Intrapartum fetal monitoring by **ST-analysis of the fetal ECG**

Michelle Westerhuis

Intrapartum fetal monitoring by ST-analysis of the fetal ECG
Thesis, Utrecht University, with a summary in Dutch
Proefschrift, Universiteit Utrecht, met een samenvatting in het Nederlands

ISBN	978-90-393-5247-2
Author	Michelle Elisabeth Maria Hermine Westerhuis
Cover	Painting by Katinka Hofstede, www.lasedia.nl
Lay-Out & Print	Gildeprint Drukkerijen Enschede, The Netherlands

The studies in this thesis were supported by The Dutch Organisation for Health Research and Development, ZonMW (Grant number: 945-06-557).

The author gratefully acknowledges financial support for printing of this thesis by:
Neoventa Medical AB (main sponsor of printing); Division Woman and Baby, University Medical Centre Utrecht; Abbott Diagnostics; BMA BV(Mosos); Boehringer Ingelheim BV; ChipSoft BV; Ferring BV, Hoofddorp; Radiometer Benelux BV; Siemens Healthcare Diagnostics BV.

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Intrapartum fetal monitoring by **ST-analysis of the fetal ECG**

Intrapartum foetale bewaking door
ST-analyse van het foetale ECG
(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. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 7 januari 2010 des middags te 4.15 uur

door

Michelle Elisabeth Maria Hermine Westerhuis
geboren op 31 maart 1979 te Nijmegen

Promotoren: Prof. dr. G.H.A. Visser
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Co-promotor: Dr. A. Kwee

The fetal heart is made for survival

Aan papa en mama

Voor Daan en Olivia

Table of contents

1

Introduction

General introduction

Intrapartum fetal monitoring is used to timely identify a distressed fetus in order to prevent asphyxia related neonatal and long-term morbidity, such as hypoxic ischemic encephalopathy (HIE) and cerebral palsy. For this purpose, cardiotocography (CTG) was introduced in the early 1970's. Monitoring by CTG allows continuous recording of the fetal heart rate, based on the R-R-interval of the fetal electrocardiogram (ECG). Although monitoring by CTG alone has not been associated with an improvement in neonatal outcome, it is widely applied.[1-8] Moreover, CTG monitoring alone does not provide sufficient information to discriminate between a normal or abnormal fetal adaptation during the process of labour. Only a normal CTG trace accurately corresponds to a normal fetal condition, whereas for abnormal traces fetal condition remains doubtful. Another widely accepted drawback of the CTG is its poor inter- and intra-observer agreement on classification of traces.[9-11] Given these shortcomings, during labour often fetal information in addition to CTG results is needed.

The oldest technique to obtain complementary fetal information during labour is fetal blood sampling (FBS), which has been used as a reference or 'gold' standard methodology since the introduction by Bretscher and Saling in the 1960's.[12,13] However, this method still is based on the subjective and often suboptimal screening of fetal condition by CTG.[14] Performance of FBS requires expertise, is invasive, has to be repeated when CTG abnormalities persist and still does not guarantee prevention of asphyxia. Therefore it is not widely applied.[15]

Another candidate technique was fetal pulse oximetry (FPO), in which the actual level of fetal hypoxemia is recorded.[16] Two randomised trials with respect to the usefulness of information provided by FPO have been performed. The first trial showed only a reduction in the incidence of caesarean section (CS) for non-reassuring fetal status. However, also an increase in the incidence of CS for failure to progress was seen, without a reduced overall CS rate.[17] Therefore, a second trial was started, which was ended prematurely because at the interim analysis FPO turned out not to be effective.[18]

ST-analysis of the fetal electrocardiogram

Since the 1990's, it has been possible not only to record the fetal heart rate but also the rest of the fetal ECG. Studies have shown that particularly changes in the ST-segment correspond to the fetal reaction to hypoxia. The ST-segment and the T-wave represent the repolarisation or recovery phase of the fetal heart. During hypoxia, the fetal heart consumes more energy than offered, leading to a negative energy balance. The fetus responds by a catecholamines surge and β-adrenoceptor activation, which in turn stimulates heart cells to produce energy by anaerobic breakdown of stored glycogen (myocardial glycogenolysis). In this process lactic acid is produced, which leads to metabolic acidosis. Also, potassium ions are produced, which cause an increase in T-wave amplitude of the fetal ECG. A persisting negative energy balance

in the fetal heart causes myocardial ischemia and a reduction in myocardial performance, which leads to an imbalance between endo- and epicardium. The latter is represented by a depression of the ST-segment of the fetal ECG, which indicates the fetal incapacity to respond to hypoxia.[19-23]

Similar to the adult ECG stress test in cardiology, ST-waveform analysis of the fetal ECG thus provides information on the ability of the fetal heart to respond to stress during labour. This allowed introduction of ST-analysis of the fetal ECG (STAN®) into clinical practice as a method for intrapartum fetal surveillance.[24] The STAN® system calculates one average fetal ECG complex from 30 consecutively qualified ECG complexes. This average ECG complex is analysed by calculating a T/QRS ratio, which is the ratio between the amplitudes of the T-wave and QRS-complex. A baseline T/QRS ratio is determined to identify significant T/QRS changes during the process of labour, leading to a so-called 'ST-event'. The types of ST-events are either a rise in T/QRS ratio or a biphasic ST-segment (Figure 1).

The STAN® methodology is based on an integrated interpretation of the CTG and ST-waveform (Figure 2). The CTG is classified according to the STAN® guidelines, which also indicate whether intervention, e.g. alleviation of a known cause of fetal distress or delivery of the baby, is recommended (Appendix A).

Figure 1 ST-segment changes of the fetal ECG during hypoxia

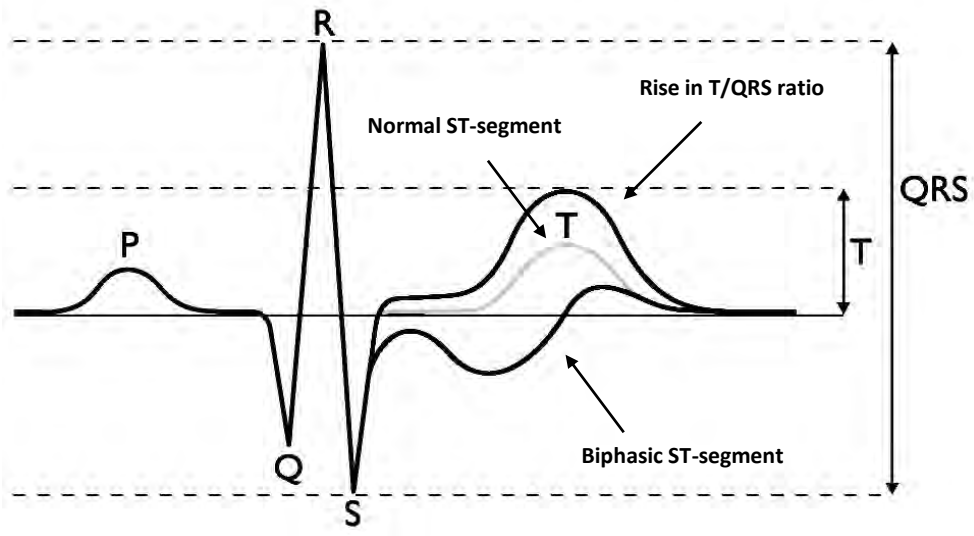
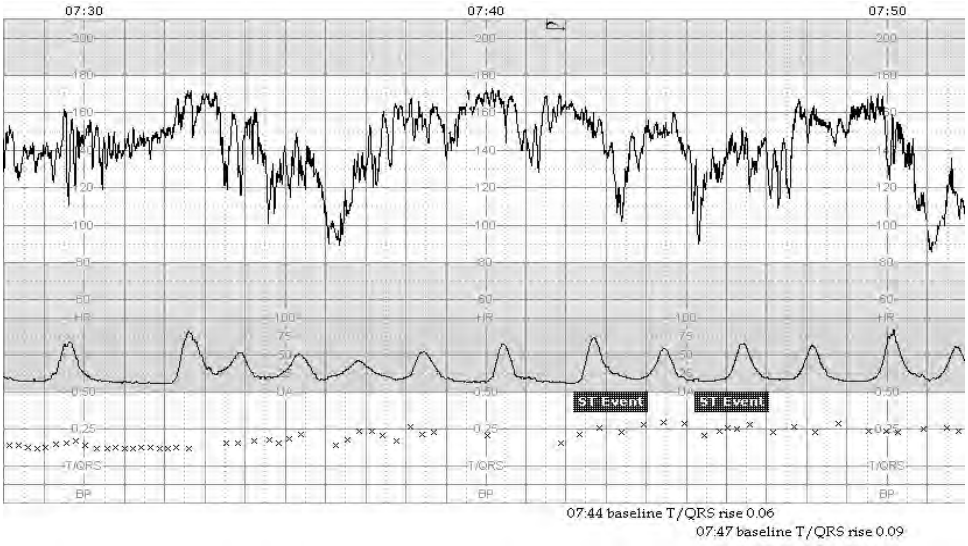


Figure 2 Example of a STAN® recording

Note: To enhance interpretation, a paper speed of 1cm/minute instead of 2cm/minute is used



From top to bottom: the fetal heart rate, uterus activity and T/QRS ratio indicated as crosses. The fetal heart rate shows complicated variable decelerations resulting in classification of the CTG as abnormal. The T/QRS ratio shows a variable pattern, leading to two significant T/QRS rises indicated by the black horizontal bars stating 'ST Event'. Per ST-event exact time, type and quantification of the T/QRS rise are explained below the recording. According to the STAN® guidelines (Appendix A) there is an indication to intervene based on the combined presence of an abnormal CTG and significant ST-events (baseline T/QRS rise of 0.06 and 0.09).

Diagnostic accuracy

Alike therapies, also (new) diagnostic devices or tests should undergo a rigorous and phased evaluation before their introduction in clinical practice. Following the initial technical evaluation of a new diagnostic device, diagnostic accuracy studies (usually observational by design) are executed.[25,26] The STAN® method was introduced in Europe via a 'centre of excellence' structure in the year 2000. Ten departments, including the department of Obstetrics of the University Medical Centre in Utrecht, participated in a European Community multicenter project. The aim was to study the clinical usefulness of the STAN® methodology. This led to the start of several observational studies on the diagnostic accuracy of ST-analysis results to detect the presence or absence underlying fetal distress leading to neonatal acidosis.[27-33]

Table 1 Overview of results of published observational studies reporting on the diagnostic accuracy of ST-analysis of the fetal ECG to detect neonatal metabolic acidosis (MA)
Data are presented as n (%) or % (n/N)

Study	*n*	Definition MA	*n* MA	Sensitivity	Specificity	PPV	NPV
Amer-Wahlin 2002[27]	573	pHa<7.05 & BD>12	15 (2.6)	100 (15/15)	95 (530/558)	35 (15/43)	100 (530/530)
Kwee 2004[28]	449	pHa<7.05 & BD>12	18 (4.0)	61 (11/18)	88 (381/431)	18 (11/61)	98 (381/388)
Luttkus 2004[29]	911	pHa<7.05 & BD>12	20 (2.2)	95 (19/20)	97 (867/891)	44 (19/43)	100 (867/868)
Dervaitis 2004[30]	143	pHa<7.15 & BD>12	7 (4.9)	43 (3/7)	74 (101/136)	8 (3/38)	96 (101/105)
Devoe 2006[31]	530	pHa<7.05 & BD>12	1 (0.2)	100 (1/1)	NR	NR	NR
Vayssiere 2007[32]	411	pHa<7.05 & BD>12	7 (1.7)	57 (4/7)	NR	NR	NR
Melin 2008[33]	506	pHa7.00-7.09 & lact≥10	48 (9.5)	63 (30/48)	52 (239/458)	12 (30/249)	93 (239/257)

pHa = umbilical cord-artery pH; BD = base deficit (mmol/L); lact = lactate (mmol/L); FBS = fetal blood sampling; PPV = positive predictive value; NPV = negative predictive value; NR = not reported in paper

An overview of the accuracy of ST-analysis of the fetal ECG based on the results of seven publications, is presented in Table 1.[27-33] The results show that both sensitivity and specificity ranged from 43 to 100%. So, in some studies still a substantial number of false-positive and false-negative cases occurred. Negative predictive values were high in all studies, which implies that in absence of significant ST-events almost no fetal distress was present and thus no metabolic acidosis will develop. However, increasing clinical use and experience with the STAN® methodology showed that with normal ST-waveform analysis still some infants with adverse outcome are born, indicating no 100% negative predictive value.[34]
Drawing inferences about the clinical usefulness of ST-analysis of the fetal ECG based on these diagnostic accuracy studies only, is limited. The clinician is merely interested in how the STAN® test results guide further decision making to prevent metabolic acidosis at birth. Moreover, a reference test for measuring intrapartum fetal distress other than the 'true' absence or presence of neonatal metabolic acidosis measured after birth, is lacking. Another limitation concerns the comparability of the results of these studies, which is difficult due to variation in used definitions of metabolic acidosis.

Clinical effectiveness

Diagnostic tests by themselves do not improve patient outcome, only via the treatment strategies indicated or chosen based on its results.[35] Randomised comparison of a strategy with and without ST-analysis was therefore needed, to assess whether the ST-analysis results do guide or change therapeutic decisions of clinicians and thus neonatal outcome.[36]

Before the start of the studies described in this thesis, two large randomised clinical trials on the effectiveness of ST-analysis had been performed. These trials showed a reduction in metabolic acidosis, operative deliveries for suspected fetal distress and neonatal encephalopathy in favour of monitoring by ST-analysis of the fetal ECG.[37-39] Two smaller trials showed no improvement in neonatal outcome. However, in contrast with the two larger trials, these trials showed significantly reduced rates of performance of FBS in the patients monitored by ST-analysis.[40,41]

Introduction of ST-analysis in the Netherlands

In 2000, the STAN® method was introduced in the department of Obstetrics of the University Medical Centre in Utrecht. Between 2000 and 2002, 637 high-risk labours were monitored by ST-analysis of the fetal ECG. In this group, FBS was performed in 142 (22%) deliveries and in total 22 (3.5%) infants were born with metabolic acidosis. In 449 women all data were available for analysis, of which 18 (4.0%) neonates were born with metabolic acidosis. All five cases with an umbilical cord-artery pH (pHa) below 7.00 were preceded by significant ST-changes occurring 18 to 31 minutes before birth. In seven of the 13 newborns born with pHa between 7.00 and 7.04, an indication to intervene according to the STAN® guidelines was missing. For the latter group, five-minute Apgar scores were above seven and there were no neonatal admissions. In this study it was concluded that monitoring by STAN® was more accurate in detecting fetal acidemia than monitoring by CTG alone.[28]

The same authors also showed that ST-events occurred frequently in combination with a normal CTG and even with a similar incidence during normal and abnormal CTG traces during first stage of labour. In a subgroup of normal CTG traces, more ST-events occurred between 36-37 weeks of gestation and in boys.[42] The frequent occurrence of ST-events during normal CTG traces was also found by others.[33,43,44] This may be explained by the fact that ST-events are more related to general fetal stress and physical forces during labour, than to actual fetal distress caused by hypoxia. In animal studies it has been shown that also moderate hypoxemia without acidosis may cause an adrenaline surge, β-adrenoceptor activation and myocardial glycogenolysis, leading to an increase in T-wave amplitude of the fetal ECG.[21-23] So, besides fetal hypoxia and acidosis, ST-changes may also be generated by the general arousal and stress associated with normal labour. In these cases a normal CTG pattern indicates a reactive and healthy fetus, capable of responding to the stress of labour.

The results of both studies directed the inception, in 2005, of the studies described in this thesis.[28,42]

Aim of the thesis

The main aim of this thesis is to quantify the (cost) effectiveness of intrapartum fetal monitoring by ST-analysis of the fetal ECG in women with a singleton term pregnancy in cephalic position. The following questions will be addressed:

1) What is the existing evidence regarding effectiveness of ST-analysis of the fetal ECG?
2) What are limitations and drawbacks of ST-analysis of the fetal ECG in clinical practice?
3) Is a strategy of fetal monitoring by ST-analysis of the fetal ECG more cost-effective than monitoring by CTG only?
4) To what extent does correct adherence to clinical guidelines for a strategy of fetal monitoring by ST-analysis prevent cases with adverse neonatal outcome, as compared to monitoring by CTG only?
5) Which patients still need FBS in addition to monitoring by ST-analysis of the fetal ECG?
6) Can neonatal metabolic acidosis at birth be predicted by characteristics both before and during labour?

Outline of the thesis

Chapter 2 contains a review of the randomised clinical trials comparing intrapartum fetal monitoring by CTG combined with FBS versus monitoring by ST-analysis of the fetal ECG, in the period 1975 to 2008. Furthermore, the use of FBS in the Netherlands is described.
Chapter 3 describes a study on inter- and intra-observer agreement of monitoring by ST-analysis of the fetal ECG.
Chapter 4 describes limitations of the use of ST-analysis of the fetal ECG in clinical practice, based on three cases with adverse neonatal outcome. Recommendations for adjustment of STAN® clinical guidelines are given.
Chapter 5 describes the study protocol of a Dutch multicentre randomised clinical trial quantifying the cost-effectiveness of a strategy of monitoring by CTG plus ST-analysis of the fetal ECG compared to CTG only.
Chapter 6 describes the main results of this randomised clinical trial.
Chapter 7 describes a study in which further improvements in fetal monitoring were assessed, based on a subgroup of the above mentioned trial including all cases with adverse neonatal outcome.
Chapter 8 describes a study in which the STAN® clinical guidelines were evaluated with respect to recommendations for performance of FBS in addition to ST-analysis. This study was performed in a subgroup of the above mentioned trial including all deliveries monitored by ST-analysis in combination with FBS.
Chapter 9 describes the cost-effectiveness of fetal monitoring by CTG plus ST-analysis of the fetal ECG compared to CTG only.

Chapter 10 describes a study in which parameters obtained before and during labour are identified to predict neonatal metabolic acidosis in women with a singleton term pregnancy in cephalic position.
Chapter 11 contains a summary, conclusions, general discussion and recommendations for further research.

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Modified from: Ned Tijdschr Geneeskd 2009; 153: B259

2

Intrapartum fetal monitoring: from stethoscope to ST-analysis of the fetal electrocardiogram

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Ben Willem J. Mol, Gerard H.A. Visser, Anneke Kwee

Abstract

- Since the 1970s, intrapartum fetal monitoring has been managed by continuous recording of the fetal heart rate together with uterine activity (cardiotocogram; CTG).
- The use of the CTG without additional fetal information leads to unnecessary interventions due to the high number of false-positive results.
- Fetal blood sampling (FBS) leads to a reduction in the number of false-positive results, but is neither widely nor consistently applied.
- Automated ST-analysis of the fetal electrocardiogram (ECG) with the aid of STAN® equipment, combined with the visual assessment of the CTG, may lead to a reduction of neonatal metabolic acidosis, fewer interventions and fewer fetal blood samples.
- Despite the disadvantage of high inter- and intra-observer variability in the visual interpretation of the CTG, the STAN® method appears to be a useful addition to clinical practice.

Introduction

In order to avoid child mortality or damage due to lack of oxygen during labour, intrapartum fetal monitoring is performed. For this, it is important that the number of subsequent unnecessary obstetric interventions, with their associated maternal and neonatal morbidity, is limited as far as possible. The ideal method of monitoring has not yet been found, which is apparent from the fact that the number of obstetric interventions for suspected fetal distress has increased without neonatal outcomes having clearly improved.[1-3]

In the Netherlands, for low-risk deliveries, which are supervised by a midwife or general practitioner, auscultation of the fetal heart beat is performed. If there is an abnormal heart rate, women are referred to a hospital (secondary care). In women with high-risk pregnancies, cardiotocography (CTG) is used to monitor fetal condition.

The CTG was introduced in the 1970's without its diagnostic accuracy, let alone its effectiveness concerning patient outcome, having been thoroughly evaluated.[4,5] A disadvantage of the CTG is the high percentage of false-positive registrations,[6,7] with their causes including strong inter- and intra-observer variation.[8,9] In a high-risk population, during the phase of dilatation the CTG shows anomalies in 10% of cases and this percentage increases to 60-90 during the phase of active pushing. Without additional diagnostics, this leads to unnecessary interventions due to the large number of false-positive results and the relatively low prevalence of acidosis.[10]

With CTG anomalies, additional investigation must be performed. In this chapter, we provide an overview of the randomised studies into two methods of such additional investigation: fetal blood sampling (FBS) and ST-analysis of the fetal electrocardiogram (ECG) with the aid of the STAN® monitor. For the literature described here, we restrict ourselves to the randomised trials in which the effectiveness of intrapartum fetal monitoring by means of the CTG combined with FBS or the STAN® monitor was studied. The overview of these studies is derived from a search of the literature in *PubMed* and the Cochrane database over the period 1975-2008 using the following keywords: 'fetal monitoring', 'cardiotocography', 'CTG', 'fetal blood sampling', 'fetal ECG' and 'ST-analysis'.

Fetal blood sampling

The only technique up to the present time for additional fetal information with an abnormal CTG is FBS.[11-13] In this, blood is obtained by means of a small incision in the skin of the fetal scalp, from which the pH, the PCO_2 and the base excess can be determined. In general, for a pH < 7.20 it is advised to deliver the baby within a short period of time by means of an assisted vaginal delivery or caesarean section.

Literature on fetal blood sampling

In 2006, the data from 12 randomised trials on the effectiveness of the CTG were presented in a Cochrane meta-analysis.[4] Fetal monitoring, whether in combination with FBS or not, was compared with intermittent auscultation. Continuous monitoring by means of the CTG without FBS leads to a significant increase in the number of caesarean sections (odds ratio (OR) 1.96; 95% confidence interval (CI) 1.24-3.09), without a positive effect on neonatal outcome. If, however, FBS was performed alongside the CTG, a less prominent increase in the number of caesarean sections was found (OR 1.50; 95% CI 1.10-2.06) with a 50% reduction of neonatal convulsions (OR 0.49; 95% CI 0.29-0.84).[4]

The results on the effectiveness of monitoring by means of the CTG combined with FBS originate from 6 of the 12 trials that were performed in the period 1976-1989. This therefore concerns results of relatively old trials in which the frequency of caesarean sections varies from 2.3 - 35%.[4]

Long-term follow-up of these trials is restricted to one study, which revealed that the lower incidence of neonatal convulsions was not associated with an improved outcome over time.[14] . There are no studies in which continuous CTG monitoring without FBS is compared to monitoring with FBS.

Application of fetal blood sampling

Performance of FBS has an added value compared to monitoring by CTG only and offers a solution to the large number of false-positive CTG recordings when it is compared with intermittent auscultation.[4,5] In its 'Fetal Monitoring' ('Foetale bewaking') guidelines of 2004, the Dutch Society for Obstetrics and Gynaecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie, or NVOG) thus advises that for intrapartum fetal monitoring with a CTG there must be the possibility to perform FBS with little impediment. With an anomalous CTG, FBS generally has preference over the immediate ending of labour (www.nvog.nl).

Yet there is the impression that FBS is not used consistently in all Dutch clinics. A significant reason for this is that this investigation only gives a result at a specific point in time and with a persistent anomalous CTG it must be repeated. In addition, FBS is invasive, technically difficult and patient-unfriendly. In at least 10% of attempts, performing FBS is unsuccessful and it can thus be a time-consuming procedure.[15] In addition, the training in performing FBS appears to be inadequate in many hospitals and proper logistics for determining the same are lacking.[16] The relatively large quantity of blood that is required to determine the pH is also stated as a disadvantage of FBS.[17]

A possible alternative to the pH measurement of the FBS sample is determination of lactate concentration. For the latter, less blood is required (5 µl) than the 30-50 µl for the determination of the pH.[17] A recent, major randomised study reveals a lower percentage of unsuccessful attempts for lactate determination (1.2) than for pH determination (10.4), but without this having an effect on the neonatal outcome or the number of assisted deliveries.[18]

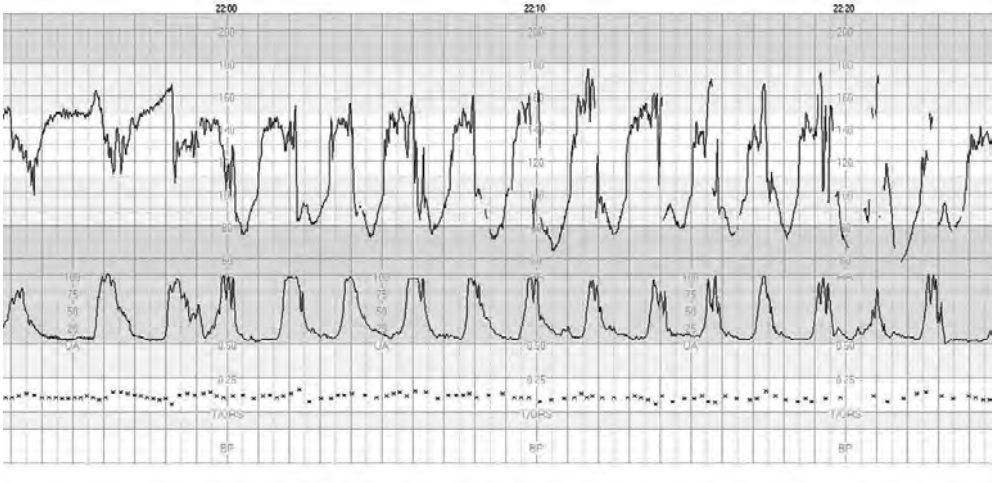
ST-analysis

Since 2000, it has been possible via a scalp electrode not only to register the fetal heart rate but also the rest of the fetal ECG. The fetal heart and the fetal brain appear to be equally sensitive to a shortage of oxygen and thus information on myocardial function also indirectly provides information on the oxygenation of the fetal brain.
It has been shown from experimental animal research that changes in the ST segment of the ECG correlate with fetal hypoxia that occurs or worsens during labour.[19,20] The ST analyser (STAN® monitor; Neoventa Medical, Goteborg, Sweden) was developed in order to be able to combine the CTG with the analysis of the ST segment of the ECG. Changes in the shape of the ST segment are noted automatically and for a significant ST change an alarm is generated, a so called 'ST event'. The associated STAN® guidelines then state whether intervention is required (Appendix A).[21]
The STAN® concept is thus based on a combined interpretation of CTG and ST changes. The relevance of an ST change depends on the visual assessment of the CTG that, according to the criteria of the International Federation of Gynaecology and Obstetrics (FIGO), is classified as 'normal', 'intermediary', 'abnormal', or '(pre)terminal'.[22] If a CTG is normal, any ST change on the STAN® monitor can be ignored. When a CTG is (pre)terminal, immediate intervention is advised, irrespective of ST changes. In case of an intermediary or abnormal CTG, the STAN® guidelines indicate for what ST changes intervention is advised. This intervention may consist of solving a cause of fetal distress, such as hypertonia or hyperstimulation, or proceeding to birth of the child. The STAN® guidelines can be used from a gestational age of 36 weeks onwards.
Examples of STAN® recordings are shown in figures 1 and 2. The NVOG advice is to use a paper speed of 2 cm/min, but in the figures a paper speed of 1 cm/min was chosen in order to be able to show more information.

