and presence of epidural analgesia.

Furthermore, we planned to perform a subgroup analysis in women that gave birth to a neonate with adverse neonatal outcome to evaluate any association between the presence of fever and the positive predictive value of ST-waveform analysis to the occurrence of adverse neonatal outcome. Adverse neonatal outcome was defined as a woman who gave birth to a neonate with one of more of the following characteristics: umbilical artery pH<7.00, presence of metabolic acidosis (as described above), five-minute Apgar score<7 and admission to a neonatal intensive care ward because of neonatal asphyxia.

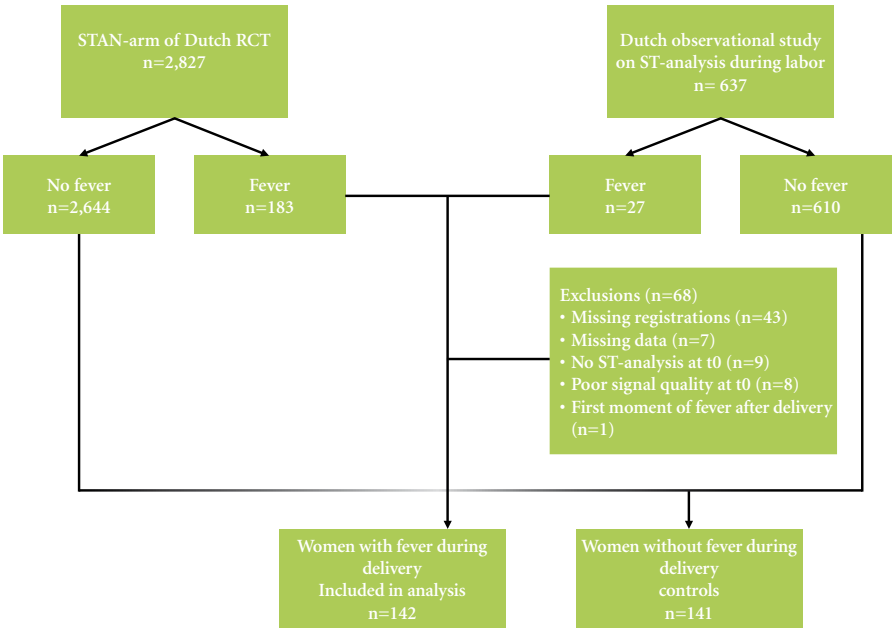
Results

Study population

In the two previous cohort studies fever was present in 183/2,827 (6.5%) and 27/637 (4.2%) patients. After exclusion of recordings with technical failure or missing data, a total of 142 women with intra-partum fever and 141 controls were appropriate for analysis (Figure 1). Baseline characteristics of the study population are shown in Table 1. Women with fever were significantly older than controls (median age 32.0 yrs compared to 30.3 yrs, $p<0.05$), had more frequent epidural analgesia during labor (83.3% compared to 38.3%, $p<0.001$) and had a higher number of caesarean deliveries (31.0% compared to 7.8%, $p<0.001$).

Among the women with fever, 125 (88 %) developed fever during the first stage of labor, 13 (9.2%) women developed fever during the second stage of labor, and four (2.8%) women already had fever before labor had started. Mean highest temperature during labor was 38.3 (±0.3) degrees Celsius. 41 (28.9%) women had a body temperature above

Figure 1: flowchart



38.5 degrees Celsius of whom nine (6.3%) had a temperature above 39.0 degrees Celsius. 108 women with fever (76.1%) were treated with antibiotics, mostly with amoxicillin/clavulan. 35 women (24.6%) also received acetaminophen suppositories.

ST changes

Mean duration of registration after T0 among women with fever was 178 minutes (SD ±136.56), compared to 151 minutes (SD ±117.342) in controls. There were no significant differences in number of women with any type of ST-events, nor in the amount of women with significant ST-events between the index and the control group in the first two hours after T0 (Table 2). Also when adjusted for other variables such as presence of epidural and time interval of ruptured membranes before birth we found no significant association between the presence of fever and the presence of (any kind of) ST-event within the first 2 hours after T0 (Table 3).

Subgroup analyses for women with a temperature ≥38.5°C (n=41), or ≥39.0°C (n=9), or women who gave birth to neonates with a perinatal infection (n=28) showed no significant difference in presence of (any kind of) ST-events within two hours after T0 when compared to the control group (data not shown).

Table 1: Baseline characteristics of women with and without fever during delivery

Characteristics Median (IQR) or numbers (%)	Fever n = 142	No fever n = 141	P-value
Median patient age (yrs)	32.0 (6.67)	30.3 (5.57)	0.038
Nulliparity	127 (89.4)	126 (89.4)	0.984
Median gestational age	284 (14)	285 (12)	0.852
Prolonged gestational age (>42wks)	19 (13.4)	13 (9.2)	0.270
Induction of labor	47 (33.1)	58 (41.1)	0.162
Meconium stained amniotic fluid	49 (34.5)	43 (30.5)	0.472
Epidural analgesia	119 (83.3)	54 (38.3)	<0.001
Duration rupture of membranes 12-24 hours 24-48 hours >48 hours	 59 (41.5) 19 (13.3) 15 (10.6)	 28 (19.9) 22 (15.6) 10 (7.1)	 0.068
Mode of delivery Spontaneous Instrumental vaginal delivery Caesarean section	 67 (47.2) 31 (21.8) 44 (31.0)	 102 (72.3) 28 (19.9) 11 (7.8)	 <0.001
Median dilatation on T0	8 (4)	8 (4)	

IQR: interquartile range

Table 2: Total number and type of ST-events of women with and without fever during delivery

		0-1 hour after T0			
Events	Fever n = 142 (%)	No fever n = 141 (%)	OR	95% CI	P-value
Events absent	116 (81.7)	109 (77.3)			
Events present* Baseline rise Episodic rise Biphasic event Significant event	26 (18.3) 20 (14.1) 3 (2.1) 11 (7.7) 17 (12.0)	32 (22.7) 25 (17.7) 3 (2.1) 6 (4.3) 13 (9.2)	0.76 0.76 0.99 1.89 1.34	0.43-1.36 0.40-1.44 0.20-5.00 0.68-5.26 0.62-2.87	*0.36* *0.40* *0.99* *0.22* *0.45*
		1-2 hour after T0			
Events	Fever n = 116† (%)	No fever n = 110† (%)	OR	95% CI	P-value
Events absent	93 (80.2)	80 (72.7)			
Events present* Baseline rise Episodic rise Biphasic event Significant event	23 (19.8) 17 (14.7) 2 (1.7) 6 (5.2) 16 (13.8)	30 (27.3) 27 (24.5) 3 (2.7) 2 (1.8) 13 (11.8)	0.66 0.53 0.63 2.95 1.19	0.36-1.23 0.27-1.04 0.10-3.82 0.58-14.92 0.55-2.61	*0.19* *0.06* *0.61* *0.17* *0.66*

* Each recording can have several types of ST-events

† 26 women with fever and 31 women without fever delivered in the first hour after T0.

Secondary outcomes

There were also no differences between women with fever and controls for metabolic acidosis or other umbilical cord pH cut-off values (Table 4). 90 neonates (63.4%) of women with intra-partum fever were admitted to a neonatal ward, compared to 22 neonates (15.6%) of the control group. 79 (87.8%) neonates in the index group were admitted because of a suspicion of a perinatal infection, compared to 6 (27.3%) neonates in the control group. Five cases (3.5%) were admitted to a neonatal intensive care unit (NICU), because of perinatal infection (n=3), asphyxia (n=1) or a combination of asphyxia, perinatal infection and meconium aspiration syndrome (n=1). Among the controls one (0.7%) neonate was admitted to the NICU because of seizures.

Among the neonates whose mothers had fever during delivery, 114 (80.3%) had no signs of infection; 28 neonates (19.7%) had clinical signs of infection with an increased level of serum CRP (n=26) or clinical signs of infection and positive blood cultures (n=2). Among the controls four (2.8%) neonates had clinical signs of infection with an increased CRP (n=3) or clinical signs of infection with positive blood culture (n=1).

Only seven neonates with fever and four neonates without fever were classified as having adverse neonatal outcome. Subgroup analysis in these groups was therefore not possible (data not shown).

Discussion

Our results show that intrapartum fever is not associated with a higher occurrence of ST-events when using ST-analysis of the fetal ECG despite a significant higher amount of perinatal infections. Adjustment for other differences between women with and without fever did not change this null association. These results suggest that intrapartum monitoring using ST-analysis of the fetal ECG seems not affected by maternal fever. Interpretation of ST changes in laboring women with fever may be similar to that in other situations.

Very little is known about the possible effects of infection on the fetal ECG. In our study in term fetuses we did not find evidence for the hypothesis that infection may alter the balance and the performance characteristics within the myocardial wall, resulting in more or specific ST events. These results are in agreement with those of an experimental animal study[20] in which the myocardial response to infection was investigated in preterm and near-term fetal lamb. Chronically instrumented fetal lambs were exposed to lipopolysaccharide (LPS), and the fetal electrocardiogram ST-waveform was examined using STAN. In the near-term fetal lambs no specific ST-changes were observed after LPS-exposure. This was in contrast to the preterm lambs in which decreased arterial pressure, negative T waves, tachycardia, and an increase in fetal heart rate variability occurred when being exposed to the same amount of LPS.

The presence of maternal fever in labor is a strong risk factor for adverse neonatal outcomes, such as neonatal encephalopathy and neonatal death.[21–23] This has already been found for maternal temperatures ≥ 37.5°C. Fever might be causal, such as in case of an elevated maternal temperature with the use of epidural analgesia, or might reflect an antepartum or intrapartum process, such as infection. Since there is a strong association of presence of clinical or histological chorioamnionitis with adverse outcomes[12] and a two-to threefold risk of early and late neonatal death in presence of infection-related fever in term singleton live birth[23], infants that are exposed to hyperthermia due to chorioamnionitis should be considered at high risk for adverse outcome.

Although one study did not show a multiplicative interaction between intrapartum maternal fever and neonatal acidosis using a logistic regression model[5], several case controlled studies have shown an excess neonatal injury when maternal pyrexia or infection is present in addition to other risk factors for adverse outcome.[11,12,21] This has also been shown in animal models studying the synergistic effects of inflammatory responses and hypoxia-ischemia: endotoxin has been shown to sensitise and to dramatically increase the lesion size in the immature rat brain following hypoxic-ischemic injury.[24,25] Although the exact mechanism of this interaction is unclear, it has been shown to be mediated through microglia and Toll-like receptors.[26]

In the light of the above, it is of crucial importance to consider the fetus that is exposed to fever (whether or not in combination with infection) as being at increased risk of adverse neonatal outcome. Therefore, intervention in case of suspected fetal asphyxia should be more aggressive in the presence of maternal pyrexia. In the expert-based recommendations to the STAN clinical guidelines this is emphasized by considering ST-events significant and requiring action, already in case of minor fetal heart rate changes ('intermediary heart rate pattern').[27] Although this study was not designed to demonstrate differences in neonatal outcome when fever was present during delivery, we found no scientific ground to validate these recommendations since both the number and type of ST-events were comparable between women with and without fever during delivery. However, since low numbers of neonates born with an adverse neonatal outcome didn't allow for subgroup analysis, we are not informed about any possible association between the presence of fever and the positive predictive value of ST-waveform analysis for adverse neonatal outcome.