Literature on ST-analysis
An updated Cochrane meta-analysis from 2009 contains four randomised clinical trials in which monitoring by CTG was compared to monitoring by CTG plus ST-analysis of the fetal ECG in 9671 labouring women (Table 1).[23-27] Use of monitoring by ST-analysis was associated with a lower incidence of metabolic acidosis at birth (relative risk (RR) 0.73, 95% CI 0.49-1.09) and of neonatal encephalopathy (RR 0.37, 95% CI 0.14-1.00).[27] There was a reduction in the number of operative vaginal deliveries in favour of ST-analysis (RR 0.87, 95% CI 0.78-0.96) without a difference in the number of Caesarean sections (RR 0.97, 95% CI 0.84-1.11).[27] In all studies, in both groups it was permitted to perform FBS on the clinician's initiative or on indication. When ST-analysis was used, the frequency of performance of FBS was significantly lower (RR 0.65, 95% CI 0.59-0.72).[27]

Figure 1 Example of a STAN® recording

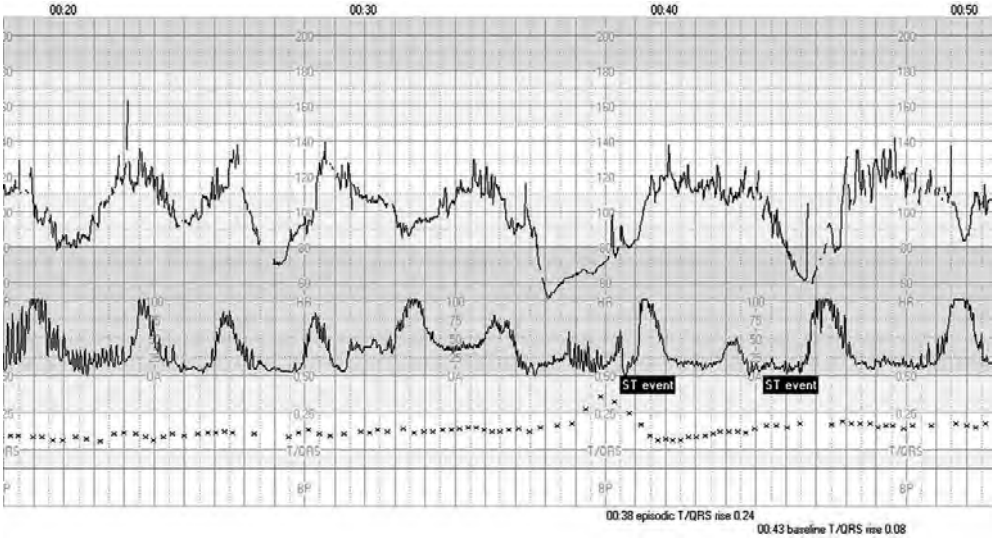
Note: To enhance interpretation, a paper speed of 1cm/minute instead of 2cm/minute is used



From top to bottom: the fetal heart rate (in this case with frequent decelerations), uterus activity and T/QRS ratio (in this case stable; no ST-events) and no reason for intervention.

Figure 2 Example of a STAN® recording

Note: To enhance interpretation, a paper speed of 1cm/minute instead of 2cm/minute is used



Example of a STAN® recording, with an indication for intervention based on the assessment of the CTG (in this case abnormal) combined with a significant ST-event (both episodic T/QRS elevation of 0.24 and baseline T/QRS elevation of 0.08).

Application of ST-analysis

The STAN® method is being applied on an ever-increasing scale within Europe. The difficulties and pitfalls in the use of the method in daily practice are thus becoming clearer.[28] Recently, a number of shortcomings in the STAN® clinical guidelines have been adapted following consensus within a European group of experts.[29]

Table 1 Overview of the most important outcome measures of four clinical trials in which women were randomised to either fetal monitoring by cardiotocography (CTG) or CTG plus ST-analysis of the fetal ECG (CTG+ST)*

	Metabolic acidosis**		Interventions for suspected fetal distress		Incidence of FBS	
Author	CTG %	CTG+ST %	CTG %	CTG+ST %	CTG %	CTG+ST %
Westgate[23] N=2434	1.40	0.55	**9.1**	**5.0**	9.4	7.6
Amer-Wåhlin[24] N=4966	**1.44**	**0.57**	**8.0**	**5.9**	11.0	9.0
Ojala[25] N=1472	0.7	1.7	8.5	7.0	**15.6**	**7.0**
Vayssiere[26]*** N=739	2.8	3.0	37.0	33.6	**62.0**	**27.0**

* Significant differences (p<0.05) are in bold. All four trials are included in a Cochrane meta-analysis.[27]

** Metabolic acidosis is defined as an umbilical cord-artery pH < 7.05 combined with a base deficit > 12 mmol/L.

*** The inclusion criteria of this trial differ from the other trials and were limited to labouring women with abnormal CTG and/or meconium stained amniotic fluid.

Situation in the Netherlands

Fetal blood sampling

Due to the lack of clarity concerning the application of FBS in the Netherlands, we sent a questionnaire to all 98 obstetric clinics. The questionnaire contained questions on the use, or lack of use, of FBS, its availability outside office hours, the method of determination, the logistics and the percentage of deliveries in which FBS is performed.

All institutions responded to this survey. FBS is performed in 88% (86/98) of the clinics, including all teaching hospitals. Table 2 shows the percentages of deliveries in which FBS is performed.

Of the clinics that perform FBS, 19% (16/86) answered that they always perform FBS in case of an abnormal CTG. In 41% (35/86) of the clinics, this was usually the case, in 28% (24/86) sometimes and in 13% (11/86) seldom. In 37% (32/86) of the clinics, FBS was only performed during the stage of dilation and in 63% (54/86) of the clinics during both stages of dilation and active pushing. In all clinics where FBS is performed, this could be done 24 hours a day.

Table 2 Percentage of clinics and deliveries in which fetal blood sampling (FBS) is performed, categorised according to type of clinic

Category	**Clinics that perform FBS n (%)**	**Average % of deliveries in which FBS is performed***
University clinics N=8	8 (100)	12.3
Non-university teaching clinics N=36	36 (100)	14.9
Non teaching clinics N=54	42 (77.8)	2.7

Number of clinics in relation to percentage of deliveries in which FBS is performed						
	<1%	**1-5%**	**5-10%**	**10-15%**	**15-20%**	**>20%**
Number of clinics (n)	15	29	12	7	7	16

* The average percentage of deliveries is calculated or estimated based on the number of full-term births reduced by the number of primary Caesarean sections.

ST-analysis

In the Netherlands, 20 of the 99 obstetric clinics have one or more items of STAN® equipment. Currently, a major randomised clinical trial, performed within the Dutch Obstetric Consortium (www.studies-obsgyn.nl/stan), is being completed in which monitoring by CTG plus ST-analysis is compared to monitoring by CTG only (www.controlled-trials.com/isrctn/pf/95732366).[30,31]

Conclusion

The intrapartum CTG has a low specificity. If no additional monitoring techniques are used, it leads to many unnecessary interventions. This partly explains the significant increase in the number of Caesarean sections in the last few decades. The CTG must therefore not be used without FBS.

From our survey, it is apparent that FBS is not available everywhere and is not always performed consistently, although this is expressly recommended in the NVOG guidelines. That FBS is a difficult technique is also apparent from the fact that in many western countries FBS has disappeared entirely from labour wards, with relatively higher Caesarean section percentages than in our country.

The use of ST-analysis leads to a drop in false-positive CTG interpretations and reduces the necessity for FBS, but does not replace it entirely. The first randomised studies reveal a reduction in interventions and children born in poor condition, but the results are not unequivocal.

A shortcoming of the STAN® method is the necessity for visual assessment of the CTG, with which great inter- and intra-observer variability are associated. Assessment of the CTG according to fixed guidelines with computer analysis may offer a solution. On-going training and discussion of the casuistics are and will remain important.

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BJOG 2009; 116: 545–551

3

Inter- and intra-observer agreement of intrapartum ST-analysis of the fetal electrocardiogram

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Abstract

Objective

The objective of this study was to quantify inter-and intra-observer agreement on classification of the intrapartum cardiotocogram (CTG) and decision to intervene following STAN® guidelines.

Methods

A prospective, observational study was performed within the Department of Obstetrics of a tertiary referral hospital. STAN® recordings of 73 women after 36 weeks of gestation with a high-risk pregnancy, induced or oxytocin-augmented labour, meconium-stained amniotic fluid or epidural analgesia were viewed by six observers. They decided if and when they would suggest an intervention. Proportions of specific agreement (Ps) and kappa values (K) were calculated. Main outcome measures were the agreement upon classification of the intrapartum CTG and decision to perform an intervention.

Results

Agreement for classification of a normal and a (pre)terminal CTG was good (Ps range 0.50–0.84), but poor for the intermediary and abnormal CTG (Ps range 0.34–0.56). Agreement on the decision to intervene was higher, especially on the decision to perform 'no intervention' (Ps range 0.76–0.94). Overall inter-observer agreement on the decision to intervene was considered moderate in five of six observer combinations according to the kappa (K range 0.42–0.73). Intra-observer agreement for CTG classification and decision to intervene was moderate (K range 0.52–0.67 and 0.61–0.75).

Conclusions

Inter-observer agreement on classification of the intrapartum CTG is poor, but addition of information regarding fetal electrocardiogram, especially in case of intermediary or abnormal CTG traces, results in a more standardised decision to intervene.

Introduction

Since the introduction of continuous fetal heart rate (FHR) monitoring in the 1960s, there has been a wide variation in interpretation of FHR patterns and therefore in clinical decision-making.[1] Although FHR monitoring, using the intrapartum cardiotocogram (CTG), did not live up to its original expectations, it is still the primary method to monitor fetal wellbeing during delivery and is widely used.[2] One of the major disadvantages of the intrapartum CTG is its low specificity, that is many false-positive test results for poor neonatal outcome. Additional techniques for fetal surveillance have been developed, notably fetal blood sampling (FBS).[3] For several reasons, however, FBS is not widely applied.[1,4–6] 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 metabolic acidosis of the fetus.[7,8]

The STAN® technology seems promising by reducing metabolic acidosis, incidence of FBS and operative deliveries.[2,9–12] But, as the intrapartum CTG is still part of the STAN® technology and variation in interpretation of this CTG is large,[13,14] guidelines for its classification are important. Over time, many guidelines have been introduced, of which the FIGO (International Federation of Obstetrics and Gynecology) guidelines for fetal monitoring have probably reached best consensus.[15,16] Current guidelines on STAN® methodology are based on these FIGO guidelines to guide labour ward staff to systematically assess and classify a FHR trace (Appendix A). In practice, however, also these STAN® guidelines have limitations, which mostly concern (variability in) interpretation of the CTG.[17,18]

Two studies have shown a better inter-observer agreement - with respect to the decision to intervene - for fetal monitoring using CTG plus ST-analysis of the fetal ECG in comparison with monitoring by CTG alone.[19,20] A study in the USA on STAN® usage showed high percentages agreement on intervention decisions.[21] Interestingly, no study has yet been performed that examined reproducibility or intra- and inter-observer agreement regarding assessment or classification of the intrapartum CTG, together with ST information of the fetal ECG, according to the STAN® clinical guidelines.

The aim of our study was to systematically quantify the inter- and intra-observer agreement upon classification of the intrapartum CTG and of the decision to perform an intervention following the clinical guidelines of the STAN® methodology (Appendix A). Furthermore, we studied the association between the level of experience with use of STAN® and the inter- and intra-observer agreement.

Methods

Patients

Seventy-five intrapartum STAN® recordings were selected from a large database of 637 women who were monitored using a STAN® S 21 fetal heart monitor (Neoventa Medical).[22] The selection consisted of 11 STAN® recordings of deliveries complicated by metabolic acidosis and 64 randomly chosen STAN® recordings. Metabolic acidosis cases were defined as a cord artery pH < 7.05 and base deficit in the extracellular fluid compartment (BDecf) > 12.0 mmol/l using the Siggaard-Andersen acid–base chart algorithm.[23]

The equipment and use of the STAN® method have been described elsewhere.[7–9] Women were eligible after 36 weeks of gestation and had high-risk pregnancies, induced or oxytocin augmented labour, meconium-stained amniotic fluid or epidural analgesia. Deliveries were managed by registrars or midwives under supervision of a gynaecologist. Two recordings were excluded because of technical problems and poor signal quality, leaving 73 STAN® recordings for analysis.

Observers

Six observers, divided into three categories according to their level of experience with intrapartum ST-analysis, were asked to participate in the study. Observer category A contained two 'expert' gynaecologists with at least 15 years of clinical experience in obstetrics and about 7 years experience with intrapartum ST-analysis (A1 and A2), which were considered the 'reference observers' in the inter-observer analyses. Observer category B contained two senior registrars with at least 3 years of clinical experience in obstetrics and at least half a year of experience with intrapartum ST-analysis (B1 and B2). Observer category C contained two junior registrars with at least 1-year of clinical experience in obstetrics and less than half a year of experience with intrapartum ST-analysis (C1 and C2).

All observers are medical doctors in a tertiary referral centre with 1800 deliveries per year and daily use of the STAN® method. They attended a standard user training at time of the introduction of the STAN® method or at the moment of their introduction in the hospital. They attended monthly case analysis meetings as standard part of the clinical STAN® training.

Before the start and during the period of this study, observers were not additionally trained.

Measurements

From each STAN® recording, the last 2 hours were selected. These 2-hour periods were subdivided into four parts of 30 minutes (t1–t4), printed on paper, using a paper speed of 2 cm/minute, and consecutively presented to the six observers.

In November 2006 (T0), all six observers were asked to score the following two outcomes for each 30-minute recording:

1. Classification of CTG: each subsequent 30 minutes of CTG tracings had to be classified as normal, intermediary, abnormal or (pre)terminal (categorical outcome)

according to the STAN® clinical guidelines as presented in Appendix A. If a 30-minute episode contained more than one CTG category, the observer was asked to classify the part with longest duration and/or to choose the worst category.

2. Decision to intervene: after classification of the CTG, observers were asked to interpret possible ST events and to decide whether (dichotomous outcome) they would perform an intervention and at what time that intervention should take place, according to STAN® clinical guidelines (Appendix A). In case observers decided to perform an intervention, they were also asked to indicate whether the intervention was based on the interpretation of the CTG combined with ST data or on CTG only. Observers were not asked to further specify their interventions.

In case an intervention was suggested before the end of the 2 hours recording, the following part of the tracing was not revealed to them anymore. Observers were only provided with information on stage of labour (dilatation or active pushing), without knowledge of other clinical parameters or neonatal outcome, and blinded to each others' results.
In January 2007 (T1), this entire procedure was repeated. The same 73 cases were presented to the six observers in random order to allow for quantification of the intra-observer agreement or reproducibility.

Data analysis

Observations at T0 and T1 by the same observer were used to quantify the intra-observer agreement or reproducibility, whereas the inter-observer reproducibility was quantified by first comparing the observations across the different observers both at T0 and at T1.
For the dichotomous outcome 'decision to intervene', we estimated the kappa statistics (K) to quantify inter- and intra-observer agreement. Kappa is a measure of reproducibility or agreement in which chance-expected agreement is incorporated.[24] Kappa values <0.40 were considered poor agreement, between 0.40 and 0.75 as moderate and >0.75 as excellent agreement.[24] For the outcome 'classification of CTG', a categorical variable with four categories, we used proportions of agreement or reproducibility. Inter-observer agreement of 'CTG proportions of agreement' is often calculated according to Grant.[25] We explicitly chose to calculate the so-called proportion of specific agreement (Ps) according to Fleiss[24] since the latter is a conditional probability, here the probability that an observer will make an assignment to a certain category conditional on the same categorisation of another randomly selected observer. The Ps was also calculated for the categorical outcome classification of CTG.

Results

Inter-observer agreement

CTG classification outcome

All observers successfully assessed the 73 recordings at T0 and T1. Table 1 shows percentages agreement on the four 30-minute CTG traces between observer A1 and A2 ('experts', considered as reference) at T0. The number of cases that could be classified decreased from 73 in t1 to 51 in t4 since decisions to perform an intervention before t4 excluded cases from analysis of the subsequent 30-minute episodes (Table 1). Similar results were found for the observers in the categories B (B1 and B2) and C (C1 and C2) as given in Figure 1. Figure 1 also shows the large variation in CTG classification between the six observers, which increased over the CTG traces from t1 to t4. The first episode (t1) predominantly showed a normal CTG class among all observers, whereas the last episode (t4) showed more intermediary and abnormal classes. Although this pattern applied to all six observers, the extent of the variation considerably differed between observers. The recordings at T1 showed similar results with the same pattern over the four time recordings (from t1 to t4), only slightly higher percentages of agreement (data not shown).

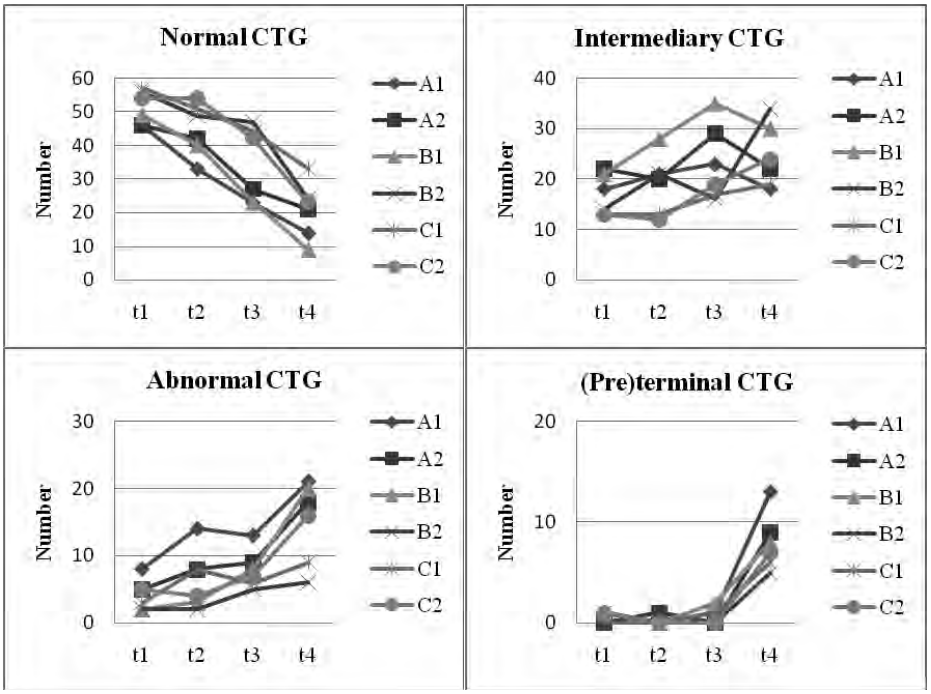
Table 1 Agreement on CTG classification for the 4 time intervals of the registration (t1-t4) for observers of category A (A1 versus A2), at T0

	Episodes t1 – t4			
CTG class	**t1** N=73	**t2** N=67	**t3** N=59	**t4** N=51
Normal CTG	40	29	18	11
Intermediary CTG	10	9	14	7
Abnormal CTG	2	6	4	10
(Pre)terminal CTG	NA	NA	NA	NA
Total agreement	52 71.2%	44 65.7%	36 61%	28 54.9%

NA: not applicable, no cases in which both observers decided to assign this class.
For details on the type of observer and time intervals see text

The left part of Table 2 shows that across all types of observers at T0, there was poor agreement for each CTG classification with the exception of the normal and (pre)terminal trace. For a normal CTG class, observers of category C agreed best (Ps 0.84). Between categories for all CTG classes, observers A1 and B1 agreed best (Table 2, right part, Ps 0.51–0.80). Agreement was again highest for the normal CTG class in which observer A1 had equal agreement with B1 and C1 (Ps 0.77–0.78), whereas observers B1 and C1 agreed less (Ps 0.70). Again, similar results (Ps values) were found when analysing the T1 observations.

Figure 1 Course of CTG classification throughout time by six observers at T0



For details see Observers section in text.

Table 2 Proportions of specific agreement (P*s*) on CTG classification for several inter-observer combinations at T0 (N=73)

	Inter-observer combinations for agreement on CTG classification					
	Within observer categories			**Between observer categories**		
Ps	**A1-A2**	**B1-B2**	**C1-C2**	**A1-B1**	**A1-C1**	**B1-C1**
Normal CTG	0.79	0.71	0.84	0.78	0.77	0.70
Intermediary CTG	0.49	0.45	0.49	0.56	0.41	0.41
Abnormal CTG	0.52	0.38	0.42	0.51	0.37	0.34
(Pre)terminal CTG	NA	0.67	NA	0.80	0.67	0.50

NA: not applicable, no cases in which both observers decided to assign this class
For details on the type of observers see Observers section in text.

Decision to intervene outcome

At T0 in 43 of the 73 cases (59%), at least one observer decided to perform an intervention. In 25.6% (11/43) of cases, observers decided to intervene on the CTG alone: in 9 of these 11 cases, this decision was made by one or two observers and in the remaining 2 cases by five or six observers. In the other 74.4% (32/43) of the cases, at least one observer decided to intervene based on ST information.

According to the proportions of agreement, the inter-observer agreement to perform 'no intervention' was highest (Table 3), although the Ps for 'intervention' was also high, except for B1-B2 (only 0.50). At T1, similar results were found, except that the Ps for intervention for B1-B2 was 0.75 instead of 0.50. Overall agreement on the decision to intervene was considered moderate in five of six observer combinations according to the kappa (K range 0.42–0.73) (Table 3). Within categories (left side of Table 3), observers of category C (C1-C2) had excellent agreement (K = 0.81), which was also shown by highest proportions of specific agreement (Ps 0.94 for no intervention and 0.86 for intervention). At T1, agreement for observer pair C1-C2 was somewhat lower (K = 0.68), but they still showed highest proportions of specific agreement (Ps 0.92 for no intervention and 0.76 for intervention). Between different observer categories (right side of Table 3), observers of category A and B appeared to agree best (K = 0.73), which was also indicated by the high proportions of specific agreement (Ps 0.86–0.87). At T1, again the agreement between different categories of observers was similar except that the agreement for observer pair A1-C1 had a kappa of 0.36 instead of 0.49 at T0.

Table 3 Kappa values (K) and proportions of specific agreement (P*s*) on decision to intervene for several inter-observer combinations at T0 (N=73)

	Inter-observer combinations for agreement on decision to intervene N=73					
	Within observer categories			**Between observer categories**		
K or P*s*	**A1-A2**	**B1-B2**	**C1-C2**	**A1-B1**	**A1-C1**	**B1-C1**
K	0.67	0.42	0.81	0.73	0.49	0.50
P*s* no intervention	0.86	0.76	0.94	0.87	0.80	0.80
P*s* intervention	0.80	0.50	0.86	0.86	0.68	0.69

For details on the type of observers see Observer section in text.

Regarding the timing of intervention, there was complete agreement between the six observers in 15 of 43 cases (34.9%). In 11 cases (25.6%), there was agreement within a time frame of 30–60 minutes. In ten cases (23.3%), there was agreement in a time frame of 60–90 minutes (n = 8) or 90–120 minutes (n = 2). In the remaining seven cases (16.2%), only one observer decided to intervene. In 10 of the 11 metabolic acidosis cases, an intervention was suggested by at least one observer (Table 4). In six of these, the timing to intervene did not

differ more than 30 minutes between the six observers, and in three cases, this range was 60 minutes. In one case (number 19), only one observer (B1) decided to perform an intervention, and in the remaining one (number 57), no intervention was decided upon at all. Only in two cases (numbers 10 and 68), all observers decided to intervene for the same reason.

Table 4 Timing of decision to intervene in cases of metabolic acidosis at T0 (pH<7.05 and BD>12; N=11)

	Timing of decision to intervene according to observers A1-C2					
Case	**A1**	**A2**	**B1**	**B2**	**C1**	**C2**
10	S - 4	S - 4	S - 4	S - 4	S - 4	S - 4
19	N	N	S - 4	N	N	N
20	C - 3	S - 4	S - 4	N	C – 3	N
25	S - 1	S - 3	S - 3	N	N	N
34	S - 4	S - 4	S - 4	S - 4	N	S – 4
41	C - 2	S - 4	S - 4	N	S – 4	S – 4
51	N	N	C - 3	N	S – 4	C – 4
57	N	N	N	N	N	N
68	C - 1	C - 2	C - 1	C - 1	C – 2	C – 1
69	C - 2	S - 4	C - 3	C - 2	C – 3	C – 3
70	S - 3	C - 4	C - 3	S - 3	S – 4	S – 3

C, intervention according to CTG; N, no intervention; S, intervention according to CTG+ST
1,2,3,4 = first, second, third and fourth part of registration

Intra-observer agreement

Table 5 shows the results of the intra-observer agreement. Kappa statistics indicate higher agreement compared with inter-observer agreement results. Observer B1 has the highest agreement when comparing T0 and T1. Overall, the intra-observer agreement for classification of the CTG and decision to intervene was moderate.

Table 5 Intra-observer agreement on CTG classification and decision to intervene for T0 and T1, expressed by Kappa values

	A1	**A2**	**B1**	**B2**	**C1**	**C2**
CTG classification	0.64	0.59	0.67	0.52	0.62	0.54
Decision to intervene	0.72	0.68	0.75	0.61	0.62	0.64

Discussion

We have shown that there is large variation in classification of the intrapartum CTG, even when FIGO guidelines are used. Inter-observer agreement for the normal CTG was good but

decreased when the CTG became intermediary or abnormal. (Pre)terminal traces again showed a moderate to good inter-observer agreement. The slightly higher percentages of inter-observer agreement at T1 (compared with T0) may be explained by a small learning effect of reading and classifying CTG traces.

For the normal CTG, observers with little (category C) and much (category A) STAN® experience agreed better than observers with half a year of experience (category B). This might be due to the fact that training of 'beginners' is still fresh and they therefore follow the guidelines more strictly than other observers. Experts may agree better because of their larger experience. For all CTG classes, agreement between 'experts' and observers with at least half a year of experience with ST-analysis (A1-B1) appeared to be best.

The observers agreed better on the decision to intervene than on the CTG classification, especially on the decision to perform no intervention. Observers with less than half a year of experience with ST-analysis ('beginners') agreed best. However, their agreement with more experienced observers was poor to moderate. This may indicate that although 'beginners' agree well with each other, their judgement concerning decision to intervene seems to be different and perhaps wrong compared with more experienced observers, assuming the latter to make more often the correct decision ('reference').

In our study, we found excellent agreement for 'beginner' observers at T0, whereas at T1 for this group agreement was considered moderate. Perhaps, their excellent agreement at T0 was accidentally achieved, also due to relatively small numbers.

In the STAN® methodology, the decision to intervene or otherwise depends on both CTG interpretation and interpretation of ST events. Our study indicates that the efficacy of this method of fetal surveillance, although proven to be promising,[9,12] seems hampered by a poor to moderate agreement for CTG interpretation. It was reassuring that agreement on normal and (pre)terminal CTG traces was relatively good since with such heart rate patterns additional information on ECG waveforms is not required. Although agreement for CTG interpretation was moderate, the observers agreed quite well on the timing of an intervention, which in the end is the most important decision in daily clinical practice. Possibly, the availability of ST information and use of STAN® guidelines result in a more standardised assessment of the CTG and the total clinical situation, which may eventually result in better agreement on decision to intervene.

There are some possible limitations of this study that have to be discussed. The first may seem the relatively low number of abnormal and (pre)terminal CTG traces in the selected women. We, however, explicitly decided not to overrepresent such traces to ensure that observers were not exposed to abnormal CTGs only and that they paid full attention to the whole spectrum of CTG tracings. For fetal surveillance, agreement on both normal and abnormal CTG assessments is important: disagreement on abnormal CTGs may result in infants being damaged by hypoxia and disagreement on normal CTGs may cause unnecessary interventions. It is therefore necessary to consider agreement for abnormal and normal CTG assessments separately.

Second, since this study concerns classification of CTG traces, it is possible that some observer bias has played a role because a 30-minute CTG trace may both show intermediary and abnormal parts. Although in advance, observers were asked to classify such traces in the worst category, this still may have increased inter-observer variability.
Third, for simplicity, we choose to present data on 'between category' agreement for CTG classification and decision to intervene only for the first observer combinations A1-B1, A1-C1 and B1-C1. Agreement for observer pairs A2-B2, A2-C2 and B2-C2 was similar.
Finally, a drawback of this study may be the use of paper printouts for CTG assessment, which may create a situation without optimal mimicry of clinical practice.
In conclusion, we found a large variation in classification of the intrapartum CTG, despite the use of FIGO guidelines and availability of ST information. Agreement for the normal and (pre)terminal CTG trace was good but decreased when CTG traces were intermediary or abnormal. Agreement was better on the decision to intervene, especially on the decision not to intervene and on the timing of the intervention. This suggests that addition of information regarding fetal ECG, especially in case of intermediary or abnormal CTG traces, results in a more standardised decision to intervene or otherwise.

Acknowledgements

This research was supported by a grant from ZonMW, the Dutch Organisation for Health Research and Development (grant number: 945-06-557).

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4

Limitations of ST-analysis of the fetal electrocardiogram in clinical practice

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Abstract

Objective

To examine detailed intrapartum events in cases of neonatal metabolic acidosis despite monitoring using STAN (cardiotocography (CTG) plus ST waveform analysis of fetal electrocardiogram (ECG)).

Methods

In high-risk pregnancies monitored by STAN® a retrospective case note review was performed in newborns with metabolic acidosis where no significant ST changes in the fetal ECG occurred prior to birth.

Results

Detailed review of three cases identified poor signal quality, difficulties in CTG interpretation, failure to comply with STAN® clinical guidelines and deterioration of the CTG without ECG alert as the leading causes of these adverse outcomes.

Conclusions

The cases illustrate some of the pitfalls associated with the clinical application of the STAN® technology which prevent severe metabolic acidosis being eradicated completely. It may be useful to expand the STAN® guidelines protocol towards the identification of exceptional clinical situations, such as in our cases, and towards appropriate additional interventions, as this may lead to a further reduction in adverse neonatal outcomes.

Introduction

It has been reported that a combination of cardiotocography (CTG) and ST waveform analysis of the fetal electrocardiogram (ECG) during labour provides information on the fetal response to hypoxia.[1-3] This observation resulted in the development of a CTG plus ST waveform analyser (STAN®; Neoventa Medical, Göteborg, Sweden).[4] Two large randomised clinical trials comparing CTG versus CTG and ST-analysis showed a significantly lower rate of metabolic acidosis at birth and fewer operative deliveries for fetal distress when CTG and ST-analysis were used.[5,6] This finding could not be reproduced in a recent, small randomised clinical trial.[7]

The most important issue in intrapartum fetal monitoring concerns false-negative test results, leading to the birth of an infant with severe metabolic acidosis. Even with use of the recently introduced STAN® technique, such cases may still occur. This relatively new method of intrapartum fetal monitoring has some limitations in clinical practice, which need to be addressed to prevent future adverse events.

To this end, we report three cases from three different hospitals in which newborns with evident metabolic acidosis were born without significant ST changes in the fetal ECG, and we discuss some of the possible pathophysiological explanations for these apparent false-negative recordings. More importantly, we discuss some of the pitfalls associated with the clinical application of the STAN® technology in these cases.

Case reports

Case 1

A 36-year-old para 0 had an uncomplicated pregnancy until 41 completed weeks of gestation, when she was referred to hospital because of rupture of membranes of duration more than 24 hours and maternal fever.

Observations during labour

The recording was started at 19:00 hours and showed a base-line fetal tachycardia (170–180 beats per minute [bpm]), which was thought to be related to maternal pyrexia (39.2C; treated with antibiotics intravenously). There were signs of reactivity with accelerations present and stable T/QRS ratios (Figure 1A). At 21:30 hours, pethidine was given, and there-after, no accelerations were noted and heart rate variability became reduced (Figure 1B). Fetal blood sampling (FBS) at 22:15 hours showed a pH of 7.29. An oxytocin infusion was started.

At 02:00 hours (8–9 cm dilatation), uniform and late decelerations and reduced variability were noted with frequent contractions (Figure 1C). This pattern continued until full dilatation at 03:55 hours (Figure 1D). There were no ST events. With the onset of active pushing at 04:25 hours, a further reduction in heart rate variability was noted (Figure 1E). At 05:00 hours, a second FBS was obtained with pH 6.78, and an outlet vacuum extraction was performed at 05:30 hours. ST-analysis showed adequate signal quality until the end of the first stage, with only intermittent ST information thereafter.

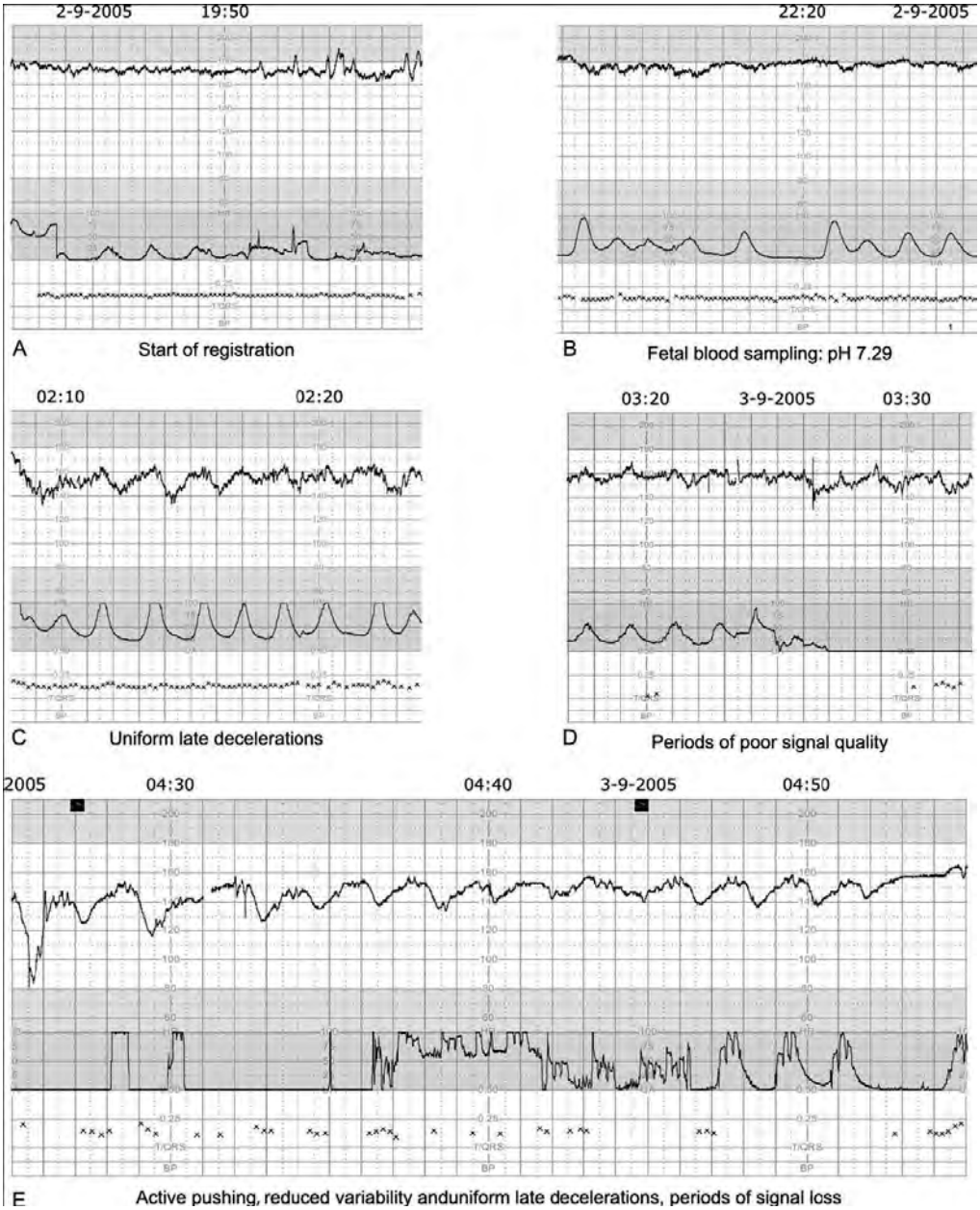
Neonatal outcome

At 5:30 hours, a boy weighing 4700 g was born. Apgar scores were 1, 4 and 7 at 1, 5 and 10 minutes, respectively.

Umbilical cord acid–base values were as follows: arterial pH (pHa) 6.78, PaCO2 90, extracellular fluid base deficit (BDecf) 22.1 mmol/l and venous pH (pHv) 6.84, PaCO2 70, BDecf 22.3 mmol/l.

The baby received active resuscitation and respiratory support, with dopamine and antibiotics added to manage group B streptococcus (GBS) infection that was confirmed by blood cultures, placental histopathology (marked chorioamnionitis and umbilical funiculitis) and elevation in C-reactive protein of 121 mg/l. Neonatal seizures were noted on the second day. Ultrasound and magnetic resonance imaging (MRI) examination of the brain showed no abnormalities. After 1 week, the newborn was discharged home in good clinical condition.

Figure 1 STAN® registration case 1. Paper speed 1 cm/minute.



Case 2

A 24-year-old para 0 woman had an uncomplicated pregnancy until 40 weeks of gestation. Labour was induced because of oligohydramnios and reduced fetal movements.

Observations during labour

Dinoprostin was administered intravaginally for cervical ripening. The CTG was normal. The next morning, the membranes were ruptured artificially and oxytocin augmentation was started.

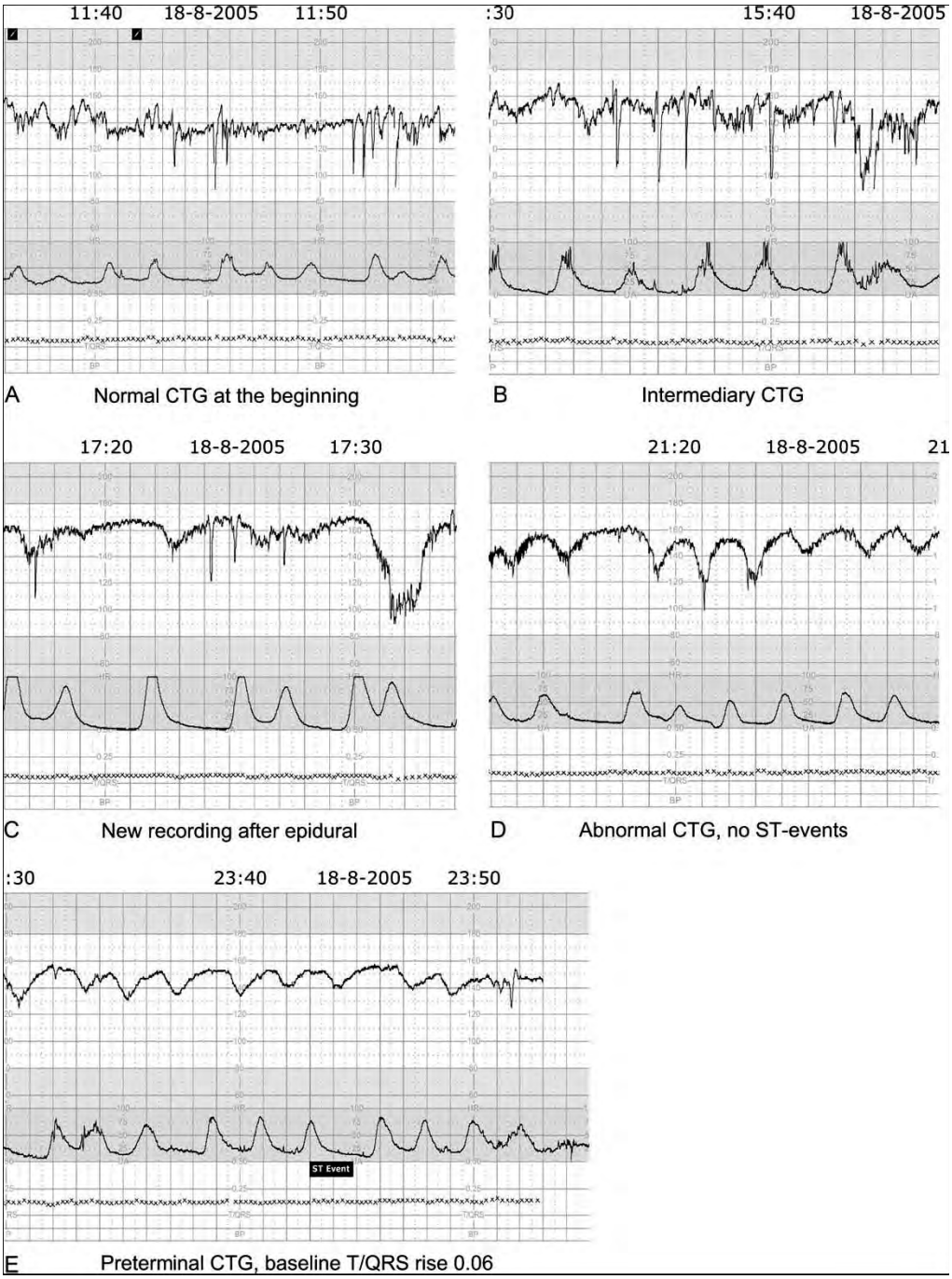
STAN® recording was started at 11:00 hours with a normal CTG and good signal quality of the fetal ECG (Figure 2A). Oxytocin infusion was started, and pethidine was administered for pain relief. At 16:00 hours, the STAN® registration was stopped because of transport of the woman to the operation theatre for administration of epidural analgesia. At that time, the CTG trace was abnormal, showing uniform late decelerations (Figure 2B). At 17:15 hours, the woman returned to the labour room, and a new STAN® registration was started with good signal quality and an abnormal CTG trace, comparable to that before epidural administration (Figure 2C). At 22:00 hours (8 cm dilatation), treatment with intravenous antibiotics was started because of maternal pyrexia. The CTG then slowly changed to a (pre)terminal trace at 22:50 hours (Figure 2D). At 23:28 hours, the epidural was stopped (full dilatation) and the CTG showed a (pre)terminal trace with a tachycardia of 160 bpm, no variability, no accelerations and uniform late decelerations (Figure 2D). At 23:44 hours, a significant ST event (baseline T/QRS rise of 0.06) was noticed and a vacuum extraction was performed (Figure 2E).

Neonatal outcome

At 23:56 hours, a girl weighing 3240 g was born, with Apgar scores of 0, 0 and 0 after 1, 5 and 10 minutes, respectively. Umbilical cord acid–base values were as follows: pHa 6.79, extracellular fluid base deficit (BDecf) 22 mmol/l.

After 18 minutes of active resuscitation, breathing and spontaneous heart activity were established. The girl was intubated, and seizures were noted. She was transported to a tertiary referral centre and admitted to the neonatal intensive care unit (NICU). The newborn suffered serious hypotensive periods. During the first 12 hours, the metabolic acidosis was treated with suppletion of sodium bicarbonate. Hypertrophic cardiomyopathy of unknown cause was diagnosed. Neurological examination showed severe hypoxic ischaemic encephalopathy, with symptoms of seizures requiring treatment with two different anticonvulsive drugs. After 2 weeks, the newborn was discharged in a moderately good clinical condition, but at 8 months, she had cerebral palsy. There were no remaining signs of a cardiomyopathy.

Figure 2 STAN® registration case 2. Paper speed 1 cm/minute.



Case 3

A 29-year-old para 0 with type I diabetes had an uncomplicated pregnancy and adequate blood glucose control. At 37 + 4 weeks, she went into spontaneous labour.

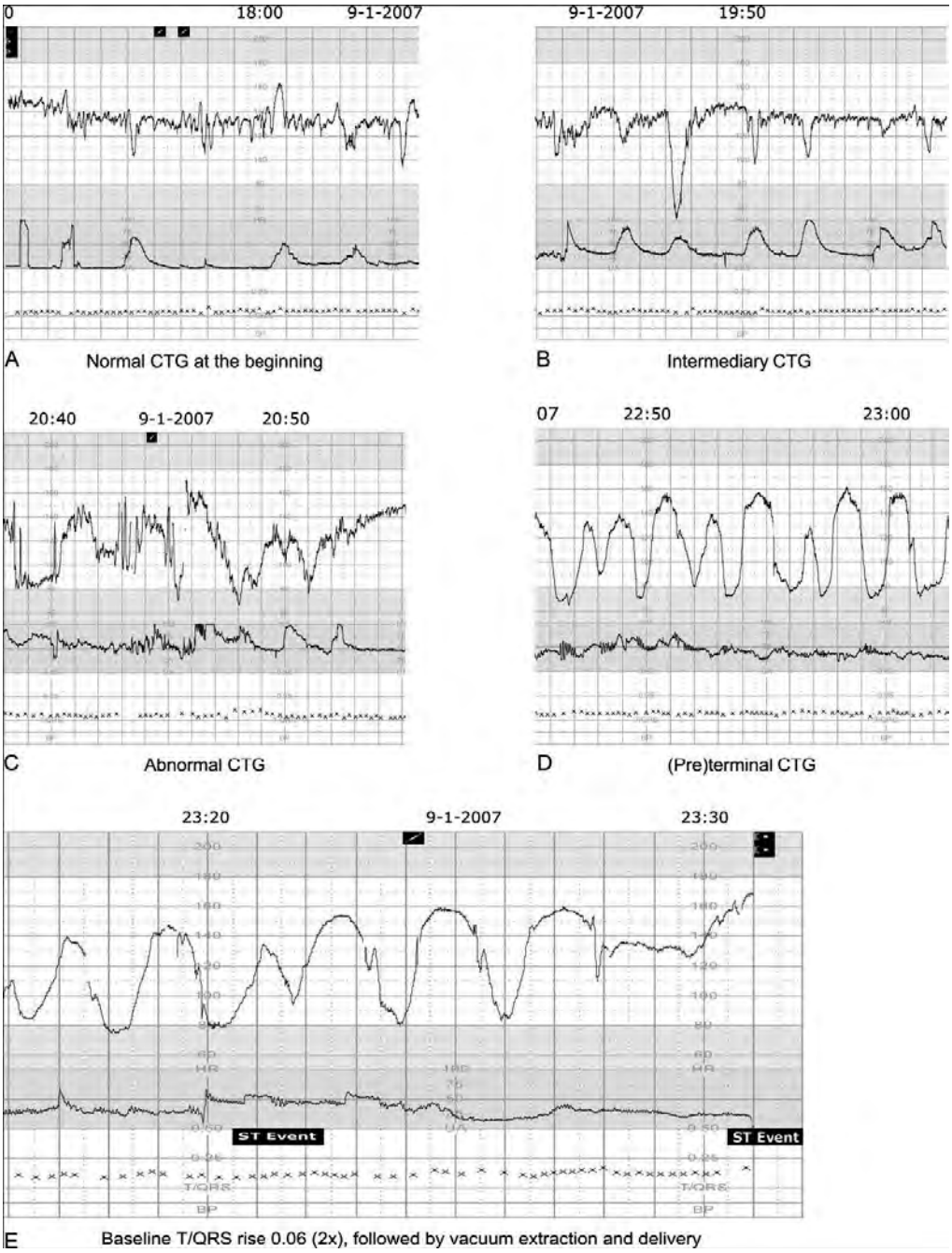
Observations during labour

STAN® recording started at 17:50 hours, with a normal CTG trace and good signal quality of the fetal ECG (Figure 3A). Oxytocin augmentation was started. At 20:00 hours (5–6 cm dilatation), the CTG trace was intermediary, showing uncomplicated variable decelerations >60 bpm. The T/QRS ratio of the fetal ECG was stable (Figure 3B). At 22:00 hours, the CTG became abnormal with complicated variable decelerations (Figure 3C). At 22:40 hours (full dilatation), the CTG trace became (pre)terminal with deep complicated decelerations and severely reduced heart rate variability. The signal quality of the fetal ECG was good, and there were no ST events (Figure 3D). At 23:09 hours, the woman had an absence or insult for about 1 minute, perhaps as a result of hyperventilation. Blood glucose values were normal. At 23:22 and 23:32 hours, there were two ST events, both with a T/QRS baseline rise of 0.06 (Figure 3E). Immediately, a vacuum extraction was performed.

Neonatal outcome

At 23:52 hours, after five vacuum tractions and shoulder dystocia, a girl weighing 3700 g was born with nuchal cord. Apgar scores were 3 and 5 after 1 and 5 minutes, respectively. Umbilical cord acid-base values were as follows: pHa 6.95, PaCO2 60, BDecf –15 mmol/l, pHv 7.00. Because of peripartal asphyxia, the newborn was admitted to the NICU. Metabolic acidosis disappeared within 1 hour after delivery, as confirmed by blood gas analysis. There was a unilateral fracture of the clavicle, likely caused by the rotation manoeuvre for shoulder dystocia, and a small subarachnoidal haemorrhage from a skull fracture at the base of the suction cup. The newborn suffered from seizures and vomiting and was treated with phenobarbital. Further neonatal evolution was normal. Fifteen days after delivery, the neurological condition had improved, and the child was discharged in good clinical condition. A paediatric check-up 3 months after delivery showed a normal clinical and neurological evolution. An MRI scan showed no abnormalities apart from remnants of the subarachnoidal bleeding.

Figure 3 STAN® registration case 3. Paper speed 1 cm/minute.



Discussion

The aim of intrapartum monitoring is to identify the fetus at risk for hypoxia and acidosis in a timely fashion, which may lead to interventions towards the prevention of neonatal and long-term morbidity. Since its introduction in the 1970s, CTG has become the standard method for intrapartum fetal monitoring.[8,9] In the presence of CTG abnormalities, FBS is recommended to identify the acidotic fetus.[10–12] Recently, STAN® technology has been introduced, which offers additional information regarding fetal oxygenation through fetal ECG analysis, thereby reducing the need for FBS.[7] However, some limitations in clinical applications of STAN® technology have already been reported. In a Swedish randomised trial, 16 of 41 cases with cord artery metabolic acidosis at birth (pH < 7.05 and BDecf > 12.0 mmol/l) had no ST events signalled by the event log.[13] In a Dutch observational study, 7 of 18 neonates with a metabolic acidosis were not identified by ST changes. These were all neonates with a pHa between 7.00 and 7.04. All five neonates with arterial blood pH below 7.00 had been identified by significant ST events 18–31 minutes before birth.[14] In both studies, all infants with metabolic acidosis not identified by ST changes had a favourable outcome.[13,14]

Here we report three cases in which the limitations of the clinical application of ST-analysis were demonstrated, as a result of which severely acidotic infants (pHa < 7.00) were born with severe neonatal morbidity. The most important limitation of ST-analysis is deviation from STAN® clinical guidelines by labour ward personnel rather than a fault in the technology. However, lack of definition of poor signal quality and absence of clear STAN® guidelines in the case of a CTG trace changing from normal to abnormal, without ST events, were also found to be limitations. Moreover, STAN® training material (CD-ROM, brochures and website) showing severely abnormal CTG traces in the absence of ST events and favourable infant outcomes may have misled clinicians.

For each case, possible pathophysiological mechanisms will be discussed to try and explain why the cases did not follow the expected norm of ST events in connection with CTG abnormalities. Furthermore, aspects of deviation from and shortcomings of STAN® clinical guidelines will be discussed. The reported cases represent 3 of approximately 2600 STAN registrations made in our three hospitals.

In the first case, the final part of the registration showed poor signal quality. Hence, STAN® might have missed T/QRS rises or biphasic ST segments. Poor signal quality was reported in 4.6% of cases in the Swedish randomised trial,[5,13] 7.9% of cases in the Dervaitis study,[15] 1.3% of cases in the Plymouth randomised controlled trial6 and 10% of cases in the Dutch observational study.[14] Unfortunately, there are no clear guidelines as to what signal quality or duration of signal loss is acceptable, especially when an abnormal CTG is present. Our case illustrates the need for clear management guidelines when poor ECG signal quality is observed.

This case also illustrates findings in association with the development of marked intrauterine GBS infection. Maternal pyrexia causes fetal heart rate and metabolism to increase and

consequently leads to a need for more oxygen.[16] It is possible that intrauterine infection interferes with the STAN®-recorded ECG signals. However, in reported studies,
there are no indications that STAN® is unreliable in the case of maternal fever or chorioamnionitis. The relationship between intrauterine and fetal infection and use of ST-analysis may need further investigation.