Our study has various issues that deserve attention to appreciate the findings. Because we measured the occurrence of fever and ST changes to a large extent at the 'same moment in time', the found associations between fever during delivery and distorted ST-analysis of the fetal ECG would not necessarily be causal, since any distortion of the ST-waveform could already have been present before the presence of fever. Secondly, pyrexia in labor might have been due to infection, epidural use or physiology. Effects on the ST segment may be expected to be different. Unfortunately, due to the limited number of neonatal

Table 3: Effect on presence of (any kind of) event within two hours of T0: multivariable logistic regression analysis

Variables	Adjusted OR	95% CI	P-value
Presence of fever (n=142)	0.77	0.43-1.40	0.39
Oxytocin augmentation (n=153)	1.24	0.57-2.69	0.59
Induction of labor (n=105)	1.40	0.65-3.04	0.39
History of CS (n=6)	2.89	0.55-15.08	0.21
Presence of meconium (n=92)	1.03	0.59-1.80	0.91
Presence of epidural (n=173)	0.76	0.42-1.39	0.37
Prolonged ruptured membranes (n=66)	0.76	0.41-1.44	0.41

IQR: interquartile range

Table 4: Neonatal outcome

Outcome Mean (SD) or number (%)	Fever n = 142 (%)	No fever n = 141 (%)	P-value
Mean birthweight (gr)	3691 (492.7)	3528 (488.9)	0.006
Apgar-scores 1 minute <4 5 minutes <7	 5 (3.5) 4 (2.8)	 0 0	 0.025 0.045
Umbilical cord gasses† Arterial pH <7.00 <7.05 <7.10 Metabolic acidosis*	 3 (2.1) 7 (4.9) 16 (11.3) 3 (2.1)	 2 (1.4) 4 (2.8) 11 (7.8) 1 (0.7)	 0.652 0.357 0.312 0.327
Admission neonatal ward	90 (63.4)	22 (15.6)	<0.001
NICU	5 (3.5)	1 (0.7)	0.101
Neonatal infection	28 (19.7)	4 (2.8)	<0.001
Positive blood cultures	2	1	Not Calculated
Clinical infection and CRP rise	26	3	Not Calculated

† Umbilical cord gas data were missing from 2 neonates of women with fever and 1 neonate of a woman without fever; * Metabolic acidosis: pH <7.05 and BDecf >12 mmol/L

infections (28/142) and the lack of placental histological analyses, we could not perform a detailed analysis on this outcome.

In conclusion, we found no association between maternal intra-partum fever and ST-

analysis of the fetal ECG, indicating that the fetal ECG might not be affected by pyrexia. Interpretation of ST changes in laboring women with fever may be similar to that in other situations.

Although we found no evidence to consider any ST-event as being significant when fever is present, the clinician has to remain cautious in case of suspected fetal distress and maternal pyrexia, given their synergistic adverse effect the infant's brain, and the fact that we could not study the association between the presence of fever and the positive predictive value of ST-waveform analysis.

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Disclosure of interest

There are no known financial, personal, political, intellectual or religious interests of any of the authors.

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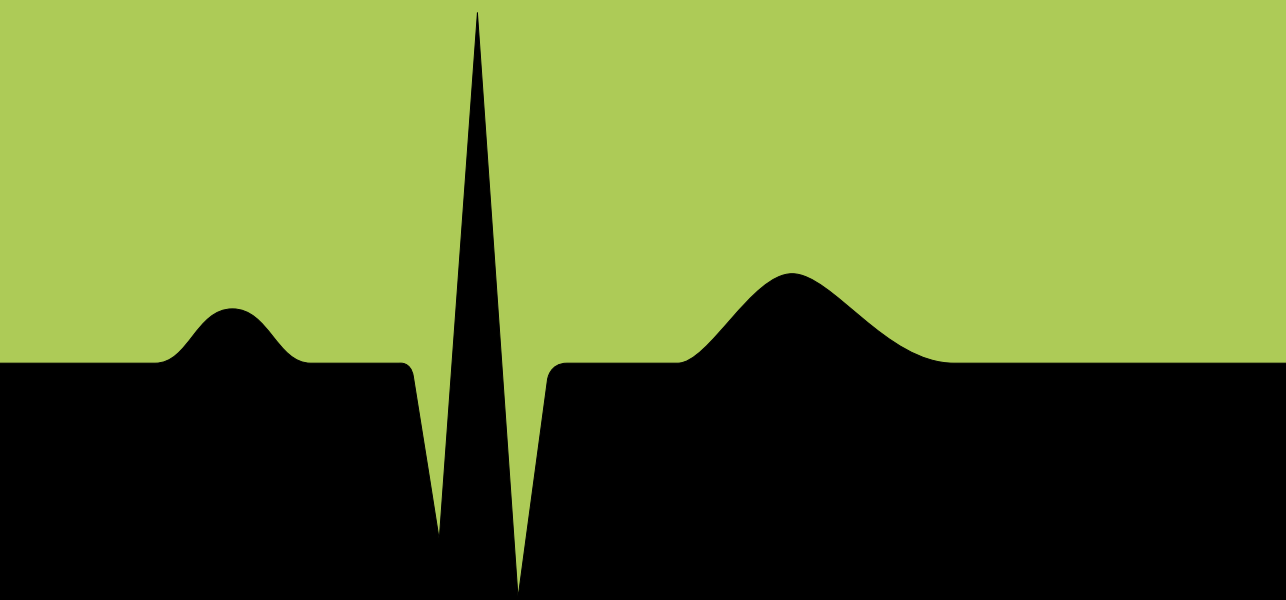
Intrapartum epidural analgesia and ST-analysis of the fetal electrocardiogram



Chapter 8

Jeroen H Becker, Timme P Schaap, Michelle EMH Westerhuis, Leo van Wolfswinkel, Gerard HA Visser, Anneke Kwee

Abstract

Objective
To evaluate the influence of intrapartum epidural analgesia on the occurrence of ST-events of the fetal ECG.

Design
Nested case-control study

Setting
Single-centre academic hospital in the Netherlands

Population
Laboring women with a high-risk singleton pregnancy in cephalic position beyond 36 weeks of gestation.

Methods
Data of 72 women who received epidural analgesia using bupivacaine combined with sufentanil and 72 controls were collected and analyzed. Moment of epidural infusion was defined as T0. In the control-group, T0 was defined by matching dilatation in centimeters. STAN-registrations from one hour before until two hours after T0 were classified and number and type of ST-events were counted and judged according to the STAN clinical guidelines. T-QRS ratios were collected from one hour before T0 until two hours after T0 and differences were compared between the two groups

Main outcome measures
Number and type of ST-events and mean T-QRS before and after T0.

Results
There were no significant differences between cases and controls regarding number of ST-events, type of ST-events and whether they were significant (intervention advised) or not. Correction for outliers (3 cases and 3 controls) did not change the results. Differences of T-QRS ratios before and after T0 were comparable between cases and controls.

Conclusion
Epidural analgesia has no effect on the number or type of ST-events when using ST-analysis of the fetal ECG.

Introduction

ST-analysis of the fetal electrocardiogram (ECG) is a relatively new method for intrapartum monitoring.[1–4] The method is based on the ability of the ST-interval to reflect the function of the fetal heart muscle. Changes in fetal ECG associated with hypoxia are an increase in T-wave, quantified by the ratio T-wave to QRS-amplitude (T/QRS), or a biphasic ST-pattern. An increase in T-wave amplitude requires active adaptation of the fetus to hypoxia and can be an episodic rise (rise of T/QRS which returns to normal in 10 minutes) or a baseline rise (increase of T/QRS that lasts for more than 10 minutes). A depression of the ST segment signifies a situation of acute hypoxia in which the fetal heart has no time to respond, nor has the capacity to react.

Epidural analgesia is an effective method for relieving labor pain and is increasingly being used during labor. However, epidural analgesia is associated with various side-effects such as hypotension, more frequent oxytocin augmentation, longer second-stage of labor and maternal fever.[5,6] Moreover, the placental intervillous space is known to act as a site of drug deposit for bupivacaine as well as fentanyl.[7,8] In one study on the fetal ECG and bupivacaine, Phillips et al. found a significant increase in fetal heart rate and a significant decrease of the T-QRS ratio.[9] This was a basic research paper not conducting effects on fetal outcome. It is uncertain if there is significant fetal metabolism or drug uptake by the fetus, despite the high rates of placental transfer.

We hypothesized that epidural analgesia could influence intrapartum ST-analysis via different pathways: first, epidural induced hypotension can result in a decreased utero-placental perfusion and induce fetal distress manifesting as late or prolonged fetal heart rate (FHR) decelerations.[10] When using STAN during epidural analgesia, this could lead to an increase in incidence of ST-events. On the other hand, Phillips et al. described a significant decrease of the T-QRS ratio as a result of bupivacaine.[9] Following this finding, monitoring with STAN (which marks increases of the T-QRS ratio as a possible sign of fetal hypoxia) might lead to a reduction of ST-events, which even might result in a reduced reliability of STAN in the ability to detect fetal distress.

It was therefore the purpose of this study to evaluate the possible influences of epidural analgesia on intrapartum ST-analysis of the fetal ECG.

Materials and Methods

A nested case-control study of STAN-registrations was performed at the University Medical Centre Utrecht (UMCU). Cases and controls were selected from a cohort study in which the UMCU participated.[11]

Inclusion criteria were high risk pregnancies with an indication for continuous intra-uterine fetal monitoring, singleton fetus in cephalic presentation and gestational age above 36 weeks. Fetal heart rate was recorded with a STAN21® fetal heart rate monitor

(Neoventa Medical, Gothenburg, Sweden), using a scalp electrode. All patients who received continuous epidural analgesia with complete STAN registrations were included in the study. For every case one control was matched on parity and gestational age (±7 days). Controls were selected at random using a random number generator provided by Random.org.
Charts of all woman were reviewed for parity, gestational age, onset of labor, reason for continuous fetal monitoring, use of oxytocin augmentation, use of other pain medication, use of tocolytics, meconium stained amniotic fluid, mode of delivery, reason for intervention, sex of neonate, birth weight, Apgar-scores and umbilical blood gasses. In the case group, additional information was collected about type and quantity of epidural analgesia used and amount of intravenous saline preload administered. Blood pressures were collected before epidural analgesia, 1 hour after and the lowest measurement in between. Hypotension was defined as a systolic arterial blood pressure reading below 90 mmHg or a 20% decrease from baseline.
Dilatation in centimeters at the start of epidural was defined as T0. In controls, T0 was defined as the moment at which the control had comparable dilatation. Blood pressures were not routinely measured in the control group.

To study the effect of epidural analgesia on the number of ST-events, STAN-recordings were evaluated by two researchers (MW and AK) from 1 hour before T0 until two hours after T0 in intervals of 30 minutes. Researchers were blinded for use of epidural analgesia and neonatal outcome. CTG recordings were classified as normal, intermediate, abnormal or preterminal according to STAN clinical guidelines[12] (Appendix 1). Number and type of ST-events were counted and classified as significant (intervention needed) or not significant (no intervention needed) based on STAN clinical guidelines.

To study the effect of epidural analgesia on the T-QRS ratio of the fetal ECG, T-QRS ratios were collected from one hour before T0 until two hours after for both cases and controls. The mean T-QRS ratio was calculated for all three time frames (i.e. one hour before T0, first hour after T0 and second hour after T0). Differences of mean T-QRS ratios between the final two time frames and the first time frame were calculated and compared for both cases and controls.

Statistical methods

Statistical analysis was performed using SPSS 15.0 for Windows. Descriptive information is given in absolute numbers (%), median and/or mean (±SD). For continuous variables, Mann-Whitney test were used to test if cases differ significantly from controls. Categorical data were compared using the x^2 test or Fisher's exact test. P-values <0.05 were considered significant.

Results

Of 637 patients who participated in the original study, a total of 107 (17%) patients received epidural analgesia. 35 cases were excluded because of missing or incomplete STAN-registrations. 72 cases were included for analysis, together with a random selection of 72 controls without epidural analgesia.

All case group patients received epidural analgesia composed of bupivacaine 1,25 mg/ml and sufentanil 0,5 µg/ml. Patients received a test dose of the solution with a mean volume of 4.4 ml (SD ±0.88), followed by a bolus of the same solution with a mean of 5.2 ml (SD ±1.03). Continuous infusion was delivered by syringe pump with a mean infusion of 6.1 ml (SD ±0.61) per hour. Baseline characteristics and neonatal outcome for cases and controls were comparable (Table 1). One or more periods of hypotension occurred in 12 cases (17%). One of those cases received one dose of 5 mg ephedrine to treat the hypotension and one case needed two doses of 5 mg ephedrine. All blood pressures returned to acceptable values after ephedrine was administered. Information about blood pressure measurements was missing in eleven cases, one of which had received 5 mg of ephedrine which most likely indicates a period of hypotension. There was no difference in number of events before and after the moment of epidural in the cases of hypotension. Neonatal outcome was favorable for all cases with hypotension during delivery.

There were no significant differences between CTG-patterns in any of the periods (Table 3). Abnormal CTG patterns did not occur persistently in the same patients. Preterminal CTG patterns were not seen in any of the groups. We analyzed all types of ST-events and combinations for the two groups. A similar number of cases and controls had no ST-events one hour before T0 and during the two hours of registration after T0 (54% vs. 58%). Most of the ST-events consisted of baseline rises, 35% and 26% for cases and controls, respectively (n.s.). Additionally, all other ST-events were analyzed e.g. biphasic, episodic ST-events and all possible combinations, again showing no significant differences.

There were no significant differences in total number of ST-events between case and control groups (Table 4). Three cases and three controls were identified as outliers with a significant higher amount of ST-events combined with normal fetal heart race tracings, i.e. not reflecting threatened fetal conditions. Results were comparable when these six outliers were excluded from analysis (data not shown).

For the evaluation of the possible effects of epidural analgesia on the ST-segment of the fetal ECG, data was available for 65 cases and 61 controls. For 7 cases and 14 controls, the T-QRS data could not be extracted from the original STAN registration files. Mean T/QRS changed from 0.13 before the moment of epidural to 0.13 in the first and 0.12 in the second hour after epidural. For the controls, mean T/QRS was 0.12 before T0 and remained 0.12 in both hours after T0 (Table 2). Statistical analysis showed no difference for the change in mean T/QRS between cases and controls.

Table 1: Baseline characteristics and fetal outcome

Characteristic	Cases (%) n = 72	Controls (%) n = 72	P-value
Nulliparity	61 (84.7)	61 (84.7)	1.00
Gestational age (days)	284 ± 8.9	283 ± 8.2	0.73
PIH/PE	7 (9.7%)	13 (18.1)	0.15
Post date	14 (19.4)	8 (11.1)	0.17
Induction of labor	24 (33.3)	29 (40.3)	0.39
Meconium	34 (47.2)	27 (37.5)	0.24
Oxytocin augmentation	70 (97.2)	67 (93.1)	0.25
Fever	8 (11.1)	5 (6.9)	0.38
Mode of delivery Instrumental delivery Caesarean section	 11 (15) 23 (31.9)	 18 (25) 10 (13.9)	 0.54 0.06
Indication SC: FTP SFD Combination	 18 (25) 3 (4.2) 2 (2.8)	 6 (9.7) 3 (4.2) 1 (1.4)	 0.35
Male fetal gender	38 (52.8)	31 (43.1)	0.24
Mean birth weight	3591 ± 578	3567 ± 531	0.80
Apgar-score 5min Median (range)	 10 (7-10)	 9 (6-10)	 Not calculated
Umbilical cord gasses Arterial pH BD pCO2 Acidosis**	 7.19 ± 0.07 9.75 ± 2.8 49 ± 11 1 (1.6)	 7.18 ± 0.09 10.24 ± 3.6 49 ± 10 5 (8.1)	 0.55 0.40 0.65 0.09
Admission NICU/MC Mean Duration (days)	 26 (36.1) 2.3	 17 (23.6) 2.3	 0.10

Data are expressed as n (%) or mean (± SD) ** Acidosis defined as: pH ≤ 7,05 and BD >12mm/L

One newborn in the control-group had a 5-min Apgar score of less than 7 (6) and none of the newborns in the case-group. One case had a metabolic acidosis (pH <7.05 and BD >12 mmol/l) compared to five in the control group. Two cases were admitted to the neonatal intensive care compared to three controls. 16 controls were admitted to the medium care compared to 30 controls, mostly due to a higher number of admissions because of perinatal infection in the case group (12 vs. 4). None of the differences in neonatal outcome were statistically significant.

Table 2: Mean T/QRS before and after T0 for cases and controls

	Cases (n = 72)	Controls (n = 72)	P-value
*One hour before T0**			
Mean T/QRS (SD)	0.13 (.07)	0.12 (.05)	
First hour after T0			
Mean T/QRS (SD)	0.13 (.07)	0.12 (.05)	
Difference from one hour before T0	-0.0016 (.02)	0.0012 (.02)	0.57
Second hour after T0			
Mean T/QRS (SD)	0.12 (.06)	0.12 (.05)	
Difference from one hour before T0	-0.0078 (.03)	-0.0011 (.02)	0.37

T0 reflects the moment of epidural analgesia for the cases and the moment of a comparable amount of dilatation for the controls

Table 3: CTG classification in the different time frames

Characteristic	Cases (%) n = 72	Controls (%) n = 72	P-value
60 minutes – 30 minutes before T0			
Normal Intermediary Abnormal	50 (69.4) 19 (26.4) 3 (4.2)	55 (76.4) 16 (22.2) 1 (1.4)	0.47
30 minutes before T0 – T0			
Normal Intermediary Abnormal	52 (72.2) 18 (25.0) 2 (2.8)	58 (80.6) 11 (15.3) 3 (4.2)	0.33
T0 – 30 minutes after T0			
Normal Intermediary Abnormal	52 (72.2) 15 (20.8) 5 (6.9)	58 (80.6) 11 (15.3) 3 (4.2)	0.49
30 minutes – 60 minutes after T0			
Normal Intermediary Abnormal	53 (73.6) 13 (18.1) 6 (8.3)	62 (86.1) 7 (9.7) 3 (4.2)	0.17
60 minutes – 90 minutes after T0			
Normal Intermediary Abnormal	47 (65.3) 20 (27.8) 5 (6.9)	57 (79.2) 12 (16.7) 3 (4.2)	0.18
90 minutes – 120 minutes after T0			
Normal Intermediary Abnormal	50 (69.4) 14 (19.4) 8 (11.1)	60 (83.3) 10 (14.1) 2 (2.8)	0.08

Table 4: Total numbers of events in the different time frames

	calculation	Cases (n=72)	Controls (n=72)	P-value
1 hour before epidural	total number of events	44	30	0.74
	mean	0.61 ± 1.78	0.42 ± 0.98	
	Median (range)	0 (0-11)	0 (0-5)	
	Baseline rises	32	28	Not calculated
	Episodic rise	1	1	Not calculated
	Biphasic ST	11	1	Not calculated
	Significant events	1	0	Not calculated
Time of epidural=T0				
1st hour after epidural	total number of events	56	32	
	mean	0.78 ± 1.76	0.44 ± 0.92	0.11
	Median (range)	0 (0-12)	0 (0-4)	
	Baseline rises	40	28	Not calculated
	Episodic rise	1	0	Not calculated
	Biphasic ST	15	4	Not calculated
	Significant events	0	1	Not calculated
2nd hour after epidural	total number of events	50	52	
	mean	0.69 ± 2.41	0.72 ± 0.60	0.21
	Median (range)	0 (0-19)	0 (0-10)	
	Baseline rises	31	43	Not calculated
	Episodic rise	1	2	Not calculated
	Biphasic ST	18	7	Not calculated
	Significant events	1	6	Not calculated
Total 1st and 2nd hour after epidural	total number of events	106	84	
	mean	1.47 ± 3.31	1.17 ± 2.25	0.71
	Median (range)	0 (0-21)	0 (0-12)	
	Baseline rises	71	71	Not calculated
	Episodic rise	2	2	Not calculated
	Biphasic ST	33	11	Not calculated
	Significant events	2	7	Not calculated

Discussion

To our knowledge this is the first study to address the possible effects of administration of epidural drugs during delivery to ST-analysis of the fetal ECG. This study shows that there is no increase in ST-events when using epidural analgesia during fetal monitoring with ST-analysis of the fetal ECG. Earlier we speculated on a possibly increased number of ST-events as a result of hypotensive episodes or as a result of a possible drug effect. In two studies an increased incidence of periods of hypotension following epidural analgesia has been described, although neonatal outcome was usually not affected.[5,13] Possible effects of epidural drugs were also addressed by Phillips in 1996. Assessing the effects of epidural bupivacaine on the fetal myocardial conducting system by evaluating its effect on the fetal electrocardiogram, he found a significant fall in T-QRS ratio following epidural bupivacaine.[9]

The results of our study however, showed no effects of hypotensive episodes or drug-induced fetal ECG changes on the number of ST-events. No differences were found in number and type of ST-events in any of the time periods, mean T-QRS ratio, nor in neonatal outcome between the groups. The small reduction in mean T/QRS that we found in the two hours after the start of epidural analgesia was not statistically significant compared to the control group. Overall we can conclude that our study demonstrates no effect of epidural analgesia on number of ST-events.

To appreciate the current results, it needs to be addressed that this study is limited by relatively small numbers. Especially in the first hour after epidural, these small numbers may result in underestimation of the effect of epidural analgesia on the total number of ST-events. However, as long as these ST-events are not related to CTG abnormalities, clinical significance is lacking, even in the presence of significant difference in total number of events between the groups.