The most significant finding in this case was the progressive reduction in variability, with the CTG pattern becoming (pre)terminal. To what extent ST-analysis provides additional information in such a situation is unclear but is likely to be related to the extent to which the myocardium is being affected. An interesting issue is the extent to which sepsis or hypoxia was the primary cause of the events. Although there was marked acidosis, such acidosis could be caused by inadequate peripheral blood flow not affecting the central organs.[17] The lack of MRI abnormalities would also support sepsis as the primary cause and not hypoxia per se. Finally, a (pre)terminal CTG trace started 65 minutes before delivery and 35 minutes before FBS was performed. As such, the STAN® guidelines were not followed because they indicate immediate delivery in the case of a (pre)terminal CTG. This case illustrates the difficulty of classification of the CTG, especially the assessment of fetal reactivity, which should be carried out continuously. This seems to be the most problematic issue clinically.

In the second case, STAN® signal quality was good. Furthermore, as the registration started with a normal CTG, we assume that the ST-analysis started with a normal T/QRS baseline ratio. Unfortunately, the STAN® registration was stopped during the administration of epidural anaesthesia. When STAN® registration is stopped, all ST information is closed, including the T/QRS baseline ratio needed to analyse T/QRS rises or biphasic ST segments in the case of developing hypoxia. When a new registration is started, STAN® has to recalculate the T/QRS baseline, which may be different from before. In this case, the CTG was abnormal when STAN® was restarted, in contrast to the normal CTG in the first registration. It is possible that the T/QRS baseline at the beginning of the second part of the registration differed from that in the first part, thereby obscuring a rise in T/QRS ratio. To prevent problems of missing ST information, it is recommended that the ‘pause’ function on the STAN® monitor be used. If this function is used, a woman can be disconnected for 2 hours without losing any ST information.

The CTG trace presented in Figure 2B may be indicative of uniform late decelerations. Therefore, the recording was disconnected in the presence of an abnormal CTG trace. In this case, a possible significant ECG alert may have been missed during the placement of the epidural. From the presented observations, it is unclear whether or not relevant information was missed during monitor disconnection, but the traces for case 2 illustrate once more the difficulties encountered in CTG interpretation, even when international Federation of Obstetrics and Gynecology (FIGO) criteria are used.

An important finding in this case is neonatal and probably also fetal cardiac hypertrophy. This observation indicates a fetal heart unable to react fully to the stress of labour. The pattern illustrated in this case is that of progressive loss of fetal heart rate variability, with a

(pre)terminal CTG pattern persisting for at least 1 hour before birth, which should have been acted upon at an earlier stage. The slow fetal ST response in connection with the developing asphyxia and metabolic acidosis does not follow the common pattern of reaction and may be associated with the blunted ability of a dysfunctional myocardium to respond.

In the third case, registration started with a normal CTG pattern, signal quality was good and registration was not interrupted. This trace showed an abnormal pattern 80 minutes before the first ST event (and 110 minutes before delivery), with a (pre)terminal pattern 42 minutes before this event and 72 minutes before delivery. This case therefore shows, or at least suggests, that a CTG can slowly change from abnormal to (pre)terminal, without significant ECG alerts. This contradiction illustrates that the search for more measures should continue for the assessment of intrapartum fetal heart rate variability in relation to developing acidosis.[18,19]

Perhaps the most important lesson from this case is that one should continue to assess the CTG rather than relying solely on ST events arising. In this case, the transition from abnormal to (pre)terminal CTG should have prompted either delivery or FBS, irrespective of ST waveform. In the Swedish randomised trial, a (pre)terminal CTG (defined as absent variability) was an indication for intervention regardless of ST waveform, as was an abnormal CTG persisting for 60 minutes.[5] However, this advice is not included in the STAN® guidelines.[16] These guidelines should therefore be adjusted and should include clear recommendations on situations in which (missing) ECG alerts are to be ignored and decisions are to be made on clinical and/or CTG information only.

An important finding in this case was the occurrence of sudden maternal hyperventilation. Hyperventilation may cause maternal respiratory alkalosis, which has been associated with fetal distress and adverse perinatal outcome.[20] Acute hyperventilation causes alterations in ionised calcium, and hypocalcaemia has been reported in association with loss of fetal beat-to-beat variability on CTG and a prolonged QT interval on ECG.[21,22] In this case, the QT interval was markedly increased in connection with loss of beat-to-beat variability of the CTG, but this can only be observed on the raw ECG signal and was not indicated by a warning from the STAN® monitor. This situation may warrant further investigation in efforts to improve the STAN® technology.

Finally, another important limitation of the STAN® clinical guidelines is the narrow time window of only 20 minutes to deliver in the case of a significant ST event. As is illustrated in our third case, this short time interval may not be long enough to effect delivery before the onset of metabolic acidosis, which obviously depends on how obstetric care is organised locally.

The STAN® technique is a relatively new device for intrapartum fetal monitoring, and randomised clinical trials have shown promising results towards the reduction of neonatal metabolic acidosis and operative interventions. The cases presented in this report illustrate some of the limitations of this methodology in the prevention of peripartum metabolic acidosis. Poor signal quality, difficulties in correct interpretation of CTG signals and in compliance with the STAN® clinical guidelines and our, as yet, incomplete knowledge of

intrapartum fetal pathophysiology may still result in unexpected unfavourable outcomes. We recommend that the STAN® clinical guidelines should include more detailed instructions regarding the correct identification of 'difficult cases' and suggest adequate interventions.

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BMC Pregnancy Childbirth 2007; 26: 7-13

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A randomised clinical trial on cardiotocography plus fetal blood sampling versus cardiotocography plus ST-analysis of the fetal electrocardiogram for intrapartum monitoring: study protocol

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Abstract

Background

Cardiotocography (CTG) is worldwide the method for fetal surveillance during labour. However, CTG alone shows many false positive test results and without fetal blood sampling (FBS), it results in an increase in operative deliveries without improvement of fetal outcome. FBS requires additional expertise, is invasive and has often to be repeated during labour. Two clinical trials have shown that a combination of CTG and ST-analysis of the fetal electrocardiogram (ECG) reduces the rates of metabolic acidosis and instrumental delivery. However, in both trials FBS was still performed in the ST-analysis arm, and it is therefore still unknown if the observed results were indeed due to the ST-analysis or to the use of FBS in combination with ST-analysis.

Methods

We aim to evaluate the effectiveness of non-invasive monitoring (CTG + ST-analysis) as compared to normal care (CTG + FBS), in a multicentre randomised clinical trial setting. Secondary aims are: 1) to judge whether ST-analysis of fetal electrocardiogram can significantly decrease frequency of performance of FBS or even replace it; 2) perform a coST-analysis to establish the economic impact of the two treatment options.

Women in labour with a gestational age ≥ 36 weeks and an indication for CTG- monitoring can be included in the trial. Eligible women will be randomised for fetal surveillance with CTG and, if necessary, FBS or CTG combined with ST-analysis of the fetal ECG.

The primary outcome of the study is the incidence of serious metabolic acidosis (defined as pH < 7.05 and BDecf > 12 mmol/L in the umbilical cord artery). Secondary outcome measures are: instrumental delivery, neonatal outcome (Apgar score, admission to a neonatal ward), incidence of performance of FBS in both arms and cost-effectiveness of both monitoring strategies across hospitals. The analysis will follow the intention to treat principle. The incidence of metabolic acidosis will be compared across both groups. Assuming a reduction of metabolic acidosis from 3.5% to 2.1 %, using a two-sided test with an alpha of 0.05 and a power of 0.80, in favour of CTG plus ST-analysis, about 5100 women have to be randomised. Furthermore, the cost-effectiveness of CTG and ST-analysis as compared to CTG and FBS will be studied.

Discussion

This study will provide data about the use of intrapartum ST-analysis with a strict protocol for performance of FBS to limit its incidence. We aim to clarify to what extent intrapartum ST-analysis can be used without the performance of FBS and in which cases FBS is still needed.

Trial Registration Number

ISRCTN95732366

Background

The aim of intrapartum fetal monitoring is to identify fetuses at risk for neonatal and long-term injury due to asphyxia. Although cardiotocography (CTG) is applied on a large scale, this technique is still subject to debate.[1-3] Long-term follow-up studies on intrapartum fetal heart rate monitoring have shown no or little benefit on neonatal outcome and a significant increase in operative deliveries.[4-6] Fetal blood sampling (FBS) can be used in addition to CTG, but requires expertise, is invasive, has to be repeated when CTG abnormalities persist and may cause complications.[7,8] As a consequence, it is not widely applied.[9] In The Netherlands, FBS is available in only 50 % to 70 % of the hospitals.

Because changes in the ST-segment of the electrocardiogram (ECG) are related to metabolic acidosis of the fetus, detection of changes in this part of the fetal ECG, in combination with CTG, is a non-invasive and promising alternative for FBS.[10,11] A recent study in more than 600 women showed that ST-changes were present in all cases with severe metabolic acidosis and that CTG plus ST-analysis was more specific in detecting fetal acidemia than CTG alone.[12]

Two large randomised trials comparing CTG and ST-analysis of the fetal ECG showed a decrease in metabolic acidosis and interventions for fetal distress in favour of the CTG plus ECG-group.[13,14] The rate of infants with encephalopathy was also significantly lower in the CTG plus ECG-group.[15] However, in both trials FBS was still frequently performed in both arms. Hence, it remains difficult to conclude if the observed improved outcome was indeed due to management to address metabolic acidosis based on ST-analysis results or on FBS results.

Just before the initiation of the present study a third and much smaller randomised trial on ST-analysis versus conventional CTG appeared. This study showed, although not significant, an opposite effect on the incidence of neonatal acidemia or metabolic acidosis, compared to previous trials.[16] The caesarean section and vacuum outlet rate was comparable in both groups. The only significant difference was the incidence of FBS, which was much lower in the ST-analysis group (7.0%) than in the CTG group (15.6%). The results of this trial further stress the need for subsequent research.

In this paper we describe the study protocol of a recently started randomised trial to compare the cost-effectiveness between conventional CTG versus ST-analysis of the
fetal ECG, in which the use of fetal blood sampling in the ST-analysis group was a priori restricted to well-defined situations.

Rationale for ST-analysis (STAN®)

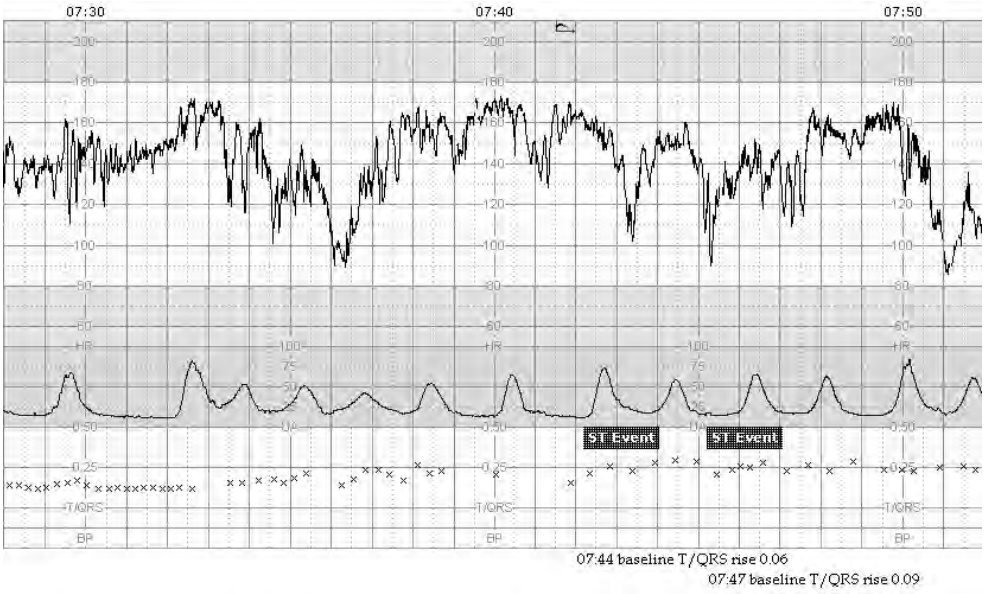
In adult cardiology, ST-analysis of ECG is performed to assess and diagnose myocardial insufficiency. The STAN® concept is similarly based on the association between the ST-interval of fetal ECG and the function of the fetal myocardium during stress. The fetal heart and brain are equally sensitive to oxygen deficiency. As a result, the information relating to

the function of the fetal myocardium provides an indirect measurement of the condition of the fetal brain during labour.

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 (Figure 1). An increase in T-wave and subsequently in T/QRS-ratio has been associated with a catecholamine surge, activation of β-adrenoreceptors, myocardial glycogenolysis, and metabolic acidosis.[10,11,17] 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 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.[10,11,17]

The integrated CTG and fetal ECG monitor, i.e. the so-called STAN®-monitor, is a device that automatically analyses the fetal ECG through a scalp electrode applied to the fetal head.[18] STAN® guidelines are based on an integrated CTG and fetal ECG interpretation. According to the STAN® guidelines ST-changes are only thought to be of clinical relevance if they coincide with intermediate or abnormal CTG traces (Appendix A). In case of a normal or (pre)terminal CTG, the high sensitivity of the CTG only, is considered sufficient to ignore abnormalities in the ECG.

Figure 1 Example of a STAN®-registration with an abnormal CTG and two significant ST-events (1 cm/minute)



In spite of the above-mentioned evidence on the potential improvement in fetal surveillance using intrapartum ST-analysis,[12-14] there is at present still a dilemma for gynaecologists on its true clinical value (i.e. without the use of FBS), let alone that its cost-effectiveness is known. ST-analysis requires financial investment, not only related to the procure of the ST-monitor (34000 Euro per monitor), but also related to the necessity of repeated training of labour ward personnel.[19]
Our randomised trial aims to quantify this cost-effectiveness of fetal monitoring with CTG plus ST-analysis of the fetal ECG, as compared to conventional CTG plus FBS.

Methods

Aims

The primary aim of our randomised trial is to quantify whether the incidence of metabolic acidosis is decreased by the use of a strategy of fetal monitoring with CTG plus ST-analysis of the fetal ECG, compared to usual care consisting of CTG plus FBS, when indicated.
Secondary aims are to quantify the cost-effectiveness of CTG in combination with non-invasive ST-analysis of the fetal ECG for fetal monitoring during labour as compared to usual care and the differences in incidence of operational deliveries and performance of FBS across both groups.

Study design

The trial is a pragmatic randomised diagnostic study. We have chosen a randomised design because ST-analysis of the fetal ECG is an example of a new test that might provide better or other information, potentially leading to other treatment choices than the existing reference (CTG plus FBS). In such a situation there is an indication to do a randomised study rather than a conventional accuracy study in which ST-analysis is compared to CTG plus FBS, to quantify its value on patient outcome.[20-22] A design with randomisation at the moment that the CTG group and the ST-analysis group provide discordant test results was not feasible, as this would require randomisation at the moment of medical emergency.[21]

Setting

This study is set in the Dutch Obstetric Consortium, a collaboration of obstetric clinics in the Netherlands. The study will be carried out in nine hospitals, including academic hospitals and non-academic teaching hospitals.[23]

Participants / Eligibility criteria

Women will be eligible if they are in labour with a singleton fetus in vertex position, a gestational age $\geq$ 36 weeks and a medical indication for electronic fetal monitoring. A medical indication is defined by either a high-risk pregnancy, induction or augmentation of labour,

epidural anaesthesia, meconium stained amniotic fluid or non-reassuring fetal heart rate.

Exclusion criteria

Exclusion criteria: breech presentation, twin pregnancies, maternal age < 18 years or absent informed consent.

Procedures, recruitment, randomisation and collection of baseline data

Eligible women will receive the patient study information around 36 weeks of gestation, in the outpatient clinic. Women, having their prenatal controls under supervision of a midwife and being referred to the hospital during labour, will be informed and asked for consent by the attending doctor or midwife at arrival at the hospital.

After consent, women are randomised through a computer-generated randomisation sequence. Stratification will be applied for centre and parity (no previous vaginal delivery versus one or more previous vaginal deliveries). Randomisation will be 1:1 for either monitoring by CTG plus ST-analysis or CTG plus FBS. Both strategies will be performed according to strict protocols (see below).

Women who decide not to participate in the study will be asked for their reasons of refusal. They will be monitored with CTG and, if indicated, FBS.

In each centre an independent gynaecologist will be responsible for the centre specific data collection. Per centre a research nurse or midwife will monitor the protocol also via patient meetings and feedback on potential protocol violations.

At baseline, demographic, past obstetric and medical history data will be recorded for all women.

Intervention

Control group: CTG

In women randomised to the control group, a scalp electrode will be applied to the fetal head and connected to the conventional CTG-monitor conform routine practice. CTG-interpretation will be guided by the FIGO guidelines (Appendix A).[24] Fetal blood sampling is recommended in case of an intermediate or abnormal CTG.

If the pH of the first FBS measurement is below 7.20 delivery is recommended, unless the cause of fetal distress can be alleviated. If the pH is between 7.20 and 7.25, FBS will be repeated after 30 minutes. If the pH is above 7.25, FBS is repeated according to the consecutive CTG pattern on discretion of the attending doctor or midwife.

Intervention group: CTG and ST-analysis

In women randomised to the intervention group, a scalp electrode will be applied to the fetal head and connected to the STAN®-monitor. This electrode will allow both standard fetal heart rate monitoring (CTG) as well as ST-analysis of the fetal ECG. The CTG will be classified as normal, intermediate, abnormal or preterminal according to the FIGO-guidelines for fetal

heart rate monitoring (Appendix A).[24] Clinical management will be supported by computerised ST waveform assessment and will be guided by the STAN® guidelines, indicating when intervention is recommended.[25] The ST log automatically alerts the attending doctor or midwife if a significant ST-event occurs. Delivery is recommended when there are significant ST-changes unless the cause of fetal distress can be alleviated (Appendix A).
Preferably, FBS will not be performed in this group. This, however, does not suffice in all cases. The aim is to keep the performance of FBS as low as possible, limited to three well-defined situations: 1) poor signal quality of the fetal ECG in combination with an abnormal CTG; 2) STAN®-registration starts with an abnormal CTG; 3) 60 to 90 minutes of abnormal CTG recording during first stage of labour without ST-events and the attending doctor decides not to intervene by caesarean section. In the second stage of labour it is advised to perform an instrumental delivery (if possible) in case of the before mentioned situations.
Furthermore, we will also consider the incidence of FBS in both groups as secondary outcome.

Follow up
Children who were admitted to the neonatal intensive care or high care after delivery because of birth asphyxia or other delivery trauma, will be checked upon at 6 months post-delivery. These check-ups are part of the regular controls of children.

Outcome measures

Primary outcome measures
The primary outcome will be the incidence of serious metabolic acidosis defined as a pH < 7.05 and a BDecf > 12 mmol/l in the umbilical cord artery.[26]

Secondary outcome measures
Secondary outcomes are:
1. Instrumental delivery rate because of fetal distress, failure to progress or a combination of the two;
2. Neonatal outcome defined as Apgar scores < 4 after 1 minute and/or < 7 after 5 minutes;
3. Need for admission to neonatal medium or intensive care unit;
4. Incidence of performance of FBS in both groups;
5. Cost-effectiveness of both monitoring strategies in general and across hospitals

Statistical issues

Sample size
The sample size calculation is based on the primary endpoint, which is metabolic acidosis in the umbilical cord artery.

Although in the two previous randomised trials the incidence of metabolic acidosis decreased from 1.5 % to 0.5 % in favour of the CTG + ST-analysis group,[13,14] we assume that the incidence of metabolic acidosis in our higher-risk population (women delivering in the hospital with a medical indication/risk factor) is higher and estimated on 3.5 %, as found in our preliminary study.[12] Based upon the numbers of the largest clinical trial with a relative risk of 0.5 the required sample size would then yield 2400 cases (1200 per arm), using an alpha of 0.05 (2-sided) and a power of 0.80.[13] However, soon after the start of our study a third randomised clinical trial appeared, although much smaller and non-significant, but yielding an opposite effect.[16] A meta-analysis of the three clinical trials showed the varying relative risks of 0.5, 0.4 and 2.4.[27] Hence, to be conservative we used the meta-analysis overall relative risk of 0.6 for our power calculation, implying a reduction of metabolic acidosis, in favour of ST-analysis, from 3.5% to 2.1%. With an alpha of 0.05, a two-sided test – given conflicting results in the literature – and a power of 0.80, about 4638 women should be randomised (2319 per arm). Accounting for 10% loss to follow-up, the study requires inclusion of about 5100 women in order to obtain 4638 analysable cases.

Data analysis

The analysis of the primary endpoint will follow the intention to treat principle. Since this is a randomised trial, we would anticipate minimal differences in baseline characteristics. The relative risk with 95% confidence interval of metabolic acidosis in the CTG plus ST-analysis group compared to the CTG (plus FBS) group will be calculated, accounting for the stratified randomisation by centre and parity. Relative risks and 95% confidence intervals will also be calculated for the dichotomous secondary outcomes, i.e. instrumental delivery rate, neonatal outcome, need for neonatal admission and incidence of performance of FBS across both groups.

The following planned subgroup analyses will be performed: analysis according to risk pregnancies such as women with insulin dependent diabetes mellitus, fever during delivery and start of a STAN®-registration with an abnormal trace.

Missing data rarely occur at random. Simply excluding subjects with missing values thus not only lead to loss of statistical power but also to biased study results. To decrease bias and increase statistical efficiency we will therefore impute missing values rather than perform complete case analysis only. This will be done using single and multiple imputation methods.[28-30]

Economic evaluation

The economic evaluation is primarily a cost-effectiveness analysis (CEA) to find the optimal strategy as the one with the most favourable trade-off between avoided adverse neonatal outcome (fetal distress/metabolic acidosis) and difference in cost.

For this purpose, the process of care is distinguished into two cost stages (delivery/childbirth stage and postnatal stage) and three cost categories (direct medical costs [all costs in the health care sector, such as type of intervention and maternal and fetal monitoring, lab tests,

costs associated with intrapartum complications, costs of training, maternal and neonatal care in the postnatal stage], direct non-medical costs [costs outside the health care sector that are affected by health status or health care], and indirect costs [productivity costs, costs of sick leave]).

Valuations of direct medical resources are estimated as cost per unit estimates comprising 'true' economic costs, i.e. including shares of fixed costs and hospital overheads. Cost per unit is estimated for at least one teaching and one non-teaching hospital. Direct medical volumes outside the hospital and direct non-medical volumes are valued using national reference prices.[31] Indirect costs are quantified according to the friction cost method. Study specific costs are excluded from analysis.

As we anticipate a reduction of metabolic acidosis with the use of CTG plus ST-analysis compared to CTG plus FBS, the economic analysis is planned to be a cost-effectiveness analysis. We will use bootstrap sampling to calculate 95% confidence intervals around the cost-effectiveness ratios. Sensitivity analysis will be used to explore the effect of variation of several key factors.

Baseline obstetric characteristics of first 500 randomised patients

Baseline obstetric characteristics of the first 500 enrolled patients in the study are shown in Table 1.

Table 1 Baseline obstetric characteristics of the first 500 randomised patients in clinical trial

All values are absolute numbers (%) or mean (SD).

Characteristic	CTG group **n** = 254	CTG + ST group **n** = 246
Age at delivery (yrs)	32 ± 5	32 ± 5
Nulliparous	120 (47.2%)	130 (52.8%)
Previous caesarean delivery	45 (17.7%)	30 (12.2%)
Gestational age at delivery (wks)	40 ± 1.5	40 ± 1.5
Prolonged pregnancy*	31 (12.2%)	24 (9.8%)
Induction of labour	82 (32.3%)	87 (35.4%)
Epidural analgesia	79 (31.1%)	73 (29.7%)
Meconium-stained amniotic fluid	62 (24.4%)	61 (24.8%)
Oxytocin augmentation	146 (57.5%)	156 (63.4%)
Birthweight (gr)	3506 ± 528.7	3501 ± 508.1

* Prolonged pregnancy is a gestational age > 42 wks

Ethical considerations and Safety Committee

The study protocol has been approved by the Medical Ethical Committee of the University Medical Centre Utrecht, Utrecht, The Netherlands (05/157-K). Written informed consent will

be obtained from each participating patient.
Serious Adverse Events (SAE) are defined as "metabolic acidosis (arterial pH<7.00 and BDecf >12mmol/L) and admission to a Neonatal Intensive Care Unit (NICU)" or "an Apgar score < 7 after 5 minutes and admission to a NICU". Given the conflicting results in the literature, all SAE's will be reported to the Data Safety Monitoring Committee, consisting of an independent gynaecologist, neonatologist, epidemiologist and a biostatistician. This committee will consider the reported incidence of SAE's at regular intervals to determine whether there are significantly more serious adverse events in the STAN-group and, if so, whether the study should be discontinued. For this purpose the computer program PEST, version 4, will be used.[32]

Concluding remarks

This study is the first randomised trial to quantify the cost-effectiveness of ST-analysis of the fetal ECG during labour and the first to achieve data about the use of ST-analysis with fetal blood sampling performed only in well-defined circumstances. This study aims to provide additional evidence on the true clinical value of intrapartum ST-analysis and also the clinical indications in which fetal blood sampling still might be necessary in addition to ST-analysis.

Acknowledgements

This study is subsidized by ZonMW, the Dutch Organisation for Health Research and Development (Grant number: 945-06-557).

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Submitted Clinical Trial Register, ISRCTN95732366, http://isrctn.org

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Cardiotocography plus ST-analysis of the fetal electrocardiogram versus cardiotocography only for intrapartum monitoring: a Dutch randomised clinical trial

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Abstract

Context

Intrapartum surveillance with ST-analysis of the fetal electrocardiogram (ECG) potentially improves neonatal outcome.

Objective

To quantify the effectiveness of intrapartum fetal monitoring by cardiotocography (CTG) plus ST-analysis, using a strict protocol for performance of fetal blood sampling (FBS).

Design

Multicentre randomised clinical trial.

Setting

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

Participants

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

Interventions

Participants were randomly assigned to monitoring by CTG combined with ST-analysis (index) or CTG without ST-analysis (control)**.** There were strict conditions for performance of FBS.

Main Outcome Measures

Primary outcome was neonatal metabolic acidosis defined as an umbilical cord-artery pH below 7.05 combined with a base deficit (BD) calculated in the extracellular fluid compartment above 12 mmol/L. Secondary outcome measures were metabolic acidosis in blood, operative deliveries, Apgar scores, neonatal admissions and moderate or severe hypoxic ischemic encephalopathy (HIE).