This is the first study addressing the possible effects of epidural analgesia on ST-analysis of the fetal ECG. We have found no effects of intrapartum epidural analgesia on the number and type of ST-events, or on the mean T-QRS ratio. We therefore advise that STAN clinical guidelines should also be followed when using epidural analgesia.

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Conflicts of interest

All authors declare that they had no potential conflicts of interest relevant to this article. No funding has been received for this study.

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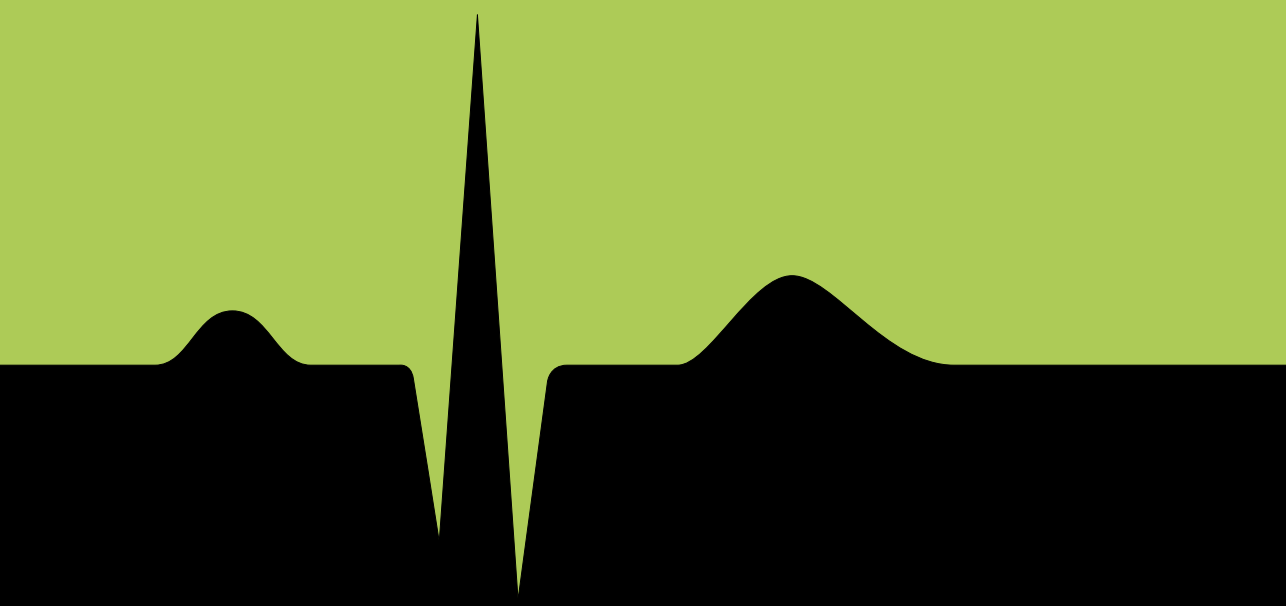
Summary and general discussion



Chapter 9

Discussion and main conclusions of this thesis

Intrapartum fetal monitoring is an important part of obstetric medicine. Although the initial thought that most cases of adverse perinatal outcome are related to labor and delivery has been adjusted, intrapartum monitoring is still considered important to reduce intrapartum fetal death and impaired (neurological) outcome. Intrapartum hypoxia and low umbilical artery pH at birth are associated with neonatal mortality, hypoxic ischemic encephalopathy, intraventricular hemorrhage, periventricular leucomalacia, and cerebral palsy.[1] Therefore, prevention of hypoxia during delivery is one of the most challenging goals of obstetric medicine. To monitor the fetus optimally, clinicians have been searching for a monitoring system that can identify all fetuses at risk for asphyxia with the lowest possible intervention rate. To serve this purpose, continuous cardiotocography (CTG) has been introduced in the 1960s. Although CTG is widely applied, it is neither very sensitive nor specific for the detection of fetal acidosis, but comes at the cost of a significant increase of the operative delivery rate.[2–9] The addition of fetal blood sampling (FBS) to the CTG produces slightly better results at a lower intervention rate.[8] However, performance of FBS is invasive, has to be repeated when CTG abnormalities persist and some studies report up to 21% failures because of technical problems.[10] Intrapartum fetal monitoring using ST-analysis of the fetal ECG (FECG) in addition to the conventional CTG (STAN) has been introduced in the 1990s as a promising new method of fetal surveillance. Although absolute cut-off values of the T-QRS ratio (i.e. the ratio of the amplitude of the T-top and the QRS-complex of the fetal ECG) were used in the first randomized trial that compared fetal monitoring with ST-analysis in combination with conventional CTG with conventional CTG alone[11], subsequent studies used changes in T/QRS over time, rather than an absolute threshold for the T/QRS, to discriminate between compromised and non-compromised fetuses.[12–15] Recommendations for expedite delivery based on ST-changes were set in STAN clinical guidelines. Following reports of infants born with adverse outcome despite adequate fetal monitoring with STAN, European experts on ST-waveform analysis formulated consensus-based criteria for CTG classification and ST-waveform interpretation. Existing STAN clinical guidelines were adjusted, now including recommendations for situations in which additional fetal information, such as by FBS, is needed to prevent false-negative results.[16] Unfortunately, additional methods of information on fetal well-being, like FBS, remain important when using ST-waveform analysis in addition to the CTG, since ST-waveform analysis by itself will not identify all fetuses at risk for asphyxia.[17]

If ST-waveform analysis of the fetal ECG does not identify all fetuses at risk for asphyxia, does it reduce the incidence of asphyxia when compared to conventional

cardiotocography? The second chapter of this thesis describes a meta-analysis comparing ST-waveform analysis of the fetal ECG in combination with cardiotocography (STAN) with continuous cardiotocography alone for several neonatal and maternal outcomes. In this meta-analysis, STAN failed to show a significant reduction in the incidence of metabolic acidosis. Because of the low incidence of more severe adverse neonatal outcomes, such as hypoxic ischemic encephalopathy, cerebral palsy or perinatal death, metabolic acidosis was the primary neonatal outcome of choice in the five included randomized trials. The presence of metabolic acidosis has been defined to be an essential criterion to define an acute intrapartum hypoxic event[18], and is related to the development of cerebral palsy.[1] The fact that this meta-analysis did not show a significant reduction in metabolic acidosis when using STAN makes it questionable if STAN should be incorporated into clinical practice. After all, improving neonatal outcome is the single most important goal of fetal monitoring. It is striking however, that the effect estimates on metabolic acidosis of the three largest of the individual trials are pretty consistent and showed a reduction in metabolic acidosis between 30 and 60 per cent[11,12,15], while two smaller trials showed a (non-significant) opposite effect.[13,14] Although one of these trials differed in inclusion criteria from the other trials[14], no other factors can be identified as possible causes for these differences in effect on metabolic acidosis. The RR for metabolic acidosis of 0.70 in the STAN arm of the combined trials and the overall low incidence of metabolic acidosis in these trials, indicates that another – even larger – randomized trial is necessary to give a definite answer on the possible favorable effects of STAN on serious adverse neonatal outcome. An alternative could be to incorporate the already published trials on STAN into an individual-patient-data (IPD) meta-analysis which will provide a more accurate estimation of the effects than a conventional meta-analysis. In expectation of the results of the randomized trial initiated by the US National Institute of Health (NIH), an IPD meta-analysis will be conducted by our study group.

Although the meta-analysis did not show a significant reduction in metabolic acidosis, it did show a significant reduction in the incidence of operative vaginal deliveries with an unaltered incidence of cesarean deliveries. Instrumental vaginal deliveries (forcipal and ventouse deliveries) were reduced with 12% when using STAN. In addition, the meta-analysis showed a 40% reduction in the need for additional fetal blood sampling (FBS) when using STAN in comparison to conventional CTG.

Reduction in the need for FBS is a valuable advantage of ST-waveform analysis, since this technique is invasive, time-consuming, requires a certain expertise and is rather patient (and doctor) unfriendly. In Chapter 3, the negative side-effects of the invasive character of FBS is illustrated by a case with cerebral spinal fluid leakage from the FBS incision site, next to an overview of published complications of FBS. Major and minor complications of FBS have been reported with an incidence varying from 0.4-6%[19–21], with fetal hemorrhage at the incision site as the complication most frequently reported.

Summary

ST-waveform analysis in combination with conventional cardiotocography (STAN) compared to conventional cardiotocography alone:

- Reduces the number of instrumental vaginal deliveries
- Reduces the need for additional fetal blood sampling
- Has not yet shown to reduce the number of metabolic acidosis at birth

The performance of a fetal monitoring tool depends on the ability of the staff to interpret the recordings and to manage the cases according to specific guidelines. The second part of this thesis therefore elaborates on the STAN guidelines and on its recommendations for additional fetal blood sampling.[16] According to the guidelines, fetal blood sampling is recommended in three situations: (1) start of the STAN registration with an abnormal CTG trace; (2) abnormal CTG trace for more than 60 minutes without ST-events; and (3) poor ECG signal quality in the presence of an abnormal or intermediary CTG trace. In the previously published Dutch randomized trial[15], these recommendations were expanded with the suggestion to perform additional FBS when the STAN registration starts with an intermediary CTG trace. In Chapter 4 we showed that FBS performed according to these criteria revealed acidosis (defined as pH<7.20) in almost 10% of the deliveries, while FBS performed in absence of these criteria showed acidosis in only 2% of deliveries. The addition of performing FBS when the CTG tracing starts with an intermediary CTG did not reveal any case of fetal acidosis. However, the consensus-based guideline recommendations to additionally check the fetal condition by FBS in case of start of the STAN registration with an abnormal CTG and in case of an abnormal CTG trace for more than 60 minutes, was shown to be effective for early identification of fetal acidosis. Since we showed that almost 40% of performed FBS were not performed according to the guidelines, the use of FBS could probably be further reduced when the criteria for FBS would be followed more strictly. Recent Norwegian and Finnish studies have indeed shown that FBS can be further reduced, without impairing neonatal outcome.[22]

Summary

Fetal blood sampling in addition to STAN:

- Although the incidence of fetal blood samples can be reduced, it remains an essential component of intrapartum surveillance
- The STAN criteria for the performance of fetal blood sampling are effective for the early identification of fetal acidosis
- The incidence of fetal blood samples can probably be further reduced when the criteria are followed more strictly

Due to the relatively new nature of intrapartum fetal monitoring with FECG ST-waveform analysis, its guidelines are still evolving. In one of the European STAN expert meetings, the hypothesis was put forward that fetuses with a high baseline T-QRS ratio (T/QRS) at the beginning of a recording, could be at higher risk for asphyxia in comparison with fetuses with a normal baseline T/QRS. This hypothesis originated from anecdotal experience that some fetuses with a high baseline T/QRS were born with low umbilical cord pH despite close intrapartum monitoring. One of the rationales behind this hypothesis could be that it will be more difficult to detect a rise in T/QRS when the reference value (i.e. the baseline T/QRS at the beginning of a recording) is already high. In chapter 5, we studies the predictive value of a high baseline T/QRS. We applied two different definitions of 'high' baseline T/QRS: 1) a T/QRS ≥0.25, which represents the cut-off value used in the past by Westgate et al.[11], and 2) a T/QRS ≥0.33, which represents two standard deviations above the mean in the Dutch study population. Neither definition of 'high' baseline T/QRS showed any additional predictive value for the prediction of adverse neonatal outcome or interventions for suspected fetal distress. In the same study, fetal sex, presence of maternal diabetes and gestational age were identified as variables that can influence the height of the baseline T/QRS.

Summary

The baseline T-QRS ratio:

- Serves only as a reference value for rises in the T-QRS ratio in the course of labor and has no additional predictive value for the prediction of adverse outcome or interventions for fetal distress
- Can be influenced by fetal sex, presence of maternal diabetes and gestational age

When using STAN for intrapartum fetal monitoring, several T/QRS events can, in combination with CTG abnormalities, lead to the decision to intervene in labor. A T/QRS baseline rise represents a rise in T/QRS for longer than 10 minutes while an episodic rise consist of a rise in T/QRS that returns to normal within 10 minutes. Biphasic events consist of a depression of the ST segment. This depression is divided into three different types by the STAN software: a class 1 biphasic event indicates that the ST slope is descending but the entire ST segment is situated above the FECG baseline level. In a class 2 biphasic event, the ST segment crosses the FECG baseline level, and in a class 3 biphasic event, the ST segment is entirely situated below the FECG baseline level. Although baseline and episodic rises are fairly easy to interpret (together with the classification of the CTG), the biphasic events are much more difficult to interpret. Although several animal studies have shown that biphasic events seems correspond with hypoxia[23,24], in human studies this correlation seems questionable. Yli et al. have shown that in laboring

women with (gestational) diabetes the presence of these events was not correlated with hypoxia, although they occurred more common in this population than in non-diabetic women. They hypothesized that in diabetic women biphasic events represent an altered ability of the fetal myocardium to response to the stress of labor, rather than representing hypoxia.[25,26] This finding was confirmed in a secondary analysis of the Swedish RCT, in which Norén et al. found biphasic events in only 2% of laboring women, not primarily associated with acidemia.[27] Furthermore, Kwee et al. have described that the majority of events consist of baseline and episodic rises, whereby biphasic events are often seen in the presence of normal CTG traces.[28] Because of the uncertain association of biphasic events with hypoxia and of the difficulties in the interpretation of these events, we hypothesized that biphasic events are of little additional value in the prediction of asphyxia. This was studied in Chapter 6. Logistic regression analysis showed no independent association of presence of *significant* (i.e. intervention advised) biphasic events with interventions for suspected fetal distress or adverse neonatal outcome. The area under the Receiver Operator Curve increased only marginally when the presence of significant biphasic events was added to multivariable logistic models for the prediction of interventions for suspected fetal distress and the prediction of adverse outcome. This shows again that the presence of significant biphasic events has no added value in the prediction of interventions for suspected fetal distress or adverse neonatal outcome. These data suggest that biphasic events might be omitted from the STAN analysis and guidelines, which would largely simplify the use of STAN FECG monitoring. However, additional data are necessary to fully clarify this issue.

Summary

Biphasic events of the fetal ECG:

- Seem to have no independent association with interventions for suspected fetal distress or with adverse neonatal outcome
- Have no added value in the prediction of interventions for suspected fetal distress or the prediction of adverse neonatal outcome in the cohort we studied
- Should therefore be the subject of further research and might be omitted in future STAN clinical guidelines when these findings are confirmed

Very little is known about the fetal ECG response to hyperthermia and infection. To investigate if STAN and its guidelines can also be used in case of these conditions we studied women with intrapartum fever monitored with STAN (Chapter 7). We hypothesized that intrapartum fever may affect the ST segment, either by an increased occurrence of hypoxia or by direct effects on the myocardium and thus may result in a higher incidence of ST-events. As a consequence, STAN guidelines might not be applicable for the prediction of fetal hypoxia when fever is present. We therefore studied the association of maternal

intrapartum fever at term with the presence of ST-segment changes of the fetal ECG. In this study, both the number and type of ST-events were comparable between women with and without fever during delivery. Also when adjusted for other variables such as presence of epidural analgesia and the time interval of ruptured membranes before birth, we found no significant association between the presence of fever and the presence of (any kind of) ST-event within the first 2 hours after the first fever measurement. However, since the low number of neonates born with an adverse neonatal outcome did not allow for subgroup analysis, we were not informed about any possible association between the presence of fever and the positive predictive value of ST-waveform analysis for adverse neonatal outcome. Since the presence of fever has been shown to be a strong risk factor for adverse neonatal outcome, such as neonatal encephalopathy and neonatal death[29–31], we still advise to consider the fetus that is exposed to fever as being at increased risk of adverse neonatal outcome, irrespective of the fact that ST-events (i.e. independent of the classification of the CTG trace) appear to occur unaltered when fever is present.

Another specific obstetric situation that is very common in everyday clinical practice and that might influence the use of ST waveform analysis during labor, is the use of epidural analgesia for pain relief. Epidural analgesia is associated with various side-effects such as maternal hypotension, more frequent use of oxytocin augmentation, longer second-stage of labor and maternal fever.[32,33] Moreover, the placental intervillous space is known to act as a site of drug deposit for bupivacaïne[34,35] as well as for fentanyl.[34,35] In one study on the fetal ECG and bupivacaïne, Phillips et al. found a significant increase in fetal heart rate and a significant decrease of the T-QRS ratio.[36] Following this finding, monitoring with STAN (which marks increases of the T-QRS ratio as a possible sign of fetal hypoxia) might lead to a reduction of ST-events, which might result in a reduced reliability of STAN in the ability to detect fetal distress. We therefore studied the possible influences of epidural analgesia on intrapartum ST-analysis of the fetal ECG (Chapter 8). When comparing 72 laboring women with epidural analgesia (cases) with 72 women without epidural analgesia (controls), we found no effects of epidural analgesia, nor of induced hypotensive episodes on the number of ST-events. No differences were found between the groups in number and type of ST-events or mean T-QRS ratio within two hours after start of epidural analgesia, nor in neonatal outcome.

Summary

Specific obstetrical situations might alter the liability of any method of intrapartum surveillance.

However:

- **Both the presence of maternal fever and the use of epidural analgesia during labor seem to have no effect on the number and type of ST-events when using ST waveform analysis of the FECG**
- **One should realize that this does not imply that STAN has the same positive predictive value in women with intrapartum fever or with epidural analgesia during the delivery.**

Strengths and limitations of these studies

There are some strengths and limitations related to the studies presented in this thesis that should be discussed. The major limitation for the majority of studies is related to their retrospective character. Although data were used from randomized trials on ST waveform analysis[12,15], these studies were designed to study the effects of STAN on neonatal outcome. Therefore, the secondary analyses performed were dependent on the data that had been collected in the trials and power to detect significant differences as to our studies was not always sufficient. For example, when evaluating the recommendations for additional fetal blood sampling (FBS) when using STAN (Chapter 3), we were unaware to what extend the recommendations had been followed in situations where no FBS had been performed. Secondly, in our secondary analysis on the predictive abilities of biphasic events of the fetal ECG, the power to detect significant differences was limited due to the low number of biphasic events, and to the low number of adverse neonatal outcome. Secondly, many of our studies were dependent of the classification of the CTG traces. Although in all studies we tried to reduce the presence of inter-observer variability by way of classifying the CTG traces by several observers, the possibility of inter-observer bias cannot be eliminated completely. However, we feel that these limitations should not be the reason to evade from the duty to create an evidence-based framework when using ST waveform analysis for intrapartum surveillance. Data collected in these randomized trials create unique opportunities to evaluate several aspects regarding the new technique of ST waveform analysis, and should therefore be used accordingly. The relevance of this thesis adds to its strength. Perinatal asphyxia is an important contributor of cerebral palsy and intrapartum fetal surveillance should therefore be evidence, rather than expert-based.

Recommendations for clinical practice

Obstetricians in the Netherlands are divided with respect to the preferred method of intrapartum fetal surveillance. Although ST waveform analysis is used in most University hospitals and in several teaching hospitals, most hospitals prefer fetal monitoring with conventional cardiotocography. In our meta-analysis we could not confirm the positive effects of ST waveform analysis on metabolic acidosis at birth, which might be the most important reason for clinicians to prefer conventional cardiotocography. However, since metabolic acidosis is rare, large studies will be needed for an accurate estimation of the effect on metabolic acidosis. It might well be that future studies, like the NIH randomized trial on ST waveform analysis, or the IPD meta-analysis that will be conducted in the near future, might show a significant reduction of metabolic acidosis when using ST waveform analysis.

Another reason why clinicians might be reluctant in adapting a new method of fetal monitoring might be the presence of additional costs. Several cost-effectiveness studies have appeared that compare STAN with conventional CTG. Westerhuis et al. found that the mean costs per patient when using STAN was only €29 higher when compared to conventional CTG, and the incremental costs to prevent one case of metabolic acidosis to be €6,667.[37] The only study focusing on long-term cost-effectiveness showed that, when including both the immediate direct costs at the hospital and the lifetime costs for individuals with severe cerebral palsy, ST-analysis is a cost-saving method. However, also when considering only the treatment costs associated with the immediate care at the hospital, this study showed that ST analysis is cost saving, which means that the additional cost of using the ST analysis device instead of CTG was more than outweighed by the costs saved by avoiding caesarean deliveries, instrumental vaginal deliveries, cases of metabolic acidosis, and cases of encephalopathy.[38]

There are at present other arguments to incorporate ST waveform analysis into daily practice. Our meta-analysis showed that ST waveform analysis reduces the incidence of operative vaginal deliveries with more than ten percent and the incidence of fetal blood sampling with 40 percent. Furthermore, the STAN methodology and its classification of the CTG trace into normal, intermediate, abnormal, and preterminal, may help the clinician by forcing him/her to translate all aspects of the CTG trace into one final classification. As a result, several studies have shown that STAN has a better (i.e. lower) inter-observer variability than conventional CTG alone.[39,40]

Implementation of any new method of intrapartum surveillance, like the STAN methodology, should be carefully executed. The trial of Amer-Wahlin et al. showed that the favorable effect of STAN was mainly obtained in the second part of the trial.[41] An interim analysis showed several protocol violations among babies born with metabolic

acidosis, after which training was repeated. Recently, observational studies have shown a decrease in incidence of metabolic acidosis after long-term use of STAN in both Sweden, Norway and Finland, occurring in the course of 5 to 10 years of use.[22,42] Cases of adverse neonatal outcome described in the literature are mainly due to problems with the interpretation of the CTG or violation of guidelines.[17]

Each clinician should decide for him/herself whether the advantages of STAN exceed the potential disadvantages. However, the same clinician has the obligation towards the mother and her unborn child, to make this decision based on the best available evidence. If future studies on ST waveform analysis show a significant reduction on metabolic acidosis, it should be considered as the new gold standard for intrapartum fetal monitoring in high risk singleton pregnancies beyond 34 weeks gestation.