Results

We randomised 5681 women (2832 index; 2849 control). The FBS rate was 10.6% in the index group versus 20.4% in the control group (relative risk (RR) 0.52; 95% confidence interval (CI), 0.46 to 0.60). The incidence of the primary outcome was 0.7% in the index group versus 1.1% in the control group (RR 0.70; 95% CI 0.38 to 1.28). When metabolic acidosis was analyzed according to pH and BD calculated in blood, these rates were 1.6% and 2.6%, respectively (RR 0.63; 95% CI, 0.42 to 0.94). The number of operative deliveries, low Apgar scores, neonatal admissions and newborns with moderate or severe HIE was comparable in both groups.

Conclusion

Addition of ST-analysis of the fetal ECG to surveillance with CTG during labour does not significantly reduce the number of newborns with metabolic acidosis calculated in the extracellular fluid compartment of umbilical cord blood. However, it does reduce the number of newborns with metabolic acidosis calculated in blood and with severe acidosis. There is no effect of monitoring by ST-analysis of the fetal ECG on Apgar scores, neonatal admissions, moderate to severe HIE or operative deliveries.

Introduction

Intrapartum fetal monitoring aims to identify fetuses at risk for neonatal and long-term injury due to asphyxia. Fetal surveillance with cardiotocography (CTG) has been introduced in the 1960s. Although a positive effect of CTG on neonatal outcome has never been shown, CTG is widely applied.[1-8]

Fetal monitoring by CTG only significantly increases the operative delivery rate, but addition of fetal blood sampling (FBS) may prevent this.[6] However, performance of FBS requires expertise, is invasive, has to be repeated when CTG abnormalities persist and still does not guarantee prevention of asphyxia.[9] Other tools for fetal surveillance, e.g. fetal pulse oximetry, have not been successful.[10]

In recent years, ST-analysis of the fetal electrocardiogram (ECG; STAN®) has been introduced.[11] This technique detects changes in the ST-segment of the fetal ECG, which are related to metabolic acidosis. These are interpreted together with the CTG.[12,13]

Two randomised trials assessing ST-analysis of the fetal ECG showed that this technique decreased metabolic acidosis, instrumental deliveries for fetal distress, and the proportion of infants born with encephalopathy, as compared to CTG alone.[14-16] However, in both trials FBS was equally performed in the two study groups. In a recent much smaller trial, the FBS percentage was significantly lower in the CTG plus ST-analysis group, but improvement in neonatal outcome could not be confirmed.[17]

Given this controversy, we designed a large pragmatic randomised trial with the aim to quantify the effectiveness of intrapartum fetal monitoring by CTG plus ST-analysis of the fetal ECG, using a strict protocol for performance of FBS.[18]

Methods

We performed a multicentre randomised pragmatic trial in three academic and six non-academic teaching hospitals in The Netherlands. The study was situated within the Dutch Obstetric Consortium, which is a collaboration of obstetric clinics in The Netherlands (www.studies-obsgyn.nl).

Training phase

Prior to our study, CTG and FBS was the standard of care in The Netherlands for fetal surveillance of high-risk deliveries. Before start of the trial, labour ward personnel of the participating centres was trained in the use of the STAN®-method by four instructors. After the training, all gynaecologists, residents and midwives in the participating centres became certified STAN®-users by passing an exam (STAN® training material; Neoventa Medical, Gothenburg, Sweden). Training and certification continued on a regular basis during the trial.

All participating centres had at least two months of clinical experience with the STAN® method before randomisation of the first patient.

Recruitment and randomisation

Labouring women aged 18 years or older with a singleton high-risk pregnancy, a fetus in cephalic presentation, a gestational age above 36 weeks and an indication for internal electronic fetal monitoring were eligible. In The Netherlands, pregnant women at low-risk are monitored by midwives or general practitioners at home or in hospital (primary care), whereas pregnant women at high-risk are monitored by gynaecologists in hospital (secondary care). High-risk pregnancies are complicated by pre-existing maternal disease, complicated obstetric history, hypertensive disorders, intrauterine growth restriction, ruptured membranes for more than 24 hours, a post date gestational age, failure to progress, need for pain relief, meconium stained amniotic fluid or non-reassuring fetal heart rate at intermittent auscultation by a midwife.

The study was approved by the institutional review board of the University Medical Centre Utrecht and had local approval from all other participating hospitals. Eligible women received both oral and written information either at 36 weeks of gestation in the outpatient clinic or in early stage during labour. After women had given written informed consent, they were randomised on a 1:1 basis through a web based computer-generated randomisation sequence with variable block size, to either monitoring by CTG plus ST-analysis of the fetal ECG (index group) or CTG alone (control group). Randomisation was stratified for centre and parity (no versus one or more previous vaginal deliveries). The (assigned) diagnostic procedure and subsequent labour were managed by the labour ward staff. Due to the explicit pragmatic nature of the trial both patients and care givers were not blinded to the allocated interventions.

Interventions

Index group

In women assigned to 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). This scalp electrode allowed both for registration of the CTG and ST-analysis of the fetal ECG. The CTG was classified according to the STAN® clinical guidelines (based on the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO)).[19] Clinical management was supported by the computerized automatic ST interval assessment, the ST-log and the STAN® clinical guidelines (Appendix A).[18]

Performance of FBS was restricted to three situations: 1) start of STAN®-registration with an intermediary or abnormal CTG trace; 2) abnormal CTG trace for more than 60 minutes during first stage 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. If the pH of a FBS was below 7.20 immediate delivery was recommended, unless the cause of

fetal distress could be alleviated. 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 follow the STAN® clinical guidelines.

Control group

In women assigned to the control group, a scalp electrode was applied to the fetal head and connected to a conventional fetal heart rate monitor. The CTG was classified and interpreted according to the STAN® clinical guidelines as normal, intermediary, abnormal or (pre)terminal.[19] FBS was performed on indication by the obstetric caregiver in case of an intermediary or abnormal CTG trace. Clinical decisions were based on CTG and/or FBS results, using the same thresholds for interventions as in the index group. In case of a FBS result with pH above 7.25, FBS could be repeated according to CTG patterns on discretion of the caregiver.

In both groups, immediately after birth the umbilical cord was doubly clamped to sample both arterial and venous cord blood. In case arterial and venous pH in cord blood differed less than 0.03, the results were considered to be from a venous sample, since the latter is more easily to obtain.

For both groups protocol monitoring was achieved by quarterly case meetings, in which controversial cases were discussed and feedback was given on potential protocol violations. In each centre a research nurse or midwife and a gynaecologist were responsible for training, study monitoring and data entry into a web based database.

Study outcomes

Primary outcome measure was the incidence of metabolic acidosis, defined as an umbilical cord-artery blood pH below 7.05 and a base deficit (BD) calculated in the extracellular fluid compartment (BDecf) above 12 mmol/L, according to the Siggaard-Andersen acid-base chart algorithm.[20]

We also defined metabolic acidosis as an umbilical cord-artery blood pH below 7.05 combined with a base deficit calculated in blood (BDblood) above 12 mmol/L.

BDblood is reported by most umbilical cord blood analyzers, and therefore these values are often used in clinical practice. However, BDecf seems to better reflect the true metabolic component of acidosis, which is associated with neonatal morbidity.[21,22]

Other secondary outcomes were the number of Apgar scores below four and seven at one and five minutes respectively, total neonatal admissions, admissions to Neonatal Intensive Care Unit (NICU, level III), operative deliveries (caesarean and/or instrumental vaginal deliveries), and number of cases with FBS.

Two neonatologists (F.G. and M.J.B.) who were blinded for randomisation allocation independently assessed all neonatal admission letters and charts, to evaluate whether signs of moderate or severe neonatal hypoxic ischemic encephalopathy (HIE) had developed,

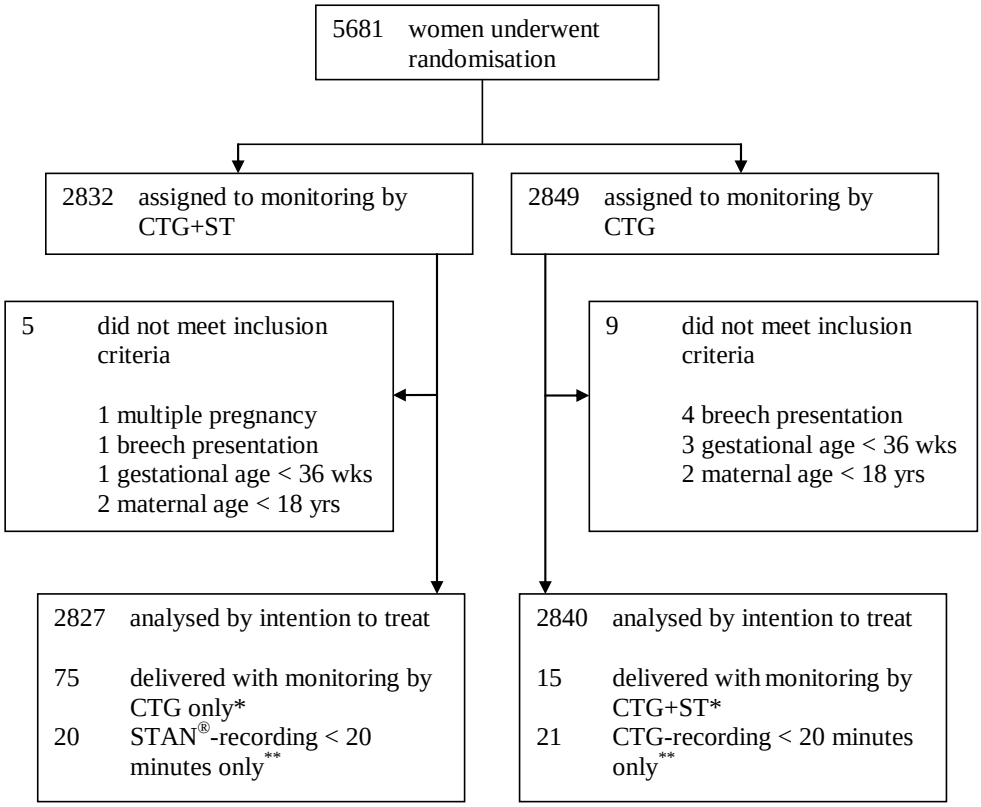
according to Sarnat.[23] Since retrospective application of the Sarnat grading system causes large variability regarding the evaluation of mild encephalopathy (Sarnat grade 1), without a strong relation of this grade to adverse neurologic outcome[24], we restricted to grading moderate and severe HIE (Sarnat grade 2 and 3).
Safety monitoring was performed by a Data Safety Monitoring Committee.[18] Three safety conditions were monitored: 1) umbilical cord-artery blood pH below 7.00 and BD above 12mmol/L, 2) Apgar score below 7 after 5 minutes and 3) admission to a NICU. Occurrence of either condition 1 and 3 or condition 2 and 3 was defined as a Serious Adverse Event (SAE).

Sample size calculation and statistical analysis
We hypothesized an incidence of our primary outcome of 3.5%.[25]An absolute reduction in the metabolic acidosis rate of 1.4% in favour of the index group was considered clinically relevant.[14,15,17] Using a two-sided alpha of 0.05 and power of 0.80 implied randomisation of 4638 women (2319 per group). Allowing for 10% loss to follow-up, our target sample size was 5200 women.
The statistical analyses were performed according to intention to treat. For dichotomous outcomes the relative risk (RR) with 95% confidence interval (CI) was estimated, adjusted for the stratified randomisation by centre and parity.
Various subjects had missing values. As these are often selectively missing, which was also the case in our study (Table 4), it is well documented that a complete case analysis likely yields biased results.[26-28] Hence, we multiply imputed missing values (ten times) before doing the analysis, using the AregImpute method in S-plus. Results of the above analyses on the ten imputed datasets were then pooled according to standard methods using Rubin's rule.[29]
All analyses including the multiple imputation were performed in S-plus 6.1 (Insightfull Corp, Seattle, Washington).

Results

The study was performed between January 2006 and July 2008. During the trial we monitored whether umbilical cord blood samples were adequately performed and outcome results were available. Since these data appeared to be incomplete for 20% (instead of the assumed 10%), the trial was extended to randomisation of 5681 women, a decision made prior to any comparison of groups.
We randomly allocated 2832 women to the index group, and 2849 to the control group. After randomisation 14 women were excluded (five in the index group, nine in the control group), because they did not meet the inclusion criteria. Data for 5667 women (2827 in the index group, 2840 in the control group) were analysed according to intention to treat (Figure 1). Baseline characteristics of these women are summarized in Table 1.

Figure 1 Flowchart of randomised women



* In the index group 75 women delivered with monitoring by CTG only, whereas in the control group 15 women delivered with monitoring by CTG plus ST-analysis.
** STAN®- and CTG-recordings had a duration of less than 20 minutes for 20 and 21 women in the index and control group, respectively.

Table 1 Baseline characteristics of the 5667 randomised women*

Characteristic	Index group N=2827	Control group N=2840
Patient age at delivery – yr	32 ± 4.8	32 ± 4.7
Gestational age at delivery – wk	40 ± 1.4	40 ± 1.5
Nulliparous – no. (%)	1616 (57.2)	1620 (57.0)
Previous caesarean delivery – no. (%)	345 (12.2)	371 (13.1)
Prolonged pregnancy (≥ 42 wks) – no. (%)	332 (11.7)	372 (13.1)
Pregnancy related hypertensive disorder – no. (%)**	333 (11.8)	345 (12.1)
Induction of labour – no. (%)	1155 (40.9)	1186 (41.8)
Cervical dilatation at randomisation – cm	4.2 ± 2.4	4.2 ± 2.4
Meconiumstained amniotic fluid – no. (%)	708 (25.0)	763 (26.9)
Epidural anaesthesia – no. (%)	1180 (41.7)	1209 (42.6)
Oxytocin augmentation – no. (%)	1032 (36.5)	1012 (35.6)
Intrapartum fever (≥ 37.8 °C) – no. (%)	228 (8.1)	242 (8.5)
Birthweight – gr	3548 ± 511	3540 ± 525
Birthweight < 2500 gr – no. (%)	53 (1.9)	68 (2.4)
Neonatal female gender – no. (%)	1297 (45.9)	1371 (48.3)

* Plus-minus values are means ± SD.
** Pregnancy related hypertensive disorder was defined as either preeclampsia or gestational hypertension.

FBS was performed less in the index group (10.6%) than in the control group (20.4%) (RR 0.52, 95% CI 0.46 to 0.59). The overall rates of caesarean or instrumental vaginal deliveries were comparable (RR 0.96, 95% CI 0.87 to 1.06), with slightly more operative deliveries for suspected fetal distress in the index group, whereas there were slightly less operative deliveries for other indications in this group (Table 2).

Table 2 Delivery outcomes*
Data are presented as n (%). For details see text.

Outcome	Index group N=2827	Control group N=2840	Relative Risk† (95% CI)
Incidence of FBS	301 (10.6)	578 (20.4)	0.52 (0.46-0.59)
Total operative deliveries**	789 (27.9)	822 (28.9)	0.96 (0.87-1.06)
Caesarean deliveries	405 (14.3)	391 (13.8)	1.02 (0.89-1.17)
Instrumental vaginal deliveries	384 (13.6)	431 (15.2)	0.90 (0.79-1.03)
Operative deliveries for fetal distress**	261 (9.2)	237 (8.3)	1.10 (0.93-1.31)
Caesarean delivery	91 (3.2)	70 (2.5)	1.31 (0.96-1.79)
Instrumental vaginal delivery	170 (6.0)	167 (5.8)	1.02 (0.83-1.27)
Operative deliveries for other indications**	528 (18.7)	585 (20.6)	0.91 (0.81-1.02)
Caesarean delivery	314 (11.1)	321 (11.3)	0.96 (0.58-1.61)
Instrumental vaginal delivery	214 (7.6)	264 (9.3)	0.82 (0.69-0.98)

* Absolute numbers (%) in this table were based on the mean of ten imputations.
** Spontaneous vaginal deliveries were used as reference category for calculation of relative risks.
† Relative risks were adjusted for the stratified randomisation by centre and parity.

Neonatal outcomes are shown in Table 3. The incidence of the primary outcome metabolic acidosis based on pH and BDecf was lower in the index group (0.7% versus 1.1% (control group), RR 0.70, 95% CI 0.38 to 1.28).

The rate of metabolic acidosis based on pH and BDblood was significantly lower in the index than in the control group (1.6% versus 2.6%; RR 0.63, 95% CI 0.42 to 0.94). For an umbilical cord-artery pH below 7.05 as well as 7.00 there were also reduced incidences in the index group (RR 0.67, 95% CI 0.46 to 0.97 and RR 0.56, 95% CI 0.31 to 1.01, respectively). The rates of low Apgar scores after 1 and 5 minutes, total neonatal admissions and admissions to a NICU did not differ between groups (Table 3).

In total, there were four newborns with signs of moderate or severe HIE (0.1%). In the index group 2 newborns were graded with a Sarnat 2 and 1 with a Sarnat 3 (also a case of perinatal death). In the control group, 1 newborn had a Sarnat grade 2 (Table 3).

In total, there were five perinatal deaths (Table 3). Three (1 in index group and 2 in control group) were caused by congenital malformations (1 transposition of the great arteries, 1 intracranial teratoma and 1 hypoplastic left heart syndrome). The other two deaths were both in the index group (Appendix B). One woman had multiple FBS for persisting abnormal CTG and two significant ST-events. After 90 minutes of active pushing a ventouse delivery for fetal distress failed and a caesarean delivery was performed. A baby with Apgar scores of 0, 0 and 3 after 1, 5 and 10 minutes respectively was born. Rupture of the uterus appeared to be the cause for distress. The baby was admitted to the NICU and died of severe perinatal asphyxia and neonatal encephalopathy (Sarnat grade 3). In the second case, immediately after applying a scalp electrode for internal fetal monitoring, the CTG showed a (pre)terminal trace,

whereas it had been normal before. At emergency caesarean delivery a severely asphyxiated infant with Apgar scores of 0 after 1, 5 and 10 minutes was born.

Table 3 Neonatal outcomes*
Data are presented as n (%). For details see text.

Outcome	Index group N=2827	Control group N=2840	Relative Risk† (95% CI)
Primary outcome			
Cord-artery pH<7.05 & BDecf>12mmol/L	20 (0.7)	30 (1.1)	0.70 (0.38-1.28)
Secondary outcomes			
Cord-artery pH<7.05 & BDblood>12mmol/L	45 (1.6)	74 (2.6)	0.63 (0.42-0.94)
Cord-artery pH<7.05	55 (1.9)	78 (2.7)	0.67 (0.46-0.97)
Cord-artery pH<7.00	18 (0.6)	34 (1.2)	0.56 (0.31-1.01)
Apgar score 1 min < 4	49 (1.7)	40 (1.4)	1.25 (0.82-1.90)
Apgar score 5 min < 7	42 (1.5)	34 (1.2)	1.24 (0.79-1.95)
Total neonatal admissions	391 (13.8)	441 (15.5)	0.90 (0.80-1.02)
Admission to a NICU	40 (1.4)	45 (1.6)	0.89 (0.58-1.35)
Hypoxic ischemic encephalopathy			
Moderate (Sarnat grade 2)	2 (0.1)	1 (<0.1)	- **
Severe (Sarnat grade 3)	1 (<0.1)	0 (0.0)	- **
Perinatal death	3 (0.1)	2 (0.1)	- **

* Absolute numbers (%) in this table were based on the mean of ten imputations.
** Relative risk (95% CI) was not calculated due to very low numbers.
† Relative risks were adjusted for the stratified randomisation by centre and parity.

Discussion

Our trial shows that fetal monitoring by CTG combined with ST-analysis of the fetal ECG decreases the incidence of acidosis by 30 to 44%, depending on its definition. However, the reduction in our primary outcome is not significant, due to a low incidence of metabolic acidosis calculated in the extracellular fluid compartment in both groups. Moreover, we do not find an effect on Apgar scores, neonatal admissions, moderate to severe HIE incidence or operative deliveries.

Our results were achieved with a 48% lower incidence of FBS in the index group, which is in accordance with previous trials.[17,30,31] FBS is a relatively invasive procedure, which has to be repeated as CTG abnormalities persist. Since the results of our trial imply that less FBS performance is needed in addition to ST-analysis of the fetal ECG, this may be considered as a positive effect.

We did not find a significant reduction in total operative deliveries, unlike some of the previous trials which showed a 8 to 12% reduction in all operative deliveries.[14,15,31] This may be due to the fact that in our study with a relatively high incidence of FBS, especially in the control group, the number of unnecessary interventions due to false positive CTG results was

low in both groups. It may be speculated that a randomised trial in a routine setting without FBS, indeed results in a considerable reduction of interventions.

Apart from a trend towards fewer total neonatal admissions in the index group, we found no impact on clinical neonatal outcomes, such as Apgar scores or HIE. It is known that most infants born at term with a low pH do well and associations between pH at birth and neonatal morbidity and mortality are only consistently found when the cord-artery pH is below 7.00.[22,32,33] In such cases about 10% of infants will develop neonatal seizures and about one-third of those will suffer from long-term impairment.[34-37] In our study only 18 cases in the index group (0.6%) and 34 cases in the control group (1.2%) had a cord-artery pH below 7.00, thus limiting the power to detect asphyxia related cerebral injury. The long-term neurodevelopmental outcome of patients in our ongoing follow-up study has therefore to be awaited.

To appreciate the present results, two issues need to be addressed. First, our trial was powered on the assumption that 3.5% of infants would have a metabolic acidosis at birth.[25] However, the overall incidence, specifically in the extracellular fluid compartment, was considerably lower. This may probably be explained by the fact that women diagnosed with acute signs of fetal distress at admission were not approached for participation.

The second issue concerns the definition of metabolic acidosis. In clinical practice the definition of metabolic acidosis is usually based on a base deficit threshold of 12 mmol/L.[38] Since BDecf is lower than BDblood[39], this will lead to a substantial lower rate of metabolic acidosis when the algorithm for BDecf is used. Although BDecf seems to better reflect the true metabolic component of acidosis[21,22], there is no consensus regarding which type of algorithm should be used. This does not only create clinical difficulties with respect to the definition of acidosis, but also introduces the problem of (in)comparability of study results when cord blood gases are used as outcomes.[39]

Data from four earlier trials have not been conclusive showing ambiguous results, with a lower incidence of metabolic acidosis in the ST-group in the two large trials[14,15], and a higher incidence of metabolic acidosis in the two smaller trials.[17,30] Meta-analysis of these trials, including 9671 women, showed reduction in metabolic acidosis with a RR of 0.73 (95% CI 0.49 to 1.09) in favour of ST-analysis[31], which is similar to our findings. Both the results of this meta-analysis and our study indicate that the use of the STAN®-method reduces the incidence of acidosis, at least in settings in which FBS is being used.

In conclusion, we found that intrapartum fetal monitoring by CTG plus ST-analysis of the fetal ECG substantially decreases the incidence of (metabolic) acidosis. There was no effect on Apgar scores, neonatal admissions, moderate to severe HIE or operative deliveries. Also long-term outcome has to be awaited before a final judgment on the value of ST-analysis of the fetal ECG can be made.

Acknowledgements

We thank all research nurses and midwives of the Dutch Obstetric Consortium, as well as the staff of the labour wards of the participating centres for their invaluable contributions to the study.

Financial support
This trial was funded by a grant from ZonMW, the Dutch Organisation for Health Research and Development (Grant number: 945-06-557).

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

The preliminary results of this trial were presented at the 2009 annual meeting of the Society for Gynecologic Investigation (SGI), Glasgow, Scotland, March 17-21, 2009, where it was awarded with the Wyeth Presenter's Award.

Table 4 Distribution of missing values for outcomes related to cord-artery pH among baseline and outcome variables

Variables in bold indicate that missingness was not completely at random but related to other subject characteristics, which indicates not to perform a complete case analysis but rather apply multiple imputation first (see text). Plus-minus values are means ± SD.

	Complete Cases (all variables completely observed) **N=4378**	**Subjects with at least one missing value N=1289**	**p - value**
Patient age at delivery – yr	32 ± 4.7	32 ± 5.0	0.96
Gestational age at delivery – wk	40 ± 1.4	40 ± 1.5	0.47
Nulliparous – no. (%)	2511 (57.4)	725 (56.2)	0.48
Previous caesarean delivery – no. (%)	566 (12.9)	150 (11.6)	0.22
Pregnancy related hypertensive disorder – no. (%)	525 (12.0)	153 (11.9)	0.91
Prolonged pregnancy (≥ 42 wks) – no. (%)	546 (12.5)	158 (12.3)	0.84
Cervical dilatation at randomisation – cm	4.2 ± 2.4	4.1 ± 2.3	0.12
Meconiumstained amniotic fluid – no. (%)	1131 (25.8)	340 (26.4)	0.70
Intrapartum fever (≥ 37.8 °C) – no. (%)	374 (8.5)	96 (7.4)	0.21
Epidural anaesthesia – no. (%)	1870 (42.7)	519 (40.3)	0.12
Oxytocin augmentation – no. (%)	3048 (69.6)	882 (68.4)	0.41
Induction of labour – no. (%)	1797 (41.0)	544 (42.2)	0.46
Birthweight (gr)	**3558 ± 513**	**3497 ± 533**	**<0.01**
Birthweight < 2500 gr – no. (%)	**79 (1.8)**	**42 (3.3)**	**<0.01**
Neonatal female gender – no. (%)	2042 (46.6)	626 (48.6)	0.22
Cord-artery pH<7.05 & BDecf>12mmol/L – no. (%)	33 (0.8)	7 (0.9)	0.65
Cord-artery pH<7.05 & BDblood>12mmol/L – no. (%)	**75 (1.7)**	**20 (2.6)**	**0.10**
Cord-artery pH<7.05 – no. (%)	90 (2.1)	20 (2.6)	0.35
Cord-artery pH<7.00 – no. (%)	37 (0.8)	9 (1.2)	0.39
Apgar score 1 min < 4 – no. (%)	73 (1.7)	15 (1.2)	0.20
Apgar score 5 min < 7 – no. (%)	61 (1.4)	15 (1.2)	0.53
Fetal blood sampling – no. (%)	684 (15.6)	195 (15.1)	0.67
Caesarean delivery – no. (%)	**579 (13.2)**	**217 (16.8)**	**<0.01**
Instrumental vaginal delivery – no. (%)	**662 (15.1)**	**153 (11.9)**	**<0.01**
Intervention for fetal distress – no. (%)	391 (31.5)	105 (28.4)	0.25
Total neonatal admissions – no. (%)	628 (14.3)	204 (15.8)	0.19
Admission to NICU – no. (%)	65 (1.5)	20 (1.6)	0.86
Moderate or severe HIE (Sarnat grade 2 or 3) – no. %	3 (0.1)	1 (0.1)	0.91
Allocation to index group – no. (%)	**2221 (50.7)**	**606 (47.0)**	**0.02**

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Submitted

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Intrapartum fetal monitoring: identification of cases with adverse neonatal outcome

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Abstract

Objective

To study cases with adverse neonatal outcome in relation to the type of intrapartum fetal monitoring, with a focus on identification of compromised fetuses.