Recommendations for future research

Although research on fetal monitoring using ST analysis is expanding, several aspects of intrapartum ST-analysis of the fetal ECG deserve further investigation. Although the STAN clinical guidelines and recommendations for additional fetal information are becoming more and more evidence-, rather than expert-based, we showed that the predictive abilities of biphasic events on adverse neonatal outcome are questionable. Since the power in our study on the predictive value of biphasic events was limited, our results should be validated in future studies. Secondly, although the outcome metabolic acidosis might be the best available alternative to study the effect of ST waveform analysis in randomized trials, the most important goal of intrapartum fetal monitoring should be to improve long term neonatal outcome. Therefore, future studies should focus on the long term effects of ST waveform analysis and on both the neurological and behavioral outcome of children who were monitored with ST waveform analysis during labor and delivery. Furthermore, ST waveform analysis has only been studied from a gestational age beyond 34 weeks. It is unknown if it could be used for deliveries at earlier gestation. Future studies should therefore focus on the effects of ST waveform analysis at earlier gestation. Like fetal monitoring with the conventional CTG, the STAN method needs classification of the CTG trace and therefore is still subject to inter-observer variability. Some interesting studies are currently being conducted on intrapartum fetal monitoring with computer analysis and alerts, a method of computerized fetal monitoring that is expected to illuminate the inter-observer variability and to reduce the human errors associated with inappropriate CTG interpretation.[43]

It could well be that any method which is based on the CTG, will never fulfill the optimal aim of fetal monitoring: to identify all fetuses at risk for asphyxia with the lowest possible intervention rate. Whether or not this goal can ever be achieved, with indirect methods of fetal monitoring like CTG and STAN, or with direct methods of fetal monitoring, like some kind of continuous fetal serum oximetry or lactate measurement, is unsure. As long as this aim hasn't been achieved however, obstetric clinicians have the obligation to continue doing research on fetal monitoring.

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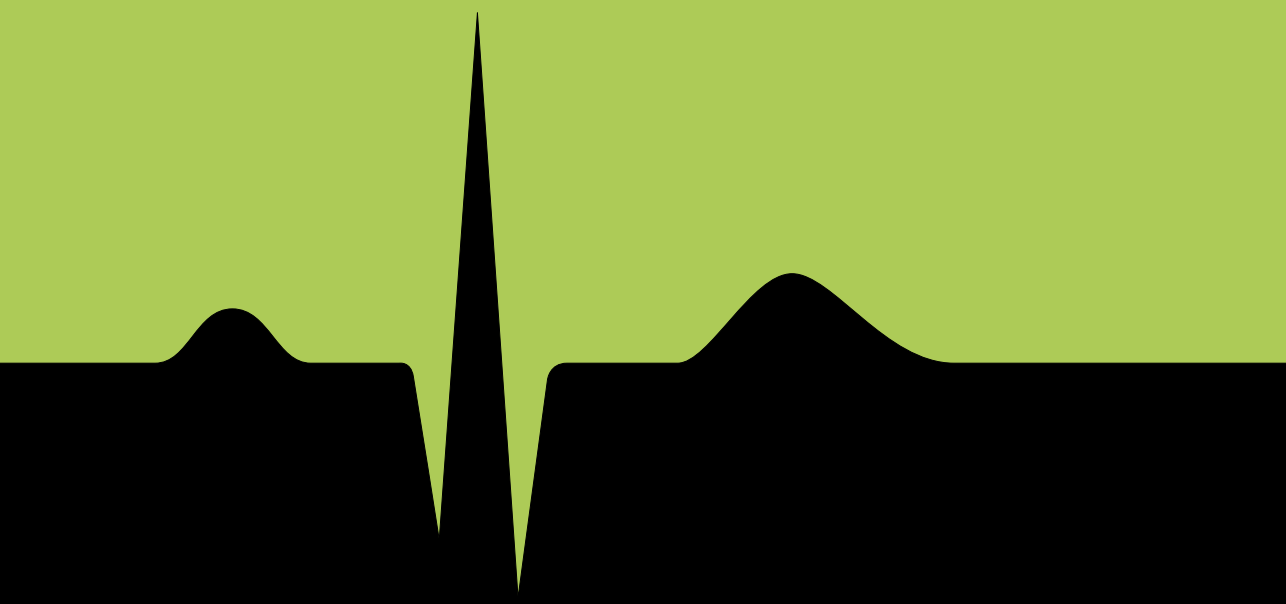
Nederlandse samenvatting

Summary in Dutch



Chapter 10

Introductie

De bewaking van het ongeboren kind tijdens de bevalling is een belangrijk aspect van de verloskunde: het voornaamste doel is om dreigend zuurstoftekort tijdig te ontdekken, waardoor sterfte of (hersen)beschadiging voorkomen wordt. Om dit op een optimale manier te kunnen doen wordt al lang gezocht naar een methode waarmee alle foetussen met een dreigend zuurstoftekort kunnen worden geïdentificeerd, zonder dat dit ten koste gaat van een onnodig hoog percentage vaginale kunstverlossingen of keizersneden. Sinds de jaren zeventig wordt in de meeste Westerse landen het cardiotocogram (CTG), waarin de foetale hartfrequentie en maternale uterusactiviteit continu worden geregistreerd, gebruikt als bewakingsmethode tijdens de bevalling. De introductie van het CTG heeft echter niet geleid tot een afname van de perinatale sterfte of van het aantal pasgeborenen met ernstig hersenletsel als gevolg van zuurstoftekort bij de geboorte[1]. Hoewel een normaal CTG patroon een goede voorspelling geeft over een goede foetale conditie, geeft een afwijkend CTG patroon geen goede voorspelling over de foetale conditie. Het gevolg is een grote toename van vaginale kunstverlossingen en keizersneden in verband met vermeend foetaal zuurstoftekort, zonder duidelijke verbetering in neonatale uitkomst. Een ander belangrijk nadeel van het CTG is de matige overeenstemming tussen beoordelaars (inter-observer variabiliteit): wat de ene hulpverlener een normaal patroon vindt, kan een andere hulpverlener beschouwen als een abnormaal patroon. Het CTG is dan ook niet de ideale methode om dreigend zuurstoftekort bij de geboorte op te sporen. Ook wanneer het *microbloedonderzoek* wordt toegevoegd aan het CTG blijven de resultaten teleurstellend. Bovendien is dit een invasieve techniek, die herhaald moet worden bij een blijvend afwijkend CTG en nogal eens mislukt en technisch lastig is.

Analyse van het ST segment van het foetale elektrocardiogram (ECG) in combinatie met het 'traditionele' CTG (STAN®) is een relatief nieuwe manier van foetale bewaking. Het ST segment van het foetale ECG geeft de elektrische geleiding van het foetale hart weer tussen de contracties van de hartkamers en het (opnieuw) opladen van de hartkamers. Veranderingen in dit ST segment zouden een weerspiegeling zijn van zuurstoftekort van de hartspiercellen, welke op hun beurt weer een weerspiegeling zijn van eventueel zuurstoftekort in de foetale hersenen. Tijdens de bevalling wordt een elektrode aangebracht op het hoofdje van de foetus waaruit het ECG afgelezen kan worden. De basiswaarde van het ST segment aan het begin van de registratie dient vervolgens als referentie om eventuele veranderingen tijdens de bevalling op te sporen. De relevantie van ST veranderingen is afhankelijk van de visuele beoordeling van het CTG, dat volgens de STAN klinische richtlijnen (zie appendix 1) wordt geclassificeerd als normaal, suboptimaal, abnormaal of preterminaal. In deze richtlijnen wordt vermeld in welke situaties obstetrische interventies nodig zijn. Een interventie kan betekenen dat de oorzaak van het foetale zuurstoftekort wordt opgeheven (bijv. door het staken

van weeënstimulatie of behandelen van een lage bloeddruk) of dat de baring wordt beëindigd.
In de STAN klinische richtlijnen worden drie verschillende *ST-events* beschreven die, in combinatie met een afwijkend CTG patroon, kunnen wijzen op (dreigend) foetaal zuurstoftekort en waarbij interventie aangewezen is. Deze events zijn:

1. Een episodische T/QRS stijging. Dit is een stijging van de T/QRS ratio ten opzichte van de referentiewaarde, of basale T/QRS ratio, die minder dan 10 minuten aanhoudt.
2. Een basislijn T/QRS stijging. Dit is een stijging van de T/QRS ratio die langer dan 10 minuten aanhoudt.
3. Een bifasisch event. Dit is wordt gedefinieerd als een schuin aflopend ST segment, dus een daling van de T/QRS ratio ten opzichte van de referentiewaarde.

Naast de koppeling tussen de beoordeling van het CTG en de ST analyse, geven de STAN klinische richtlijnen ook aanbevelingen in welke drie situaties aanvullend onderzoek (zoals bijv. microbloedonderzoek) overwogen kan worden (Appendix 2): bij het starten van de foetale ECG registratie in combinatie met een abnormaal CTG (aangezien er dan mogelijk al compensatie van de foetale hartspier plaats heeft gevonden en dit niet meer opgemerkt zal worden door de ST analyse); bij een afwijkend CTG in combinatie met een slechte kwaliteit van de ST analyse (aangezien dit laatste dan niet betrouwbaar verricht kan worden); en wanneer er gedurende meer dan 60 minuten sprake is van een abnormaal CTG patroon zonder dat de analyse van het foetale elektrocardiogram aanleiding geeft tot interventie (als reddingsmechanisme, omdat niet alle foetus met dreigend zuurstoftekort een verandering in het ST segment laten zien).
De STAN klinische richtlijnen en de verschillende ST-events zijn tot stand gekomen door resultaten van dierexperimenteel onderzoek en cohort studies, maar zijn nooit onderdeel geweest van een separate wetenschappelijke analyse.[2–5]

Het doel van de in dit proefschrift beschreven onderzoeken was:

1. Het bestuderen van de effectiviteit van foetale bewaking van STAN in vergelijking met het conventionele cardiotocogram, en
2. Het toetsen van de huidige richtlijnen voor het gebruik van STAN als foetale bewaking tijdens de bevalling.