Methods

Data were obtained from a randomised trial comparing monitoring by ST-analysis of the fetal electrocardiogram (ECG; STAN®) (index group) to CTG only (control group) in 5681 women with a term singleton fetus in cephalic position. Three observers independently assessed all cases with adverse neonatal outcome, identified by the following criteria: 1) cord-artery metabolic acidosis (pH < 7.05 & BDecf > 12 mmol/L); 2) cord-artery pH < 7.00; 3) perinatal death; and/or 4) moderate or severe hypoxic ischemic encephalopathy.

Results

61 cases (1.1%) of adverse neonatal outcome were identified (26 index; 35 control). In the index group the total number of operative deliveries was 23 (88.5%) versus 20 (57.1%) in the control group (p=0.01). Observer evaluation showed that there was an indication to intervene for suspected fetal distress in 23 (88.5%) and 19 (57.6%) cases, respectively (p=0.01). Number of cases with an indication to intervene more than 20 minutes before delivery were 13 (50.0%) and 11 (33.3%), respectively (p=0.20). In the index group, indications were mainly based on a significant ST-event (52.2%) and in the control group on a (pre)terminal CTG (73.7%). STAN® guidelines and the trial protocol were violated in 11 (42.3%) and 13 (39.4%) cases of index and control group, respectively. Correct adherence to these guidelines, leading to earlier intervention, would probably or certainly have led to better neonatal outcome in 6 (23.1%) and 4 (12.1%) cases, respectively.

Conclusion

Our results indicate that monitoring by ST-analysis of the fetal ECG is more specific and comprehensive, regarding the aim to detect and deliver compromised fetuses, than monitoring by CTG only. Correct adherence to STAN® guidelines may increase the detection rate even further. However, in 50% of cases with adverse outcome monitored by ST-analysis there were no clear signs of fetal distress more than 20 minutes before birth, indicating that these could not have been prevented.

Introduction

Electronic fetal heart rate monitoring by cardiotocography (CTG) is used to timely identify the newborn at risk for asphyxia, to prevent adverse neonatal and long-term neurological outcomes, such as hypoxic ischemic encephalopathy (HIE) and cerebral palsy.[1-3] However, the ability of CTG monitoring alone to prevent adverse outcome is limited. Techniques providing additional intrapartum fetal information are therefore necessary.[4-7] Fetal blood sampling (FBS) may be used, but this technique requires expertise, is invasive, has to be repeated when CTG abnormalities persist and is often inconsistently applied.[8] In recent years, ST-analysis of the fetal electrocardiogram (ECG; STAN®) has been introduced.[9] This technique detects changes in the ST-segment of the fetal ECG, which are related to metabolic acidosis. These are interpreted together with the CTG according to specific clinical guidelines.[10,11]

Two large randomised clinical trials (RCTs) have shown a decrease in metabolic acidosis, in instrumental deliveries for fetal distress, and in the proportion of infants born with encephalopathy, in favour of the CTG plus ST-analysis group as compared to CTG monitoring alone.[12-14] Two smaller RCTs could not confirm this improvement in neonatal outcome.[15,16] Recently, we found in a large Dutch RCT among 5681 women that the use of ST-analysis during labour reduces the incidence of (metabolic) acidosis as compared to CTG alone. We found no effects on the number of newborns admitted to a neonatal intensive care unit (NICU), with a low Apgar score or with signs of moderate to severe HIE. Also the number of operative deliveries was comparable between both groups.[17,18]

Although the STAN® method has been shown to be an effective tool for fetal surveillance, in specific with respect to the metabolic acidosis rate, [12-14,18,19] it is known that 'false negative' cases with adverse outcome do occur. In some of these cases the technique fails to detect the compromised fetus in time. However, more often human failures and inconsistent adherence to clinical guidelines underlie the birth of an infant with adverse outcome.[20-2 3]

Hence, to assess further improvements in fetal monitoring, the present subgroup study includes a detailed description of cases with adverse neonatal outcome in the ST-analysis compared to the CTG only group of the Dutch RCT.[18] Our aim was to evaluate the relation between adverse outcome and type of fetal monitoring, with a focus on timing of identification of compromised fetuses and adherence to clinical guidelines.

Methods

Patients and Measurements

Between January 2006 and July 2008 a multicentre RCT among labouring women with a high-risk singleton pregnancy in cephalic position beyond 36 weeks of gestation was performed. The aim was to evaluate the effectiveness of intrapartum fetal monitoring by CTG

plus ST-analysis of the fetal ECG, using a strict protocol for performance of FBS. Participants were randomly assigned to monitoring by CTG combined with ST-analysis (index group) or CTG without ST-analysis (control group).[17,18]

In women assigned to 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). Clinical management was supported by the computerized automatic ST interval assessment, the ST-log and the STAN® clinical guidelines (Appendix A).[17,18] Performance of FBS was restricted to three situations: 1) start of STAN®-registration with an intermediary or abnormal CTG trace; 2) abnormal CTG trace for more than 60 minutes during first stage 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. If the scalp pH was below 7.20 immediate delivery was recommended, unless the cause of fetal distress could be alleviated. 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 follow the STAN® clinical guidelines.

In women assigned to the control group, the scalp electrode was connected to a conventional fetal heart rate monitor. FBS was performed on indication by the obstetric caregiver in case of an intermediary or abnormal CTG trace. Clinical decisions were based on CTG and/or FBS results, using the same thresholds for interventions as in the index group. In case of a (pre)terminal CTG trace immediate delivery was recommended without performing FBS.

Primary outcome measure was the incidence of metabolic acidosis, defined as an umbilical cord-artery blood pH below 7.05 and a base deficit calculated in the extracellular fluid compartment (BDecf) above 12 mmol/L, according to the Siggaard-Andersen acid-base chart algorithm.[23] Secondary outcome measures were the number of Apgar scores below four and seven at one and five minutes respectively, total neonatal admissions, admissions to Neonatal Intensive Care Unit (NICU), operative deliveries and number of cases with moderate to severe HIE. For the latter outcome, grading by the Sarnat score was used.[24]

Adverse neonatal outcome

Neonatal outcome was defined as 'adverse' in case at least one of the following criteria was met: 1) metabolic acidosis in umbilical cord-artery (pH<7.05 & BDecf>12 mmol/L); 2) umbilical cord-artery pH below 7.00; 3) perinatal death; and/or 4) signs of moderate or severe HIE (Sarnat grade 2 or 3). Cases with perinatal death due to a lethal congenital disorder, born without metabolic acidosis were excluded.[18]

CTG and ECG recordings

CTG or STAN® recordings of neonates with adverse outcome (cases), mixed with randomly selected recordings with uneventful outcome (controls) (ratio 1 control : 2 cases), were independently assessed by two observers (A.K. and M.P.). No information on neonatal

outcome was provided. Controls were used to prevent that the observers would by definition know that the outcome of the neonate was adverse. In case of inconclusive results the observations of a third observer (G.V.) were decisive. All observers are obstetricians working in tertiary referral centres, with many years of experience in the field of intrapartum fetal monitoring, including ST-analysis of the fetal ECG.

CTG or STAN® recordings (according to allocated group in RCT) were reviewed using Mosos® (BMA BV, the Netherlands) or STAN® viewer (Neoventa Medical AB, Sweden) software, respectively (paper speed 2 cm per minute). Limited additional clinical information was provided: 1) time of randomisation, 2) time of active pushing, 3) time of FBS, 4) categorized result of FBS (1 = pH below 7.20, 2 = pH between 7.20 and 7.25, 3 = pH above 7.25), 5) time of intrauterine resuscitation measures (stop administration of oxytocin, use of tocolytic agent, change of maternal position etc), 6) time and mode of delivery, and 7) reason for intervention (fetal distress or other indication).

Observers were asked to assess CTG and STAN® recordings according to the STAN® guidelines (based on the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO)[25] (Appendix A)) as normal, intermediary, abnormal or (pre)terminal.[26] By taking into account the provided clinical information, the information on ST-waveform or FBS and clinical guidelines, they were asked to judge whether or not there had been an indication to intervene for suspected fetal distress. If so, they had to indicate at what time during delivery the need for an intervention appeared. Consensus regarding timing of an intervention was obtained in case the time difference between observers was less than 30 or 15 minutes, during first or second stage, respectively. They also had to point out the event that led to this need for intervention: 1) CTG classification; 2) result of FBS; or 3) significant ST-event. Finally, they were asked to evaluate whether STAN® guidelines and the RCT study protocol, with respect to correct and timely performance of an intervention, had been followed.[17,18,22] In case of violation, they had to indicate to what extent correct adherence to the guidelines might have prevented the (adverse) outcome.

Data analysis

For the present analysis, the criteria used to identify cases with adverse neonatal outcome in the index compared to the control group are presented in a descriptive way. The clinical course of cases with perinatal death was also described.

To test the differences in delivery and neonatal characteristics and the results obtained from observer evaluation between index and control group, the Fisher exact test was used for discrete variables. Student t or Mann-Whitney tests were used for continuous variables. Probability values below 0.05 were considered significant.

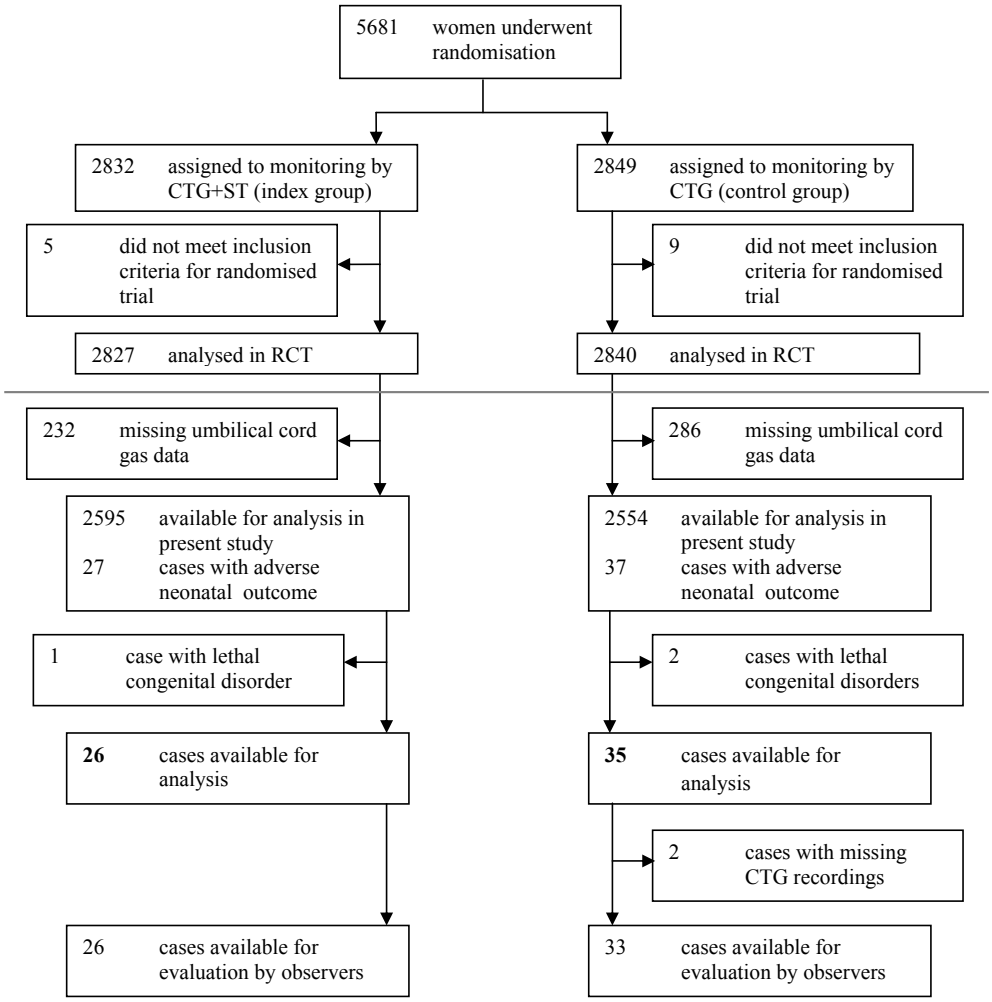
Since control recordings were only used to prevent observer bias, these results were not analysed and will therefore not be presented. Analyses were performed in SPSS for Windows version 16.0.

Results

Patients

5681 women were randomised (2832 in the index and 2849 in the control group). After randomisation 14 women were excluded because they did not meet the inclusion criteria. Main results of the RCT have been presented elsewhere.[18] For the present study, umbilical cord gas data of 518 newborns (9.1%) were missing and were, therefore, not included. Three cases with a lethal congenital disorder were also excluded, one in the index group and two in the control group. In total, 61 cases (1.1%) with an adverse neonatal outcome were identified (26 in the index and 35 in the control group) (Figure 1).

Figure 1 Flowchart: from women in RCT to cases with neonatal adverse outcome
For definition of adverse neonatal outcome see 'Adverse neonatal outcome' section of Methods.



Adverse neonatal outcome

Table 1 shows the distribution of the adverse neonatal outcome across both groups. The upper part of table 2 shows that in the index group the total number of operative deliveries was significantly higher (23 (88.5%)) than in the control group (20 (57.1%)) (p=0.01). According to the obstetric caregiver who guided delivery, in 18 (69.2%) versus 16 (45.7%) women there was a fetal reason to perform an operative delivery in index versus control group, respectively (p=0.08). FBS was performed in an almost equal number of cases in both groups (7 (26.9%) index versus 12 (34.3%) control, p=0.59).

Table 1 Distribution of neonatal adverse outcome across the index and control group of the RCT. Data are presented as n (%).

Criterium	RCT index group N=2595	RCT control group N=2554	Total N=5149
Cord-artery pH<7.05 en BDecf>12 mmol/L	17 (0.7)	23 (0.9)	40 (0.8)
Cord-artery pH<7.00	17 (0.7)	29 (1.1)	46 (0.9)
Perinatal death	2 (0.1)	0 (0.0)	2 (<0.1)
Hypoxic ischemic encephalopathy			
Moderate (Sarnat grade 2)	2 (0.1)	1 (<0.1)	3 (0.1)
Severe (Sarnat grade 3)	1 (<0.1)	0 (0.0)	1 (<0.1)
Total*	**26** (1.0)	**35** (1.4)	**61** (1.2)

* The total number of cases is calculated from a combination of several criteria.

The lower part of table 2 shows several neonatal characteristics across both groups with adverse outcome. In the index group the incidence of low Apgar scores was higher, especially for a one-minute score below four (10 (38.5%) versus 3 (8.6%), p=0.01). The total rate of neonatal admissions was almost equal in both groups (53.8% versus 62.9%, p=0.60), with in the index group fewer admissions to a medium care unit (7 (26.9%) versus 18 (51.4%), p=0.07) and slightly more admissions to a NICU (7 (26.9%) versus 4 (11.4), p=0.18). The median duration of admission to a NICU was longer in the index group, compared to the control group (3.0 (range 1 to 13) days versus 1.5 (range 0 to 9) day, p=0.25).

Table 2 Delivery and neonatal characteristics in cases with adverse neonatal outcome across the index and control group. Data are presented as n (%) or median (range).

Characteristic	RCT index group N=26	RCT control group N=35	P value
Delivery			
Mode of delivery			
Spontaneous vaginal delivery	3 (11.5)	15 (42.9)	- *
Operative vaginal delivery	15 (57.7)	14 (40.0)	0.14
Caesarean section	8 (30.8)	6 (17.1)	0.08
Total operative deliveries	23 (88.5)	20 (57.1)	0.01
Operative deliveries for fetal distress**	18 (69.2)	16 (45.7)	0.08
CTG	6 (33.3)	12 (75.0)	0.02
FBS	4 (22.2)	4 (25.0)	1.00
ST-event	8 (44.4)	NA	NA
Performance of FBS	7 (26.9)	12 (34.3)	0.59
Neonate			
Apgar score 1 min < 4	10 (38.5)	3 (8.6)	0.01
Apgar score 5 min < 7	9 (34.6)	5 (14.3)	0.07
Total neonatal admissions	14 (53.8)	22 (62.9)	0.60
Medium care unit	7 (26.9)	18 (51.4)	0.07
Intensive care unit	7 (26.9)	4 (11.4)	0.18
Duration (days)	3.0 (1-13)	1.5 (0-9)	0.25
Intubation	4 (57.1)	1 (25.0)	0.55

* Spontaneous vaginal deliveries were used as reference.
** Indication for operative delivery according to obstetric caregiver who guided delivery. NA = not applicable

Observer evaluation

In the control group two CTG recordings were missing, due to technical failures. In total, 59 cases were successfully evaluated by the observers (Figure 1), of which the results are shown in table 3, 4 and 5. An indication to intervene for suspected fetal distress according to the (STAN®) guidelines and RCT protocol was present in 23 of 26 cases (88.5%) in the index group, compared to 19 of 33 cases (57.6%) in the control group (p=0.01) (Table 3). In the index group, indications to intervene were mostly based on significant ST-events and in the control group on a (pre)terminal CTG (Table 3).

The median duration of the interval between indication to intervene and birth was comparable between groups. The number of cases in which this interval exceeded 20 minutes was 13 (50.0%) in the index group and 11 (33.3%) in the control group (p=0.29), with lower number of cases with an interval exceeding 30 or 40 minutes (Table 3).

In three and 15 cases in index and control group, respectively (11.5% versus 45.5%, p=0.01), observers concluded that additional performance of FBS would have been necessary, since the CTG had been abnormal for more than one hour. They also judged that guidelines and the RCT study protocol were violated in 11 (42.3%) and 13 (39.4%) cases of index and control group, respectively (p=0.82). In the index group, correct adherence to guidelines and the RCT study protocol would certainly, probably or possibly have led to better neonatal outcome in 2 (7.7%), 4 (15.4%) or 5 (19.2%) cases, respectively. In the control group, these numbers were 0 (0.0%), 4 (12.1%) or 9 (27.3%).

Table 3 Outcome of evaluation of cases with adverse neonatal outcome by observers across the index and control group. Data are presented as n (%) or median (range).

Observed item	RCT index group N=26	RCT control group N=33	P value
Presence of indication to intervene for SFD*	23 (88.5)	19 (57.6)	0.01
Significant ST-event	12 (52.2)	NA*	NA
(Pre)terminal CTG	9 (39.1)	14 (73.7)	NC
pH of FBS < 7.20	2 (8.7)	5 (26.3)	NC
Median time interval between indication to intervene and birth (min)	22 (1-322)	26 (9-345)	0.72
Time interval between indication to intervene and birth > 20 min	13 (50.0)	11 (33.3)	0.29
Significant ST-event	6 (46.2)	NA*	NA
(Pre)terminal CTG	5 (38.5)	9 (81.8)	NC
pH of FBS < 7.20	2 (15.4)	2 (18.2)	NC
Time interval between indication to intervene and birth > 30 min	9 (34.6)	9 (27.3)	0.58
Significant ST-event	5 (55.6)	NA*	NA
(Pre)terminal CTG	4 (44.4)	7 (77.8)	NC
pH of FBS < 7.20	0 (0.0)	2 (22.2)	NC
Time interval between indication to intervene and birth > 40 min	8 (30.8)	6 (18.2)	0.36
Significant ST-event	4 (50.0)	NA*	NA
(Pre)terminal CTG	4 (50.0)	5 (83.3)	NC
pH of FBS < 7.20	0 (0.0)	1 (16.7)	NC

*SFD = suspected fetal distress, NA = not applicable, NC = not calculated.

Perinatal death

There were two cases of perinatal death, both in the index group (Appendix B). In the first case (Table 4: case 20; Appendix B: case 1) the STAN® recording started with an abnormal CTG because of complicated variable decelerations, but pH of FBS was 7.33. Because of a persisting abnormal CTG, three additional scalp samples were performed, of which the last (114 minutes before birth) had a pH of 7.28. In spite of these normal FBS results there were three significant ST-events, of which the first arose 177 minutes before birth. After 90 minutes of active pushing a ventouse delivery for fetal distress failed. At that time the CTG was (pre)terminal and a caesarean section was performed. A baby with Apgar scores of 0, 0 and 3 after 1, 5 and 10 minutes respectively was born. Rupture of the uterus appeared to be the cause for distress. The baby was admitted to the NICU and died of severe perinatal asphyxia and neonatal encephalopathy (Sarnat grade 3).

In the second case (Table 4: case 16; Appendix B: case 2), immediately after applying a scalp electrode for internal fetal monitoring, the CTG showed a (pre)terminal trace, whereas on external CTG it had been normal before. At emergency caesarean delivery a severely asphyxiated infant with Apgar scores of 0 after 1, 5 and 10 minutes was born. Despite thorough investigation, no cause for this asphyxia could be identified.

Table 4 Detailed overview of clinical characteristics of cases with adverse neonatal outcome in the group monitored by CTG plus ST-analysis (N=26)

	Evaluation of STAN® recording by observers			Last FBS	Delivery	Neonatal outcome					
	CTG classification at start	Indication to intervene for SFD*	Time interval to birth (min)	pH / time interval to birth (min)	Mode / indication*	Gestational age (wks)	Apgar score 1'/5'	pHa / BDecf	Admission	HIE (Sarnat)	Perinatal death†
Case											
1	Normal	pH of FBS < 7.20	21	7.19 / 21	OVD / SFD	41	9 / 10	6.90 / 13	-	-	-
2	Normal	(Pre)terminal CTG	40	-	OVD / SFD	41	5 / 9	6.96 / 11	Medium care	-	-
3	Intermediary	Significant ST-event	20	-	CS / SFD	40	3 / 6	7.00 / 12	Intensive care	-	-
4 ‡	Normal	Significant ST-event	1	-	OVD / SFD	42	3 / 6	7.02 / 12	-	-	-
5	Normal	(Pre)terminal CTG	47	-	OVD / OI	42	7 / 8	6.96 / 11	-	-	-
6	Normal	(Pre)terminal CTG	14	-	OVD / SFD	38	7 / 9	7.01 / 16	Medium care	-	-
7	Normal	Significant ST-event	12	6.98 / 10	OVD / SFD	41	1 / 6	6.82 / 13	Medium care	-	-
8 ‡	Abnormal	(Pre)terminal CTG	87	7.24 / 67	CS / OI	41	1 / 7	7.00 / 14	Intensive care	-	-
9 ‡	Intermediary	(Pre)terminal CTG	117	-	OVD / OI	38	5 / 8	6.95 / 16	Intensive care	-	-
10	Normal	Significant ST-event	27	-	OVD / SFD	41	7 / 9	6.96 / 13	-	-	-
11	Normal	No indication	-	-	CS / SFD	40	6 / 9	6.92 / 13	-	-	-
12	Normal	Significant ST-event	7	-	SVD	41	9 / 10	7.03 / 12	-	-	-
13	Abnormal	Significant ST-event	6	-	OVD / SFD	39	3 / 6	6.90 / 15	Medium care	-	-
14	Abnormal	Significant ST-event	32	-	OVD / SFD	40	1 / 5	6.80 / 13	Medium care	-	-
15	Normal	Significant ST-event	49	7.02 / 19	OVD / SFD	39	9 / 8	6.97 / 15	Medium care	-	-
16	(Pre)terminal	(Pre)terminal CTG	16	-	CS / SFD	39	0 / 0	6.94 / 8	-	-	Yes
17	Normal	(Pre)terminal CTG	20	-	OVD / SFD	40	5 / 7	6.98 / 1	-	-	-
18	Normal	Significant ST-event	322	-	CS / SFD	40	5 / 7	7.10 / 7	Intensive care	S2	-
19	Normal	(Pre)terminal CTG	27	-	SVD	40	6 / 9	6.98 / 11	-	-	-
20	Abnormal	Significant ST-event	177	7.28 / 114	CS / SFD	40	0 / 0	6.96 / 15	Intensive care	S3	Yes
21	Normal	No indication	-	-	SVD	42	9 / 10	7.03 / 24	-	-	-
22	Normal	Significant ST-event	11	-	OVD / SFD	38	3 / 5	6.92 / 2	Intensive care	-	-
23	Normal	pH of FBS < 7.20	27	7.09 / 27	OVD / SFD	42	1 / 1	7.04 / 11	Intensive care	S2	-
24	Normal	(Pre)terminal CTG§	10	-	OVD / OI	42	4 / 10	6.99 / 8	-	-	-
25	Normal	Significant ST-event	92	-	CS / SFD	41	6 / 9	7.00 / 14	-	-	-
26	Intermediary	No indication	-	7.32 / 680	CS / OI	41	4 / 9	6.93 / 18	Medium care	-	-

Discussion

The overall RCT analysis showed that the incidence of (metabolic) acidosis was 30 to 40% lower in the ST-analysis group (index group), depending on the definition of acidosis. Also in the present analysis, adverse neonatal outcome was lower in the index group. Moreover, in the index group significantly more operative deliveries were carried out, mostly because of fetal distress, indicating that impaired fetal condition had been identified more frequently in the index group than in the conventionally monitored group (control group).

If guidelines and RCT protocol would have been correctly followed, monitoring by ST-analysis would have detected almost 90% of cases with adverse neonatal outcome, compared to only 60% of cases monitored by CTG only. Monitoring by ST-analysis is therefore more specific and comprehensive regarding the aim to detect and deliver compromised fetuses, than monitoring by CTG only.

However, not all cases of adverse outcome could have been prevented, since also with adequate following of guidelines in many cases indication for intervention occurred less than 20 minutes before delivery. In these cases there was hardly time to intervene earlier. Including only cases with indications to intervene that occurred more than 20 minutes before birth, to allow time for proper intervention to deliver the baby, the detection rate of monitoring by ST-analysis decreased to 50%, compared to 33% in the group monitored by CTG only. Restriction to indications occurring more than 40 minutes before delivery reduced these percentages to 31 and 18, respectively. In the latter groups, earlier intervention almost certainly would have led to a more favourable neonatal outcome.

It is known that classification and interpretation of the CTG is difficult with large inter-observer variation.[27] For a substantial part, these problems may be solved by strict adherence to guidelines regarding classification and interpretation of the CTG, obtaining additional fetal information and subsequent recommendations for obstetric interventions. This is supported by our finding that in the index group, in which STAN® clinical guidelines were used, the detection rate of distressed fetuses was higher. Obstetricians may have become more alert to CTG changes, since these were continuously accompanied by information on the ST-waveform of the fetal ECG, which alerts in case of events by reporting them in the 'ST-log'. Therefore, in women monitored by ST-analysis, CTG abnormalities may be neglected less easily compared to monitoring by CTG only.