Effectiviteit van foetale bewaking met behulp van STAN

Verschillende onderzoeken hebben de effectiviteit van foetale bewaking met STAN vergeleken met het conventionele CTG.[4,6–9] Hoewel één van deze studies heeft aangetoond dat het gebruik van STAN leidt tot een significante reductie van het aantal pasgeborenen met zuurstoftekort[6], is deze conclusie door andere studies niet bevestigd. In 2006 is er door de *Cochrane Collaboration* een meta-analyse van de op dat moment beschikbare onderzoeken verricht waarbij de effectiviteit van STAN vergeleken is met die van het conventionele CTG. Hierbij werd geen significant verschil gevonden in het optreden van zuurstoftekort (gedefinieerd als *metabole acidose*) of in het aantal keizersneden. Wel werden er minder vaginale kunstverlossingen en aanvullende microbloedonderzoeken verricht bij het gebruik van STAN.[10] In 2010 werd een groot Nederlandse *gerandomiseerd* onderzoek gepubliceerd naar de effectiviteit van STAN in vergelijking met het conventionele CTG. Hierbij werd een 30% lagere incidentie van metabole acidose gevonden bij het gebruik van STAN. Gelet op de lage incidentie van foetaal zuurstoftekort in deze studie was dit verschil niet significant. In Hoofdstuk 2 beschrijven we een meta-analyse waarbij we alle 5 tot nu toe verrichte gerandomiseerde onderzoeken op dit gebied combineren. De resultaten tonen dat STAN geen significante afname geeft van het aantal kinderen dat geboren wordt met een metabole acidose, maar wel een vermindering geeft van het aantal vaginale kunstverlossingen en aanvullende microbloedonderzoeken. Dat het reduceren van het aantal benodigde microbloedonderzoeken van belang kan zijn, wordt geïllustreerd in Hoofdstuk 3. Hierin wordt een literatuuroverzicht gegeven van de mogelijke complicaties van het microbloedonderzoek. Hoewel complicaties van microbloedonderzoek zeldzaam zijn, laat het overzicht zien dat de meest voorkomende complicaties bloedingen en abcessen zijn ten gevolge van de incisie. Ook wordt in dit hoofdstuk een casus beschreven van een pasgeborene met lekkage van de hersenvloeistof als complicatie van het microbloedonderzoek. In deze casus werden bij het verrichten van het microbloedonderzoek 4 verschillende weefsellagen van de schedel geperforeerd, inclusief de beide hersenvliezen.

STAN en de klinische richtlijnen

In dit proefschrift zijn de volgende vraagstellingen ten aanzien van de STAN klinische richtlijnen en aanbevelingen bestudeerd:

- Zijn de huidige aanbevelingen voor het verrichten van aanvullend onderzoek, zoals microbloedonderzoek, effectief in het voorkomen van foetaal zuurstoftekort (Hoofdstuk 4)?
- Wat is de associatie tussen de T/QRS referentiewaarde van het foetale elektrocardiogram, zoals die wordt berekend aan het begin van de registratie, en de neonatale uitkomst (Hoofdstuk 5)?
- Zijn bifasische ST-events geassocieerd met het optreden van een slechte neonatale uitkomst (Hoofdstuk 6)?

- Wat is het effect van maternale koorts op het foetale elektrocardiogram (Hoofdstuk 7)?
- Wat is het effect van een ruggenprik bij de moeder tijdens de bevalling op het foetale elektrocardiogram (Hoofdstuk 8)?

Zijn de huidige richtlijnen voor het verrichten van aanvullend onderzoek effectief in het voorkomen van foetaal zuurstoftekort?

Aanvullend onderzoek, zoals door de STAN klinische richtlijnen in eerder genoemde situaties wordt geadviseerd, zal in de Nederlandse situatie vaak bestaan uit het verrichten van microbloedonderzoek. In Hoofdstuk 4 wordt een studie beschreven waarbij de microbloedonderzoeken (MBO's), die verricht zijn binnen het eerder gepubliceerde Nederlandse gerandomiseerde onderzoek, beoordeeld zijn als 'conform de richtlijnen' of 'niet conform de richtlijnen'. De resultaten laten zien dat ongeveer 10% van MBO's die verricht zijn conform de richtlijnen een dreigend zuurstoftekort laten zien (gedefinieerd als een pH <7.20), terwijl dit slechts bij 2% van de MBO's die niet conform de richtlijnen verricht waren het geval was. Het lijkt er dan ook op dat de richtlijnen voor het verrichten van aanvullend microbloedonderzoek, effectief zijn voor de tijdige ontdekking van dreigend zuurstoftekort. Dit betreft vooral de MBO's die verricht worden in aanwezigheid van een abnormaal CTG patroon >60 minuten zonder aanwezigheid van ST-events. De resultaten tonen verder dat ruim 40% van de MBO's niet conform de richtlijnen verricht werden. Indien men de richtlijnen zorgvuldiger naleeft, kan het aantal benodigde MBO's waarschijnlijk nog verder gereduceerd worden.

Wat is de associatie tussen de T/QRS referentiewaarde van het foetale elektrocardiogram en de foetale uitkomst?

De T/QRS basislijn referentiewaarde is de hoogte van de T/QRS ratio aan het begin van de registratie. Eventuele veranderingen in de T/QRS ratio gedurende de baring worden door de STAN computer met deze referentiewaarde vergeleken. In de Europese STAN expert bijeenkomsten werd de hypothese geopperd dat foetussen met een hoge basislijn T/QRS referentiewaarde meer risico zouden lopen op zuurstoftekort bij de geboorte dan foetussen met een lage basislijn T/QRS referentiewaarde. Aan de grondslag van deze hypothese lag de observatie dat een aantal foetussen met een hoge basislijn T/QRS referentiewaarde geboren werden met een zuurstoftekort, ondanks adequate foetale bewaking. Een van de achterliggende mechanismen hierachter zou kunnen zijn dat er bij deze foetussen reeds een compensatiemechanisme heeft plaatsgevonden waardoor de T/QRS hoog is. Bij deze foetussen zouden de reservecapaciteiten mogelijkerwijs al aangesproken zijn en dientengevolge de T/QRS bij volgende episoden van zuurstoftekort niet meer (voldoende) stijgen. In Hoofdstuk 5 hebben wij onderzocht wat de voorspellende waarde is van een hoge basislijn T/QRS referentiewaarde op het optreden van zuurstoftekort bij de geboorte of het krijgen van een vaginale kunstverlossing of keizersnede in verband met vermeend foetaal zuurstoftekort. In deze studie werden

twee verschillende afkapwaarden voor een verhoogde basislijn T/QRS referentiewaarde gehanteerd: een waarde ≥0.25, zoals in eerdere publicaties gehanteerd[4], en een waarde ≥0.33, wat overeenkomt met twee standaard deviaties boven het gemiddelde in de studie populatie. Geen van deze afkapwaarden bleek een voorspellende waarde te hebben voor het optreden van foetaal zuurstoftekort bij de geboorte of het krijgen van een vaginale kunstverlossing of keizersnede. In hetzelfde onderzoek vonden wij dat het foetale geslacht, de aanwezigheid van maternale suikerziekte en de zwangerschapsduur gerelateerd zijn aan de hoogte van de basislijn T/QRS referentiewaarde.

Zijn bifasische ST-events geassocieerd met het optreden van een slechte neonatale uitkomst?

Hoewel de STAN klinische richtlijnen vrij duidelijk aangeven wanneer interventies geïndiceerd zijn bij de aanwezigheid van T/QRS stijgingen, zijn de implicaties van de eerder genoemde 'bifasische events' veel moeilijker te interpreteren. De relatie van deze events met een eventueel foetaal zuurstoftekort is volgens de STAN richtlijnen afhankelijk van het aantal en type events, de tijdspanne tussen de events, en de klinische situatie (zoals aan- of afwezigheid van meconiumhoudend vruchtwater, koorts etc). In eerdere studies kon het optreden van bifasische events niet direct gerelateerd worden aan het optreden van zuurstoftekort bij de pasgeborene.[5,11,12] Het doel van de studie beschreven in Hoofdstuk 6 was het bestuderen van de voorspellende waarde van het optreden van bifasische events op het optreden van foetaal zuurstoftekort of op het krijgen van een vaginale kunstverlossing of keizersnede in verband met vermeend foetaal zuurstoftekort. Bifasische events bleken geen onafhankelijke associatie te hebben met het optreden van foetaal zuurstoftekort of medisch ingrijpen vanwege vermeend foetaal zuurstoftekort en hebben dan ook geen voorspellende waarde. Het is daarmee uiterst twijfelachtig of deze parameter wel meegenomen moet worden in de STAN richtlijnen. Door de relatief kleine aantallen in ons onderzoek is er echter nog geen definitieve uitspraak te doen.

Wat zijn de effecten van maternale koorts en een ruggenprik op het foetale elektrocardiogram?

Om te onderzoeken of STAN ook gebruikt kan worden in aanwezigheid van specifieke obstetrische situaties, hebben wij de mogelijke effecten van maternale koorts en van epidurale analgesie (ruggenprik) op ST-analyse van het foetale ECG bestudeerd. De aanwezigheid van koorts zou het foetale ECG en dientengevolge het optreden van ST-events kunnen beïnvloeden door een hogere incidentie van hypoxie of door directe gevolgen van koorts op het foetale elektrocardiogram, waardoor de STAN richtlijnen mogelijk niet op dezelfde manier gebruikt zouden kunnen worden bij aanwezigheid van koorts tijdens de bevalling. Hoofdstuk 7 laat echter zien dat zowel het aantal, als het type ST-events, vergelijkbaar is tussen vrouwen mét en zónder koorts tijdens de bevalling. Ook wanneer gecorrigeerd werd voor andere variabelen, zoals de aanwezigheid van

langdurig gebroken vliezen of een ruggenprik, werd geen associatie gevonden tussen koorts en het optreden van ST-events. Een ruggenprik is een veelvoorkomende vorm van pijnstilling tijdens de bevalling en kent verschillende bijwerkingen, zoals het optreden van een lage bloeddruk bij de barende vrouw, hogere noodzaak voor *bijstimulatie* van de weeënactiviteit, een langere duur van de uitdrijving en het vaker optreden van maternale koorts. Aangezien studies hebben uitgewezen dat de medicatie die voor een ruggenprik wordt gebruikt veranderingen kan geven van de T/QRS ratio van het foetale elektrocardiogram[13], is het mogelijk dat de STAN richtlijnen niet bruikbaar zijn bij het gebruik van een ruggenprik ter pijnstilling. De gegevens beschreven in Hoofdstuk 8 tonen echter dat een ruggenprik niet zorgt voor een verandering van het aantal of type ST-events, en dat ook de gemiddelde T/QRS ratio vóór en ná een ruggenprik onveranderd blijft. Het lijkt er daarom op dat STAN ook veilig gebruikt kan worden bij het gebruik van een ruggenprik als pijnstilling tijdens de bevalling.

Belangrijkste conclusies van dit proefschrift

- Het gebruik van STAN als methode van foetale bewaking, in vergelijking met foetale bewaking met het conventionele CTG, leidt tot een afname van het aantal vaginale kunstverlossingen en tot afname van het aantal benodigde microbloedonderzoeken. Een eventuele afname van zuurstoftekort bij de pasgeborene is echter niet aangetoond.
- De STAN klinische richtlijnen met betrekking tot het verrichten van aanvullend microbloedonderzoek zijn effectief ten aanzien van een tijdige opsporing van dreigend foetaal zuurstoftekort.
- Het aantal benodigde microbloedonderzoeken kan waarschijnlijk verder gereduceerd worden indien de STAN klinische richtlijnen beter nageleefd worden.
- De basislijn T/QRS referentiewaarde heeft geen voorspellende waarde op het optreden van foetaal zuurstoftekort of het krijgen van een vaginale kunstverlossing of keizersnede in verband met vermeend foetaal zuurstoftekort.
- Bifasische events lijken geen voorspellende waarde te hebben ten aanzien van het optreden van foetaal zuurstoftekort of het krijgen van een vaginale kunstverlossing of keizersnede in verband met vermeend foetaal zuurstoftekort. Deze events moeten daarom waarschijnlijk niet meer opgenomen worden in de STAN klinische richtlijnen.
- Maternale koorts en/of de aanwezigheid van een ruggenprik ter pijnstilling lijken geen effect te hebben op het aantal of type ST-events. STAN lijkt daarom ook in deze specifieke obstetrische situaties veilig gebruikt te kunnen worden.