In the index group indications to intervene were based on significant ST-events in only 50% of cases. In almost 40% of cases a (pre)terminal CTG trace led to an indication to intervene. Although a (pre)terminal CTG is incorporated in the STAN® clinical guidelines as an indication to intervene, it makes us wonder why these fetuses were not identified earlier by significant ST-changes, particularly since six out of nine cases had a normal CTG at the start of a STAN® recording. However, in three cases (Table 4: cases 2, 5 and 24) there had been ST-events, not considered significant by the observers. In one case (Table 4: case 17) there was a ST-event 14 minutes after start of the (pre)terminal CTG and in another case (Table 4:

Table 5 Detailed overview of clinical characteristics of cases with adverse neonatal outcome in the group monitored by CTG only (N=35)

	Evaluation of CTG recording by observers			Last FBS	Delivery	Neonatal outcome					
	CTG classification at start	Indication to intervene for SFD*	Time interval to birth (min)	pH / time interval to birth (min)	Mode / indication*	Gestational age (wks)	Apgar score 1'/5'	pHa / BDecf	Admission	HIE (Sarnat)	Perinatal death†
Case											
27	Normal	No indication	-	-	SVD	40	9 / 10	6.99 / 17	-	-	-
28	Normal	(Pre)terminal CTG	26	-	SVD	41	6 / 8	6.99 / 15	Intensive care	-	-
29 ‡	Normal	(Pre)terminal CTG	109	7.31 / 139	SVD	39	6 / 8	7.02 / 13	-	-	-
30	Normal	No indication	-	-	OVD / SFD	42	9 / 9	6.99 / 15	-	-	-
31 ‡	Intermediary	No indication	-	-	SVD	38	6 / 7	6.99 / 10	Medium care	-	-
32	Normal	(Pre)terminal CTG	32	7.22 / 27	OVD / SFD	39	7 / 9	6.94 / 13	-	-	-
33	Abnormal	(Pre)terminal CTG	13	-	OVD / SFD	39	5 / 7	6.97 / 14	Medium care	-	-
34**	-	-	-	7.17 / 22	CS / SFD	42	2 / 6	6.98 / 10	Medium care	-	-
35	Normal	(Pre)terminal CTG	17	-	OVD / SFD	37	6 / 9	6.95 / 10	Medium care	-	-
36	Normal	No indication	-	-	OVD / SFD	42	6 / 6	6.95 / 12	Medium care	-	-
37	Normal	(Pre)terminal CTG	64	-	SVD	40	5 / 7	6.93 / 10	-	-	-
38 ‡	Abnormal	(Pre)terminal CTG	345	7.19 / 23	OVD /OI	37	9 / 10	6.94 / 14	Medium care	-	-
39	Normal	No indication	-	-	SVD	41	9 / 9	6.98 / 9	Medium care	-	-
40	Normal	No indication	-	7.30 / 75	CS / OI	42	7 / 8	6.94 / 15	Medium care	-	-
41	Normal	(Pre)terminal CTG	17	-	OVD / SFD	39	6 / 7	6.97 / 15	Medium care	-	-
42 ‡	Abnormal	(Pre)terminal CTG	61	-	CS / SFD	39	7 / 9	6.96 / 12	Medium care	-	-
43	Normal	pH of FBS < 7.20	48	7.10 / 48	CS / SFD	42	6 / 9	6.95 / 15	Medium care	-	-
44 ‡	Normal	No indication	-	-	CS / OI	42	6 / 9	7.00 / 13	-	-	-
45 ‡	Abnormal	(Pre)terminal CTG	37	-	SVD	42	7 / 9	6.98 / 13	Intensive care	-	-
46**	-	-	-	7.07 / 9	OVD / SFD	40	4 / 7	6.99 / 11	Intensive care	-	-
47	Normal	(Pre)terminal CTG	11	-	SVD	42	9 / 10	7.02 / 13	-	-	-
48 ‡	Abnormal	No indication	-	-	SVD	41	7 / 9	6.98 / 14	Medium care	-	-
49 ‡	Normal	No indication	-	-	SVD	39	3 / 7	6.99 / 11	Medium care	-	-
50 ‡	Intermediary	(Pre)terminal CTG	22	-	OVD / SFD	39	9 / 9	6.90 / 19	-	-	-
51	Abnormal	pH of FBS < 7.20	17	7.15 / 17	OVD / SFD	39	8 / 10	7.18 / 7	Intensive care	S2	-
52 ‡	Normal	No indication	-	-	SVD	42	6 / 8	6.99 / 14	Medium care	-	-***
53	Normal	pH of FBS < 7.20	15	7.13 / 15	OVD / SFD	40	9 / 10	6.98 / 15	-	-	-
54 ‡	Normal	pH of FBS < 7.20	13	7.13 / 13	OVD / SFD	42	5 / 8	6.97 / 15	Medium care	-	-
55 ‡	Normal	(Pre)terminal CTG	80	-	SVD	42	6 / 6	6.99 / 13	-	-	-

Table 5 Continued

	Evaluation of CTG recording by observers			Last FBS	Delivery	Neonatal outcome					
	CTG classification at start	Indication to intervene for SFD*	Time interval to birth (min)	pH / time interval to birth (min)	Mode / indication*	Gestational age (wks)	Apgar score 1'/5'	pHa / BDecf	Admission	HIE (Sarnat)	Perinatal death†
56	Normal	(Pre)terminal CTG	9	-	SVD	40	4 / 9	6.98 / 10	-	-	-
57 ‡	Normal	No indication	-	-	SVD	41	7 / 9	6.92 / 13	Medium care	-	-
58 ‡	Normal	No indication	-	-	OVD / SFD	40	8 / 9	6.99 / 15	-	-	-
59	Normal	No indication	-	-	CS / OI	42	8 / 10	7.04 / 13	-	-	-
60 ‡	Normal	No indication	-	7.33 / 78	SVD	42	3 / 6	6.94 / 15	Medium care	-	-
61	Normal	pH of FBS < 7.20	21	7.02 / 21	OVD / SFD	41	5 / 6	7.01 / 13	Medium care	-	-

* SVD = spontaneous vaginal delivery; OVD = operative vaginal delivery; CS = caesarean section; SFD = suspected fetal distress; OI = other indication
† A detailed description of clinical course of perinatal death cases, see Results section.
** CTG recordings were not observed due to technical failures.
‡ Observers agreed that there had been an indication to perform FBS (more frequently or in an earlier stage) because of an abnormal CTG > 60 minutes.
*** Case with congenital disorder: small atrial septum and muscular septum heart defect, persistent ductus arteriosus which closed spontaneously on the third day.
§ Poor signal quality.

case 16) the CTG was (pre)terminal directly after connection to the STAN® monitor, which was acted on immediately. These cases indicate that not all (pre)terminal CTG patterns are preceded by significant ST-events, as also has been described earlier.[20,21] Adequate identification of (pre)terminal CTG traces therefore remains of utmost importance. Computerized quantification of fetal heart rate variability may offer a solution.[28] More importantly, repeated training and consequent implementation of the STAN® method in clinical practice remains necessary.

To appreciate the present results, two issues need to be addressed. First, due to the lack of strict guidelines in patients treated in the control group, intensity of assessment of the fetal condition may have varied. In the control group there were no conditions as to timing of performance of FBS, unlike the strict protocol that was used in the index group. The need for guidelines is supported by the finding that although FBS was performed in more than 20% of women in the total control group of the trial, only two of 33 adverse outcome cases (6.1%) were timely detected by a scalp pH below 7.20. Moreover, in the majority of adverse outcome cases FBS was not performed at all. In 45% observers agreed that additional fetal information should have been obtained by FBS, because of persisting abnormal CTG. Timely FBS may have led to earlier intervention with better neonatal outcome.

Second, in the present analysis the three observers were not blinded for allocated randomisation outcome, since STAN® and CTG recordings were stored and presented by different software programs, thereby revealing type of monitoring. These 'open' observations may have led to a certain extent of observer bias. Blinding for knowledge of outcome, to prevent hindsight bias, was achieved by presenting a mixture of recordings of cases with both eventful and uneventful outcome to the observers.[29]

In summary, our results indicate that monitoring by ST-analysis is more specific and comprehensive regarding the aim to detect and deliver compromised fetuses, than monitoring by CTG only. Strict adherence to STAN® guidelines, especially with respect to correct classification of the CTG, may increase the detection rate even further. However, in 50% of cases with adverse outcome monitored by ST-analysis there were no clear signs of fetal distress more than 20 minutes before birth, indicating that these could not have been prevented.

Acknowledgements

This study was subsidized by ZonMW, the Dutch Organisation for Health Research and Development (Grant number: 945-06-557).

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Submitted

8

Fetal blood sampling in addition to ST-analysis of the fetal electrocardiogram: should we adjust clinical guidelines?

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Abstract

Objective

In 2007 consensus based recommendations were added to ST-analysis (STAN®) guidelines for intrapartum fetal monitoring, in which situations for complementary fetal information were formulated. The aim of our study was to evaluate these recommendations by assessing the need for fetal blood sampling (FBS) and FBS results in 2827 women monitored by ST-analysis of the fetal electrocardiogram (ECG).

Methods

Data were used of a multicenter randomised trial among 5681 women with a high-risk singleton pregnancy with a fetus in cephalic position beyond 36 weeks of gestation allocated to monitoring by cardiotocography (CTG) with or without ST-analysis of the fetal ECG.

Secondary analysis was performed on 2827 deliveries monitored by CTG plus ST-analysis in which at least one fetal blood sample was performed. Three observers assessed STAN® recordings, to examine whether FBS was performed according to the trial protocol and how pH results were related to indications and to ST-waveform analysis.

Results

Of 301 deliveries, 224 STAN® recordings were complete for analysis. A total of 296 scalp samples was performed. For 112 of 172 (65.1%) samples performed according to the trial protocol, the reason was an abnormal CTG beyond 60 minutes without ST-events. In 10 (8.9%) of these cases, fetal acidosis (pH<7.20) was present. 18 (10.5%) samples were performed because of an abnormal CTG at start, nine (5.2%) because of an intermediary CTG at start and 33 (19.2%) because of poor ECG signal quality. Two, none and four samples revealed fetal acidosis, respectively. 124 samples (41.9%) were not performed according to the trial protocol, of which 10 (8.1%) samples indicated fetal acidosis. In one of these cases there had been no ST-events.

Conclusion

The consensus based recommendation in the STAN® guidelines to additionally check fetal condition by FBS in case of an abnormal CTG of more than 60 minutes without ST-changes, is effective for timely identification of fetal acidosis. Consequent adherence to guidelines may further decrease the necessity for FBS in addition to ST-analysis of the fetal ECG.

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, monitoring by CTG has shown little or no benefit for neonatal outcome 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 requires expertise, is invasive, has to be repeated when CTG abnormalities persist and still does not guarantee prevention of asphyxia.[9]

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 labour. Several studies have identified changes in the ST-segment and T-wave of the fetal ECG in response to fetal hypoxia.[10-14] These changes are interpreted together with the CTG, according to the STAN® clinical guidelines.

Until now, four randomised trials have been performed to compare intrapartum fetal monitoring by CTG plus ST-analysis of the fetal ECG with CTG only.[15-18] The two largest 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.[15,16] 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.[17,18] Recently, we found in a large Dutch randomised trial among 5681 women 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,[19] reduced the number of newborns with (metabolic) acidosis, with a 50% lower incidence of FBS.[20]

The most important issue in intrapartum fetal monitoring concerns false-negative test results, leading to the birth of an infant with adverse outcome. Even with use of the recently introduced STAN® technique, such cases may still occur.[21,22] Following these reports, in January 2007 European experts on ST-waveform analysis formulated consensus based guidelines 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.[23]

As the present STAN® guidelines are consensus rather than evidence based, we performed a secondary analysis including all cases monitored by ST-analysis of the fetal ECG in the previously mentioned Dutch trial, in which at least one fetal blood sample had been performed.[20] The aim was to evaluate the most recent STAN® clinical guidelines, with specific focus on recommendations for situations that may require FBS in addition to ST-analysis.[23]

Methods

Patients and Measurements

A multicentre randomised clinical trial, which design and main results have been published elsewhere,[19,20] among labouring women with a high-risk singleton pregnancy in cephalic position beyond 36 weeks of gestation was performed between January 2006 and July 2008. In brief, the primary aim was to evaluate the effectiveness of intrapartum fetal monitoring by CTG plus ST-analysis of the fetal ECG, using a strict protocol for performance of FBS. Participants were randomly assigned to monitoring by CTG combined with ST-analysis of the fetal ECG (index group) or CTG without ST-analysis (control group).

5681 women were randomised (2832 in the index and 2849 in the control group). After randomisation 14 women were excluded (five in the index and nine in the control group), because they did not meet the inclusion criteria. The present study focussed on the index group of the trial (N=2827).

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). Clinical management was guided by the STAN® clinical guidelines (Appendix A). 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 during first stage without ST-events; 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.[23] Immediate delivery was recommended if the pH of FBS was 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 follow the STAN® clinical guidelines.

Analysis of cases with 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 fetal blood sample was performed. They examined whether or not additional FBS was performed according to the RCT 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. The observers were only

provided with information on the timing of FBS, without knowledge of its result, other clinical parameters obtained during labour, and of the neonatal outcome.
For each fetal blood sample the following items had to be scored: 1) classification of the CTG as normal, intermediary, abnormal or (pre)terminal in the 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 protocolised situations.

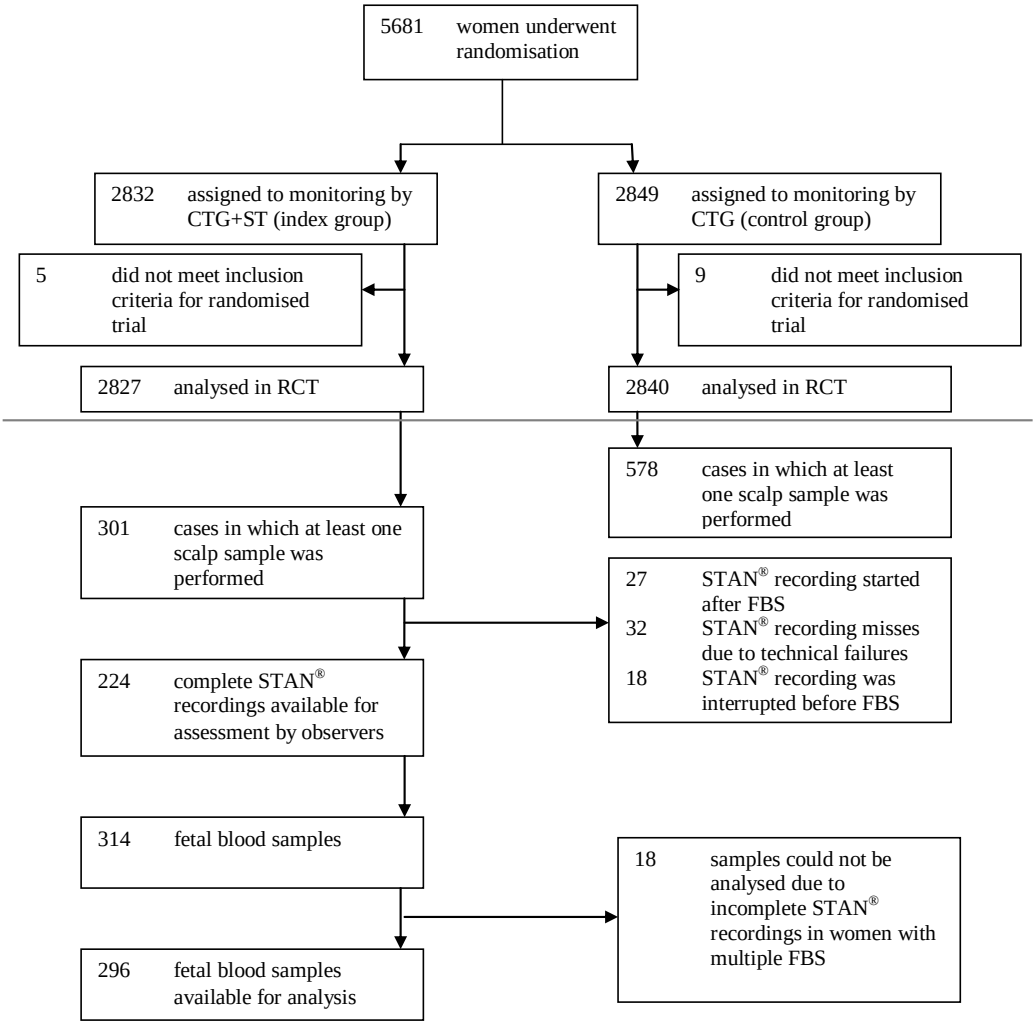
Evaluation of assessment by observers
For the fetal blood samples performed according to the RCT protocol, the relation between pH result measured by FBS and the reason to perform FBS was described. In the samples that were not performed according to the RCT protocol, the relation between pH results 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 RCT protocol' if at least one of the FBS was not performed according to the RCT protocol. This classification on patient level instead of FBS level, allowed description of observer results in relation to neonatal outcome. For the latter we defined metabolic acidosis as an umbilical cord-artery pH below 7.05 and base deficit in extracellular fluid (BDecf) above 12 mmol/L.

Data analysis
All results are presented in a descriptive way. The software used for statistical analysis was SPSS version 15.0.1 for Windows.

Results

Patients
In the index group of the trial (N=2827), at least one fetal blood sample was performed during deliveries of 301 (10.6%) women, of which STAN® recordings for assessment by the observers were complete for 224 (74.4%). 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).
In the 224 available cases, 314 fetal blood samples were performed. Due to partly incomplete STAN® recordings in women with multiple FBS, 18 (5.7%) samples could not be analysed, because ST-information at the moment of sampling was missing. In total 296 fetal blood samples were available for analysis. The study flowchart is presented in Figure 1.

Figure 1 Flowchart



Fetal blood sampling

According to the observers, 172 (58.1%) fetal blood samples were performed according to the RCT protocol; the remaining 124 (41.9%) samples were not performed according to protocol. Failed FBS procedures with missing pH results occurred in 5.1% (Table 1).

Table 1 FBS in deliveries monitored by ST-analysis of the fetal ECG related to the RCT protocol. Data are presented as mean ± SD or n (%).

	Total	**According to RCT protocol**	**Not according to RCT protocol**
Number of FBS	296 (100)	172 (58.1)	124 (41.9)
FBS result			
pH > 7.25	207 (69.9)	113 (65.7)	94 (75.8)
pH 7.20-7.25	48 (16.2)	33 (19.2)	15 (12.1)
pH < 7.20	26 (8.8)	16 (9.3)	10 (8.1)
Missing pH	15 (5.1)	10 (5.8)	5 (4.0)

FBS according to RCT protocol

In 16 of the 172 fetal blood samples performed according to the RCT protocol (9.3%), fetal acidosis was present (Table 2). This occurred in 10 of 112 (8.9%) 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 4 of 33 (12.1%) samples because of poor ECG signal quality combined with an abnormal CTG (Tables 2 and 3).

At birth, three of these infants (2.4%) had a metabolic acidosis (Table 3 and 4). In one of these cases (Table 4, case 1) 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 CTG abnormalities had lasted for 377 or 112 minutes (Table 4, case 3 and 6) before FBS was performed, making these cases more difficult to interpret.

Table 2 FBS in deliveries monitored by ST-analysis of the fetal ECG related to reasons according to the RCT protocol. Data are presented as mean ± SD or n (%).

		Reason to perform FBS according to RCT protocol			
FBS	**Total**	**Abnormal CTG at start**	**Intermediary CTG at start**	**Abnormal CTG>60 min without ST-event**	**Poor ECG signal quality**
Number	172 (100)	18 (10.5)	9 (5.2)	112 (65.1)	33 (19.2)
FBS result					
pH > 7.25	113 (65.7)	9 (50.0)	9 (100)	70 (62.5)	25 (75.8)
pH 7.20-7.25	33 (19.2)	5 (27.8)	0 (0.0)	24 (21.4)	4 (12.1)
pH < 7.20	16 (9.3)	2 (11.1)	0 (0.0)	10 (8.9)	4 (12.1)
Missing pH	10 (5.8)	2 (11.1)	0 (0.0)	8 (7.2)	0 (0.0)

Table 3 Overview of delivery and neonatal characteristics of cases with fetal acidosis obtained at FBS (N=26)

	Observer evaluation		ST-waveform	Delivery	Outcome			
	FBS with fetal acidosis				Neonatal outcome			
Case	Reason	pH / time interval to birth (min)	Indication to intervene	Mode / indication*	GA (wks)	Apgar score 1'/5'	pHa / BDecf	Admission/HIE**/ Perinatal death
1	Abnormal CTG>60min without ST-event	7.14 / 39	NA	CS / SFD	41	10/10	7.08 / 8	-
2	Abnormal CTG>60min without ST-event	7.17 / 23	NA	OVD / SFD	40	9/10	7.07 / 10	-
3	Abnormal CTG>60min without ST-event	7.18 / 109	NA	CS / SFD	42	9/10	7.23 / 6	-
4	Abnormal CTG>60min without ST-event	7.15 / 8	NA	SVD	41	7/8	7.07 / 11	-
5	Abnormal CTG>60min without ST-event	7.12 / 67	NA	CS / SFD	37	7/8	7.19 / 10	-
6	Abnormal CTG>60min without ST-event	7.09 / 42	NA	OVD / SFD	42	1/1	7.04 / 11	Intensive care/S2
7	Abnormal CTG>60min without ST-event	7.19 / 43	NA	CS / OI	40	9/10	7.21 / 1	Medium care
8	Abnormal CTG>60min without ST-event	7.15 / 53	NA	CS / SFD	40	9/10	7.17 / 1	-
9	Abnormal CTG>60min without ST-event	7.08 / 5	NA	SVD	42	9/9	7.11 / 7	Medium care
10	Abnormal CTG>60min without ST-event	7.16 / 15	NA	OVD / SFD	37	6/7	7.07 / 5	Medium care
11	Poor ECG signal quality	7.17 / 36	Poor ECG signal quality	SVD	39	8/9	7.20 / 5	-
12	Poor ECG signal quality	7.19 / 21	Poor ECG signal quality	OVD / SFD	41	9/10	6.90 / 13	-
13	Poor ECG signal quality	7.17 / 18	Poor ECG signal quality	SVD	39	9/10	7.12 / 4	-
14	Poor ECG signal quality	7.15 / 24	Poor ECG signal quality	CS / SFD	41	9/10	7.07 / 10	-
15	Abnormal CTG at start recording	7.18 / 34	No ST-events	CS / SFD	42	4/9	7.22 / 5	-
16	Abnormal CTG at start recording	7.16 / 50	No ST-events	OVD / SFD	41	6/8	7.10 / -	Medium care
17	Not according to RCT protocol	7.19 / 11	Significant ST-event before FBS	OVD / SFD	42	9/10	7.22 / 6	-
18	Not according to RCT protocol	7.13 / 117	Significant ST-event after FBS	CS / SFD	38	6/8	7.08 / 15	Medium care
19	Not according to RCT protocol	6.98 / 10	Significant ST-event before FBS	OVD / SFD	41	1/6	6.82 / 13	Medium care
20	Not according to RCT protocol	7.18 / 16	Significant ST-event before FBS	OVD / SFD	40	9/10	7.20 / 10	-
21	Not according to RCT protocol	7.18 / 100	No ST-events	CS / SFD	38	9/10	7.11 / 8	-
22	Not according to RCT protocol	7.16 / 10	Significant ST-event before FBS	SVD / SFD	41	6/10	7.17/ 9	-
23	Not according to RCT protocol	7.02 / 19	Significant ST-event before FBS	OVD / SFD	39	9/8	6.97 / 15	Medium care
24	Not according to RCT protocol	7.09 / 97	Significant ST-event before FBS	CS / SFD	42	9/10	7.16 / 8	-
25	Not according to RCT protocol	7.09 / 9	Significant ST-event before FBS	OVD / SFD	40	9/9	7.18 / 5	-
26	Not according to RCT protocol	7.11 / 26	Significant ST-event before FBS	OVD / SFD	38	8/10	7.03 / 10	-

* SVD = spontaneous vaginal delivery; OVD = operative vaginal delivery; CS = caesarean section; SFD = suspected fetal distress; OI = other indication

** S2 = moderate HIE, Sarnat grade 2; S3 = severe HIE, Sarnat grade 3; NA = not applicable

Table 4 Overview of delivery and neonatal characteristics of cases with neonatal metabolic acidosis (N=6)

	Observer evaluation				Outcome			
	Last FBS			ST-waveform	Delivery	Neonatal outcome			
Case	Reason	Duration abnormal CTG before FBS (min)	pH / time interval to birth (min)	ST-events / comment	Mode / indication*	GA (wks)	Apgar score 1'/5'	pHa / BDecf	Admission / HIE** / Perinatal death
1	Poor ECG signal quality	36	7.19 / 21	Poor ECG signal quality	OVD / SFD	41	9/10	6.90 / 13	-
2	Not according to RCT protocol	42	6.98 / 10	Significant ST-event 12min before birth	OVD / SFD	41	1/6	6.82 / 13	Medium care
3	Abnormal CTG>60min without ST-event	377	7.24 / 67	(Pre)terminal CTG 87min before birth	CS / OI	41	1/7	7.00 / 14	Intensive care
4	Not according to RCT protocol	60	7.02 / 19	Significant ST-event 49min before birth	OVD / SFD	39	9/8	6.97 / 15	Medium care
5	Not according to RCT protocol	80	7.28 / 114	Significant ST-event 177min before birth	CS / SFD	40	0/0	6.96 / 15	Intensive care / S3 / death
6	Abnormal CTG>60min without ST-event	112	7.32 / 680	No significant ST-event, abnormal CTG<60min	CS / OI	41	4/9	6.93 / 18	Medium care

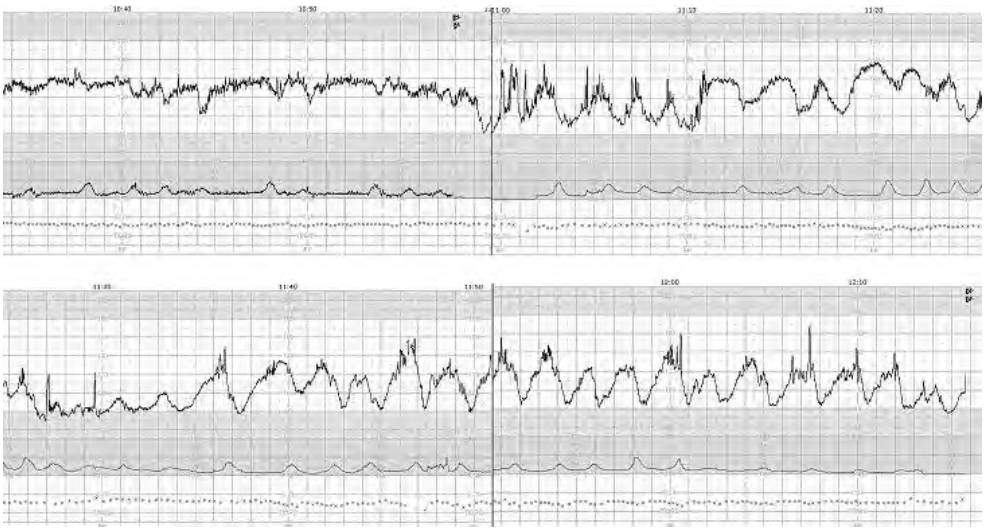
* SVD = spontaneous vaginal delivery; OVD = operative vaginal delivery; CS = caesarean section; SFD = suspected fetal distress; OI = other indication
** S2 = moderate HIE, Sarnat grade 2; S3 = severe HIE, Sarnat grade 3

FBS not according to RCT protocol

In 10 of the 124 scalp samples not performed according to the RCT protocol, fetal acidosis was found (8.1%) (Table 3). In 8 of these cases, intervention based on a significant ST-event was indicated after the decision to perform FBS, but before this sample had actually been taken. In the remaining two cases fetal acidosis was indicated without a significant ST-event before the moment of FBS. In both cases, an abnormal CTG for less than 60 minutes with rapid deterioration of fetal heart rate variability had been present. In one of these cases, a significant ST-event occurred 25 minutes after FBS (Table 3, case 18) during first stage of labour. In the other case, there were no ST-events (Table 3, case 21) and part of that recording during second stage of labour is shown in Figure 2. For both cases neonatal outcome was favourable.