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Verklarende woordenlijst

Microbloedonderzoek	Een onderzoek waarbij er een druppel bloed van de schedel van het ongeboren kind wordt geanalyseerd teneinde (dreigend) zuurstoftekort aan te tonen/uit te sluiten
Cochrane Collaboration	Internationale wetenschappelijke organisatie die zich tot doel stelt om de beslisvorming in de geneeskunde te optimaliseren door het verrichten van onafhankelijke reviews
Metabole acidose	Veel gebruikte surrogaat uitkomst voor ernstig zuurstoftekort, gedefinieerd als de combinatie navelstrengarterie pH <7.05 en base overschot >12mmol/L.
Randomisatie	Onderzoeksmethode waarbij het toeval beslist welke behandeling de patiënt krijgt.
ST-events	Veranderingen in het ST segment van het foetale elektrocardiogram die door de STAN monitor gesignaleerd en aangegeven worden.
Bijstimulatie	Het stimuleren van de natuurlijke weeën door oxytocine, een weeënopwekkend hormoon.

Appendices

Appendix I
– STAN clinical guidelines

Classification of cardiotocographic patterns based on FIGO-criteria

	Baseline heart frequency	Variability Reactivity	Decelerations
Normal CTG	• 110-150 bpm	• Accelerations • 5-25 bpm	• Early uniform decelerations • Uncomplicated variable decelerations with a duration of <60 sec and loss of *<60 beats*
Intermediary CTG	• 100-110 bpm • 150-170 bpm • Short bradycardia episode (<100 bpm for ≤ 3 min)	• >25 bpm (saltatory pattern) • <5 bpm > 40 min with absence of accelerations	• Uncomplicated variable decelerations with a duration <60 sec and loss of *>60 beats*
	A combination of several intermediary observations will result in an abnormal CTG		
Abnormal CTG	• 150-170 bpm and reduced variability • >170 bpm • Persistent bradycardia (<100 bpm for >3 min)	• <5 bpm for >60 min • Sinusoidal pattern	• Complicated variable decelerations with a duration of >60 sec • Repeated late uniform decelerations
Preterminal CTG	• Total lack of variability (<2 bpm) and reactivity with or without decelerations or bradycardia		

STAN® clinical guidelines: ST-changes that prompt clinical intervention, such as delivery or solving a cause of fetal distress

ST Events	Normal CTG	Intermediary CTG	Abnormal CTG	Preterminal CTG
Episodic T/QRS rise	• Expectant management • Continued observation	• >0.15	• >0.10	• Immediate delivery
Baseline T/QRS rise		• >0.10	• >0.05	
Biphasic ST		• 3 Biphasic log messages[2]	• 2 Biphasic log messages[2]	

[2] The time span between the Biphasic messages should be related to the CTG pattern and the clinical situation

Appendix 2
– STAN clinical guidelines

STAN® clinical guidelines: recommendations which criteria may require additional fetal information, such as fetal blood sampling

Information for use of STAN Clinical Guidelines

- Intervention depends on the cause of fetal compromise and the stage of labor. It includes qualified assessment of the CTG pattern, alleviation of cause(s) of fetal distress (such ass over-stimulation or maternal hypotension) and delivery.
- During second stage with active pushing, intervention means that immediate operative delivery is recommended unless spontaneous delivery is anticipated within the next 5-10 minutes.
- Abnormal CTG pattern for more than 60 min, or less if the FHR deteriorates rapidly, with normal ST requires qualified assessment and checking for non-deteriorating fetal state.
- With a preterminal CTG pattern intervention is always indicated, irrespective of ST data.
- Pause in the recording or poor signal quality with gaps in the T/QRS ratios for more than 4 min may result in missed ST Events: management should be related to the CTG pattern and the clinical situation.
- In the presence of maternal pyrexia even intermediary CTG pattern may be regarded as significant in combination with ST Event.

Appendix 3

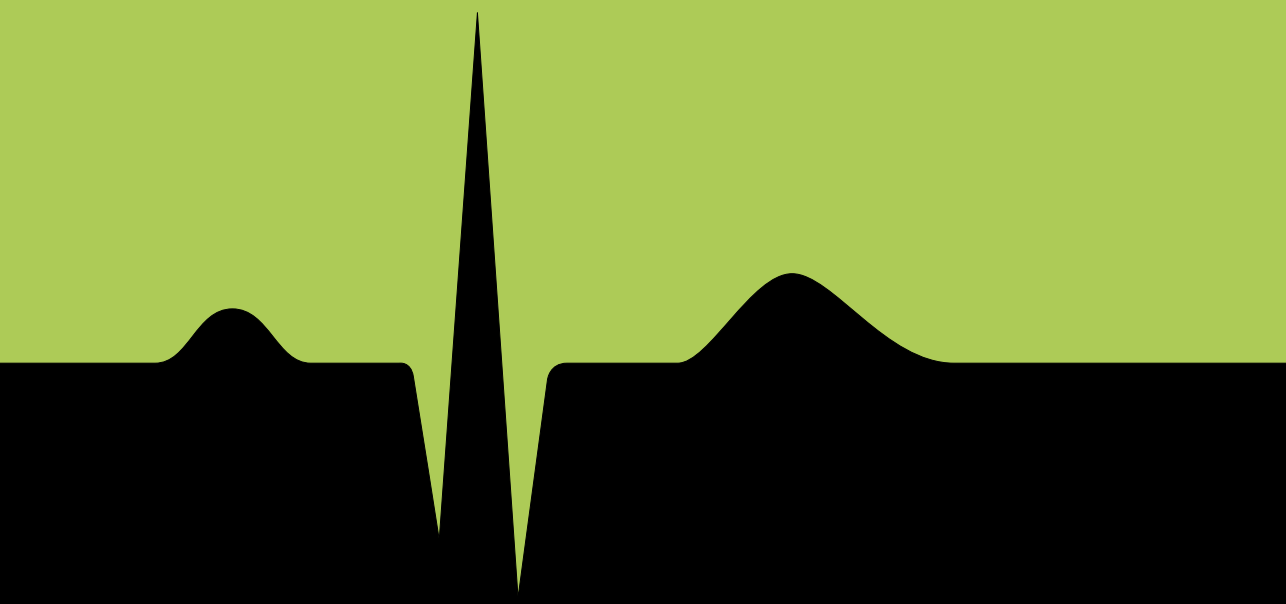
META – ANALYSIS SEARCH FILTER

(((‘st-analysis’ AND (‘fetus’/exp OR ‘fetus’ OR ‘fetal’) AND (‘electrocardiography’/exp OR ‘electrocardiography’ OR ‘ecg’/exp OR ‘ecg’) OR stan OR ‘electrocardiography’/exp OR ‘electrocardiography’ AND (‘cardiotocography’/exp OR ‘cardiotocography’ OR ‘fetal heart rate’/exp OR ‘fetal heart rate’ OR (‘heart’/exp OR ‘heart’ AND ‘rate’ AND ‘fetal’) OR ‘heart rate, fetal’/exp OR ‘heart rate, fetal’) AND (‘cerebral’ AND (‘palsy’/exp OR ‘palsy’) OR ‘cerebral palsy’/exp OR ‘cerebral palsy’ OR ‘acidosis’/exp OR ‘acidosis’ OR (‘fetal’ AND (‘hypoxia’/exp OR ‘hypoxia’)) OR ‘fetal hypoxia’/exp OR ‘fetal hypoxia’ OR ‘foetal monitoring’/exp OR ‘foetal monitoring’ OR (‘fetal’ AND (‘monitoring’/exp OR ‘monitoring’)) OR ‘fetal monitoring’/exp OR ‘fetal monitoring’ OR (‘blood’/exp OR ‘blood’ AND (‘gas’/exp OR ‘gas’) AND (‘analysis’/exp OR ‘analysis’)) OR ‘blood gas analysis’/exp OR ‘blood gas analysis’ OR (‘asphyxia’/exp OR ‘asphyxia’ AND ‘neonatorum’) OR ‘asphyxia neonatorum’/exp OR ‘asphyxia neonatorum’) AND (‘female’/exp OR ‘female’ OR ‘pregnancy’/exp OR ‘pregnancy’ OR ‘obstetric delivery’ OR (‘delivery’/exp OR ‘delivery’ AND ‘obstetric’) OR ‘delivery, obstetric’/exp OR ‘delivery, obstetric’ OR (‘perinatal’ AND ‘care’) OR ‘perinatal care’/exp OR ‘perinatal care’ OR ‘newborn infant’/exp OR ‘newborn infant’ OR (‘infant’/exp OR ‘infant’ AND (‘newborn’/exp OR ‘newborn’)) OR ‘infant, newborn’/exp OR ‘infant, newborn’) AND (‘randomisation’/exp OR ‘randomisation’ AND controlled AND trial OR controlled AND clinical AND trial OR ‘placebo’/exp OR placebo OR ‘clinical trials as topic’/exp OR ‘clinical trials as topic’ OR ‘randomisation’/exp OR ‘randomisation’ OR trial) NOT (‘animals’/exp OR ‘animals’ NOT (‘animals’/exp OR ‘animals’ AND (‘humans’/exp OR ‘humans’)))

List of abbreviations

List of publications

List of co-authors and their affiliations



List of abbreviations

ANOVA	Analysis of variances
AO	Adverse neonatal outcome
BD	Base deficit
BDecf	Base deficit calculated in the extracellular fluid compartment
CI	Confidence interval
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTG	Cardiotocography
ECG	Electrocardiogram
FBS	Fetal blood sampling / fetal scalp sampling
FECG	Fetal electrocardiogram
FHR	Fetal heart rate
FTP	Failure to progress
HIE	Hypoxic ischemic encephalopathy
IFD	(Interventions for) suspected fetal distress
IPD	Individual patient data
IQR	Interquartile range
Ln(T/QRS)	Logarithmic transformation of the T/QRS
MC	Neonatal medium care unit
NICU	Neonatal intensive care unit
NIH	US National Institute of Health
NNT	Number needed to treat
OR	Odds ratio
PE	Pre-eclampsia
PIH	Pregnancy induced hypertension
PM	The Paule-Mandel between-study variance estimate
RCT	Randomized controlled trials
ROC	Receiver operating characteristics
RR	Risk ratio
SD	Standard deviation
STAN	ST-analysis of the fetal electrocardiogram in combination with cardiotocography
T/QRS	Ratio of amplitude heights of T-top / QRS-complex of the ECG
TEER	Typical expected event rate

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