In this group, metabolic acidosis was found in 3 infants at birth (3.0%). In all three cases earlier intervention was recommended based on significant ST-events (Table 4, case 2, 4 and 5). In one of these cases multiple FBS was performed, of which the results were contradictory to ST-waveform analysis. The newborn died of severe asphyxia and encephalopathy (Table 4, case 5).

Figure 2 Recording of a case with rapid deterioration of the fetal heart rate variability without ST-events. Additional clinical information on this case is given in Table 3 (case 21).



Discussion

This study is the first to provide more evidence based recommendations with respect to intrapartum situations that require additional assessments in patients monitored by ST-

analysis of the fetal ECG. Our results largely support the recently adjusted STAN® clinical guidelines.[23]

First, the addition of the category 'abnormal CTG for more than 60 minutes with normal ST' has proven to be valuable, since 10 cases with fetal acidosis were detected this way. However, 62.5% of scalp samples performed because of an abnormal CTG trace for more than 60 minutes without ST-events, showed a pH above 7.25. Because of this large number of non-hypoxic FBS results, one may wonder whether in case 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, assuming no ST-events to have appeared in the additional 30 minutes.

Second, the results of our study showed that in the group of FBS that was performed not according to the RCT protocol, in only 8% fetal acidosis was present, of which 9 out of 10 cases were detected by significant ST-events before or shortly after FBS was taken. 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 guidelines do mention rapid deterioration of fetal heart rate pattern in combination with an abnormal CTG and normal ST as an indication to check for non-deteriorating fetal state, heart rate variability is not mentioned. 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.

Finally, in our trial protocol the category 'intermediary CTG at start 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® guidelines has not been proven to be useful in detecting fetal hypoxia. Although based on only nine cases, we do not advice addition of this category to the STAN® clinical guidelines as a recommended situation for assessment of fetal well-being.

Overall, in 10.6% of cases in the index group of our large randomised trial FBS was performed.[20] Given the fact that in more than 40% FBS was not performed according to the STAN® guidelines, with only one false-negative case, we speculate that this incidence may further be reduced when STAN® clinical guidelines are followed more strictly.

Of all 224 cases with FBS analysed in this study, only six had metabolic acidosis at birth, of which four 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.[24,25] 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 labour.[25]

There are some limitations of this study that need to be addressed. First, 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,[26] 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 incomparable. 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. Only three of the 26 cases with a scalp pH below 7.20 had metabolic acidosis at birth, which indicates the arbitrary nature of this cut-off point. Moreover, two of these cases with metabolic acidosis were identified by significant ST-events before FBS was performed, which illustrates the poor correlation between pH and ST-waveform analysis.
Furthermore, we only analysed cases in which FBS was performed. It is therefore unknown to what extent guidelines 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 guidelines are followed more strictly, this cannot be thoroughly concluded without analysing all deliveries in which no FBS was performed.
In conclusion, in our study the consensus based recommendation in the STAN® guidelines to additionally check fetal condition by FBS in case of an abnormal CTG of more than 60 minutes without ST-changes, has been effective for early identification of fetal acidosis. However, given the high number of non-hypoxic FBS results, extending the duration of abnormal CTG from 60 to 90 minutes may be considered. Consequent adherence to the STAN® guidelines may further decrease the necessity for FBS in addition to ST-analysis of the fetal ECG.

Acknowledgements

This study was subsidized by ZonMW, the Dutch Organisation for Health Research and Development (Grant number: 945-06-557).

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Submitted

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Cost-effectiveness of cardiotocography plus ST-analysis of the fetal electrocardiogram compared to cardiotocography only

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Abstract

Objectives

To assess the cost-effectiveness of addition of ST-analysis of the fetal electrocardiogram (ECG) (STAN®) to cardiotocography (CTG) for fetal surveillance during labour compared to CTG only.

Design

Cost-effectiveness analysis based on a large randomised clinical trial on ST- analysis of the fetal ECG.

Participants

Labouring women with a singleton high-risk pregnancy, a fetus in cephalic presentation, a gestational age above 36 weeks and an indication for internal electronic fetal monitoring were randomised to either fetal monitoring with CTG+ST-analysis of the fetal ECG or CTG only. Fetal blood sampling was allowed in both groups under strict indications.

Outcome measures

Primary medical outcome was the proportion of children with metabolic acidosis defined as umbilical cord-artery pH below 7.05 combined with a base deficit calculated in the extracellular fluid compartment above 12 mmol/L. Direct medical costs were estimated from start of labour to hospital discharge from a health-care provider perspective.

Results

The incidence of metabolic acidosis was 0.7% in the ST-analysis group and 1.1% in the CTG only group. Until child birth CTG+ST-analysis mean costs per patient were not significantly higher as compared to CTG only. Per delivery, the mean costs per patient of CTG plus ST-analysis (n=2827) was €1.345 versus €1.316 for CTG only (n=2840), with a mean difference of €29 (95% CI: - €9 to €77) until child birth. The incremental costs of ST-analysis to prevent one case of metabolic acidosis were €7.250, with a number needed to treat (NNT) of 250.

Conclusions

The additional costs of monitoring by ST-analysis of the fetal ECG are very limited when compared to monitoring by CTG only and very low compared to the total costs of delivery. As it substantially reduces the incidence of metabolic acidosis, monitoring by STAN® appears to be a cost-effective strategy.

Introduction

In recent years a new method for intrapartum fetal monitoring was introduced, in which cardiotocography (CTG) is combined with ST-analysis of the fetal electrocardiogram (ECG; STAN®). This technique detects changes in the ST-segment of the fetal ECG, which are related to metabolic acidosis, and are interpreted together with the CTG.[1-3]

Until now, four randomised trials have been performed to compare intrapartum fetal monitoring by CTG plus ST-analysis with CTG only.[4-8] The two largest studies have shown that monitoring by CTG + ST-analysis decreases the incidence of metabolic acidosis, the number of instrumental deliveries for fetal distress, and the proportion of infants born with encephalopathy, as compared to CTG only.[4-6] However, in both studies fetal blood sampling (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.[7,8]

In view of this controversy, we recently performed a large multicentre randomised clinical trial to evaluate the effectiveness of monitoring by CTG plus ST-analysis compared to CTG only, using a strict protocol for the performance of FBS.[9] The results of this Dutch trial demonstrated that addition of ST-analysis of the fetal ECG to surveillance with CTG during labour reduced the number of newborns with (metabolic) acidosis, without an effect on Apgar scores, neonatal admissions or operative deliveries. These results were achieved with a significantly lower incidence of FBS in the group monitored by CTG plus ST-analysis.[10]

As the use of ST-analysis thus provides an effective strategy to prevent acidosis, it is important to assess the economic consequences, e.g. increase in monitoring costs, of its introduction. Recently, the cost-utility of CTG plus ST-analysis versus CTG only were compared by integrating lifelong outcomes and costs.[11] The authors concluded that ST-analysis resulted in a gain of 0.005 quality adjusted life years (QALYs) and a reduction in costs of €56 per patient, thus ST-analysis being the dominating strategy over CTG only. This model based study using QALYs as health outcome, demonstrated that CTG plus ST-analysis is a cost-effective strategy, as short-term costs associated with ST-analysis are offset by long-term savings due to prevented cases of cerebral palsy. However, the input parameters were derived from the literature, instead of being primarily based on observed clinical trial results.

The here presented study aims to report the (short-term) cost-effectiveness analysis that was performed alongside the Dutch ST-analysis trial.[10] This analysis was primarily based on the observed trial data, of which metabolic acidosis was used as the measure of effectiveness.

Methods

Trial design

Full details of the ST-analysis trial have been reported elsewhere,[9,10] and has been registered in the clinical trial register (number ISRCTN95732366).

In short, the study was a multicentre randomised clinical trial in obstetric departments of three academic and six general hospitals in the Netherlands, conducted between January 2006 and July 2008. Labouring women aged 18 years or older with a singleton high-risk pregnancy, a fetus in cephalic presentation, a gestational age above 36 weeks and an indication for internal electronic fetal monitoring were randomly allocated by block randomisation to either monitoring by CTG plus ST-analysis of the fetal ECG (index group) or CTG only (control group).

In women assigned to 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). This scalp electrode allowed both for registration of the CTG and ST-analysis of the fetal ECG. Performance of FBS was restricted to three situations.[9,10] Further clinical management was supported by the computerized automatic ST-interval assessment, the ST-log and the STAN® clinical guidelines (Appendix A).[9] All patients in the index group were monitored clinically until hospital discharge.

In women assigned to the control group, a scalp electrode was applied to the fetal head and connected to a conventional fetal heart rate monitor. The CTG was classified and interpreted according to the STAN® clinical guidelines as normal, intermediary, abnormal or (pre)terminal. FBS was performed on indication by the obstetric caregiver in case of an intermediary or abnormal CTG trace. Clinical decisions were based on CTG and/or FBS results.

The primary outcome of this trial was the incidence of metabolic acidosis, defined as an umbilical cord-artery pH below 7.05 and a base deficit calculated in the extracellular fluid compartment (BDecf) above 12 mmol/L.

Secondary outcomes were the incidence of metabolic acidosis according to pH and the base deficit calculated in blood (BDblood), the number of Apgar scores below four and seven at one and five minutes respectively, total neonatal admissions, admissions to a Neonatal Intensive Care Unit (NICU), number of newborns with moderate to severe hypoxic ischemic encephalopathy (HIE) operative deliveries (caesarean and/or instrumental vaginal deliveries), and number of cases with FBS.

In total, 5200 women had to be randomised to reduce the risk of metabolic acidosis (based on BDecf) from 3.5 to 2.1%.

Economic evaluation

A cost-effectiveness analysis was performed alongside the trial. All unit costs were expressed in 2007 Euros using the consumer pricing index. We used a health care perspective and

compared costs and effects from the moment of randomisation to childbirth. Discounting costs and effects was not necessary because the time horizon was less than one year.

Measuring resource utilisation

Resources utilization was documented by extending the trial's Case Report Form (CRF) with specific items on health care use. In the CRF the following resource items were collected: fetal monitoring, method of delivery, medication, number of FBS and used scalp electrodes.

Unit costs

Different methods and sources were used to estimate unit costs as valuations for documented volumes of resource utilisation (Table 1).

Table 1 Cost-analyses: units of resource use, unit costs, valuation method and volume source

	Unit	Unit costs (€)	Valuation method (source)	Volume source
Specialist care				
Gynaecologist	Hour	69	Dutch costing guidelines	Annual reports
Midwife	Hour	34	Dutch costing guidelines	Annual reports
Resident- general	Hour	28	Dutch costing guidelines	Annual reports
Resident- academic	Hour	30	Dutch costing guidelines	Annual reports
Paediatrician	Hour	69	Dutch costing guidelines	Annual reports
Labour				
FBS	Procedure	15	Bottom-up calculation	CRF
Electrodes	Unit	7	Bottom-up calculation	CRF
Oxytocin augmentation	Dose	1	Pharmacotherapeutic website	CRF
Antibiotic treatment during labour	Dose	31	Top-down calculation	CRF
Anaesthesia				
Pethidin	Dose	1,10	Top-down calculation	CRF
Epidural/ Spinal	Dose	161	Top-down calculation	CRF
Intrapartum fetal monitoring				
ST-analysis	Delivery	45	Bottom-up calculation	Annual reports
CTG	Delivery	10	Bottom-up calculation	Annual reports
Type of delivery				
Caesarean section*	Delivery	1874	Top-down calculation	CRF
Instrumental vaginal delivery (vacuum/forcipal extraction)*	Delivery	1255	Top- down calculation	CRF
Spontaneous delivery*	Delivery	1062	Top-down calculation	CRF
Episiotomy*	Delivery	150	Top-down calculation	CRF

* The mean of the unit cost for an academic hospital and for a general hospital is presented. CRF = Case report form

For type of delivery, top-down unit costs estimates were available from the financial departments of one participating academic and one participating general hospital. For ST-analysis, we performed a bottom-up cost-calculation to estimate unit-costs, based on the

purchase prices and maintenance costs of STAN® equipment, as well as training costs for obstetricians and midwives. Costs of using STAN® for a single delivery also depended on the capacity and quantity of the equipment and the number of deliveries in each hospital. The unit costs of FBS and scalp electrodes were calculated using purchase prices.
For all other health care provider unit costs national standardized prices were used.[12] Costs of medication were estimated by using the prices reported in the Pharmacotherapeutic Compass.[13]

Analyses
Total costs per patient were calculated by multiplying resource use per patient by unit costs. Mean costs per patient for each study group, and mean differences in costs between study groups were estimated. Incremental cost-effectiveness ratios (ICER) were calculated by dividing the difference in costs by the difference in effectiveness (percentage prevented cases of metabolic acidosis). The 95% confidence intervals around the differences in mean costs, and cost-effectiveness ratios were determined by bootstrapping.[14]
We performed five univariable sensitivity analyses, in which per analysis one factor at the time was varied, to explore the impact of different assumptions and alternative unit-cost estimates on the results of the costs analysis.
In the first sensitivity analysis (model 1), we assessed the impact of varying the depreciation years (five or ten years) and the number of devices needed per centre (three or five) on the final results. Several assumptions were made in estimating equipment costs of ST-analysis and CTG, including years of depreciation and number of devices needed per hospital, which in turn depends on the annual number of deliveries. In the bottom-up unit cost calculation of the STAN® and CTG equipment, we assumed a depreciation period of seven years and four devices per centre in the base-case analysis.
In the second sensitivity analysis, we examined the impact of the inclusion of training costs in the ST-analysis costs by excluding these costs or vary the range of spent training hours (model 2). In this model we first excluded STAN® training costs as on the long run this training might become part of the regular medicine education training. Secondly, in this model we varied the number of training hours, because the number of training hours that were used in our base-case analysis (20 hours per person per year) could be over- or underestimated.
In the third sensitivity analysis we examined the impact of varying unit costs for fetal blood sampling (model 3).
Fourthly, we examined the cost differences between both groups if the postpartum stage was included (model 4), instead of comparing only costs generated between time of randomisation until childbirth, i.e. measurement of the primary outcome (cases with metabolic acidosis).
Finally, the impact of varying effectiveness rates was examined (model 5). A higher effectiveness rate (1% difference) was analysed by using the secondary outcome with an alternative definition of metabolic acidosis (umbilical cord-artery pH < 7.05 and BDblood >

12 mmol/L), for lower effectiveness rate we used a 0.1% difference in incidence. Statistical, economic and sensitivity analyses were performed using SPSS software (version 16.0, Chicago, IL) and Microsoft Excel.

Results

Main trial results

During the trial 2832 women were allocated to the index group and 2849 to the control group. After randomisation 14 women were excluded (five in the index group, nine in the control group), because they did not meet the inclusion criteria. Data for 5667 women (2827 in the index group, 2840 in the control group) were analysed according to intention-to-treat. The flowchart and baseline characteristics of these women are reported elsewhere.[10] There were no differences in baseline characteristics between the two groups.

Analysis of the clinical trial data showed that FBS was performed less in the index (10.6%) than in the control group (20.4%) (RR 0.52, 95% CI 0.46 to 0.59). The incidence of the primary outcome metabolic acidosis was lower in the index group (0.7% versus 1.1%, RR 0·70 (95% CI 0·38 to 1·28)). When metabolic acidosis was analysed according to pH and BDblood, these rates were 1.6% and 2.6%, respectively (RR 0.63; 95% CI, 0.42 to 0.94). The number of operative deliveries, low Apgar scores, neonatal admissions and newborns with moderate or severe HIE was comparable in both groups.[10]

Costs and cost-effectiveness

The number of patients using care, total costs in each study group, and average costs per patient are presented in Table 2. Mean costs per patient in the index group were €1.345 (95% CI: €1.013 to €2.115) and €1.316 for the control group (95% CI: €978 to €2080). Mean costs per patient were €29 (95% CI: -€9 to €77) higher in the index group as compared to the control group. This difference was mainly due to the use of STAN® equipment and accompanied training. Costs generated by spontaneous deliveries and deliveries by caesarean section were somewhat higher in the index group, whereas costs generated by vaginal instrumental deliveries were higher in the control group.

With an estimated difference in incidence of metabolic acidosis between the two groups of 0.4% in favour of ST-analysis, and a mean difference in costs per patient of €29 in favour of CTG only, the ICER is €7.250 per prevented case of metabolic acidosis.

Table 2 Number of patients using care, mean costs per patient and total costs (2007 Euros)

		Index group (N=2827)			Control group (N=2840)			
	Unit	**% patients using care**	**Total costs (€)**	**Mean costs pp (€)**	**% patients using care**	**Total costs (€)**	**Mean costs pp (€)**	**Difference (ST-CTG)**
Fetal monitoring	Unit	100%	128.071	45	100%	28.866	10	35
Oxytocin augmentation	Procedure	70%	1.103	0,39	69%	1.108	0,39	0
Medication during labour	Unit	16%	905	0,32	16%	966	0,34	-0,02
Epidural anaesthesia	Procedure	37%	189.409	67	38%	195.960	69	-2
Spinal anaesthesia	Procedure	0%	0	0	0.1%	483	0,17	-0,17
Spontaneous delivery	Procedure	72.1%	2.106.115	745	71%	2.084.560	734	11
Instrumental vaginal delivery	Procedure	13.6%	472.109	167	15.2%	528.240	186	-19
Caesarean delivery	Procedure	14.3%	760.463	269	13.8%	735.560	259	10
Episiotomy	Procedure	19%	81.983	29	19%	82.360	29	0
Fetal blood sampling	Unit	11%	36.186	13	20%	57.652	20	-7
Scalp electrodes	Unit	100%	24.878	9	100%	22.436	8	-1
Total costs			**3.801.222**	**1.345**		**3.738.191**	**1.316**	**29**

Sensitivity analyses

In table 3 results of the sensitivity analyses are shown. The base-case cost differences were not very sensitive to increasing depreciation years and decreasing number of necessary devices. Only if we decreased the number of depreciation years to five and increased the number of STAN® and CTG devices per centre to five, the mean costs per patient increased in both groups and the cost-effectiveness ratio rose to €9.542 per prevented case of metabolic acidosis (model 1).

Costs results appeared to be sensitive for variations in training costs (model 2). If training was completely excluded or only eight training hours per health care provider were assumed, mean costs of the index group, costs differences and ICERs decreased substantially. On the other hand if more training hours were assumed (40 hours instead of 20) patients in the index group generated more costs and the ICER increased (model 2). The ICER (€7.250) was not sensitive for changing the FBS unit costs (model 3). If postpartum costs (e.g. maternal and neonatal admissions) are included in the analysis, costs per patient would be doubled. In the index group three NICU admissions exceeded duration of 30 days. This highly impacts the results in case postpartum costs are included (model 4). We therefore examined the impact after exclusion of these three exceptional admissions. As can be seen from table 3 (model 4), the cost difference decreased to €17 and ST-analysis became more cost-effective (€4.347 per prevented case of metabolic acidosis).

As can be expected, the estimated cost-effectiveness was very sensitive for changing effectiveness rates. If we assumed 1% difference in the incidence of metabolic acidosis in favour of the index group, ST-analysis became more cost-effective (€2.900 per prevented case of metabolic acidosis). Assuming an effectiveness difference of 0.1% in favour of ST-analysis, the ICER rose to €29.000 per prevented case of metabolic acidosis (model 5).

Table 3 Sensitivity analyses results

Model	Description	Mean costs per patient Index group	Mean costs per patient Control group	Index minus Control	ICER
0	**Base-case scenario**	€ 1.345	€ 1.316	€ 29	€7.250
1	**Changing years of depreciation and number of equipment needed per centre**				
	5 years and 5 devices	€ 1.363	€ 1.325	€ 38	€ 9.542
	10 years and 3 devices	€ 1.340	€ 1.314	€ 26	€ 6.474
2	**STAN® training costs**				
	Exclusion	€1.321	€1.316	€ 5	€1.098
	8 hours (only introduction day)	€1.331	€1.316	€ 14	€ 3.569
	40 hours (introduction and 4 days)	€1.365	€1.316	€ 48	€12.103
3	**Changing unit costs FBS**				
	€ 6 (capillaries only)	€1.337	€1.304	€ 33	€ 8.212
	€ 32 (personnel costs included)	€1.359	€1.339	€ 20	€ 4.962
4	**Postpartum costs**				
	Inclusion all postpartum costs	€2.634	€2.552	€ 82	€ 20.597
	Exclusion of three long NICU admissions (>30 d) in index group	€2.569	€2.552	€ 17	€ 4.347
5	**Difference in % prevented cases of metabolic acidosis**				
	1%	€1.345	€1.316	€ 29	€ 2.900
	0.1%	€1.345	€1.316	€ 29	€ 29.000

Discussion

This study assessed the economic consequences of two strategies of intrapartum fetal monitoring in high-risk pregnant women with an indication for internal electronic fetal monitoring, CTG plus ST-analysis of the fetal ECG or CTG alone, from a health care point of view. This analysis was part of the Dutch trial on ST-analysis of the fetal ECG,[10] and to our knowledge, the first randomised trial-based economic evaluation. We showed that mean costs per patient are not significantly higher when monitoring by CTG plus ST-analysis as compared to CTG only (mean difference €29 (95% CI: -€9 to €77) is used.

The results of one of our sensitivity analyses show that cost differences and ICERs are highly influenced by the amount of training hours necessary for working with the STAN® equipment, which is an important aspect of the STAN® methodology. From a clinical point of view, exclusion of training and its associated costs is therefore an irrational assumption.

However, increasing use of and experience with the STAN® method may lead to training of labour ward personnel in an informal clinical setting or on the long run during education, which may limit the need for official training sessions and thereby additional costs. In the future this may lead to even smaller cost differences between ST-analysis and CTG. No training costs were included in the CTG only group because it is assumed working with CTG is common practice for labour ward personnel.

The time horizon used in this cost-effectiveness analysis has been limited to the stage between moment of randomisation and childbirth. This decision was made because in our opinion including costs generated after that period may lead to double counting due to the inclusion of consequences of the primary outcome (e.g. admissions because of metabolic acidosis).[15] In the base-case scenario costs associated with maternal and neonatal postpartum admissions were therefore not included. Including these postpartum costs would highly impact the results as can be seen from the sensitivity analyses (model 4). In the trial, no significant difference was found in the number of total neonatal admissions or admissions to a NICU, but in the group monitored by ST-analysis three NICU admissions exceeded a duration of 30 days. Logically, these exceptional cases highly impact the results of a cost- effectiveness analysis in case postpartum costs are included. However, the causes of these prolonged admissions were in no way related to intrapartum fetal monitoring or ST-analysis in specific. Therefore, including these three cases in an analysis would provide distorted results.

The primary outcome in the trial was metabolic acidosis based on calculation of a base deficit value in the extracellular fluid compartment of umbilical cord blood (BDecf), since the latter seems to best reflect the true metabolic component of acidosis.[16,17] However, blood gas analysing devices in clinical practice often provide base deficit values that have been calculated in blood (BDblood) instead of BDecf. We therefore also performed a cost-effectiveness analysis for this secondary trial outcome, since results of this analysis may better apply to current practice. Although the absolute cost difference between ST-analysis and CTG is comparable, ST-analysis is much more cost-effective when metabolic acidosis based on pH and BDblood instead of BDecf is used as outcome. On the other hand, if ST-analysis would be less effective than assumed in the base-case analysis and costs were not changed, this also highly impacts the cost-effectiveness. Both from a clinical as an economic point of view it may be important to be aware that the definition of the clinical end-point substantially affects the outcomes.

In this study we used a relatively short horizon to evaluate cost-effectiveness. This was explicitly done as detailed information was available on both costs and effects from the same, large randomised trial. On the other hand, in future research it would be interesting to include long-term effects and costs as well. One of the most important health consequences of metabolic acidosis may be the development of cerebral palsy, although existing literature about the association between cord pH and adverse outcome is not straightforward.[18] A previous cost-of illness study showed that the mean annual societal cost of intractable spastic cerebral palsy in children was €40.265.[19] Recently a Danish study group published lifetime

cerebral palsy costs of €860.000 for men and €800.000 for women.[20] Thus, on the long run introducing ST-analysis may result in cost savings due to prevented cases of cerebral palsy. A 2-year follow-up study was initiated by our study group. In future research, societal long-term costs of cerebral palsy cases due to metabolic acidosis should be estimated by using these follow-up data or extrapolating our primary trial data.

In conclusion, the additional costs of monitoring by ST-analysis of the fetal ECG are very limited when compared to those of CTG only and very low compared to the total costs of labour. ST-analysis of the fetal ECG appears to be a cost-effective strategy.

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Submitted

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Prediction of neonatal metabolic acidosis in women with a term singleton fetus in cephalic position

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Abstract

Objective

To assess whether obstetric characteristics before and during labour can predict neonatal metabolic acidosis at birth.

Methods

We studied labouring women with a high-risk singleton pregnancy in cephalic position beyond 36 weeks of gestation, which were included in a multicentre clinical trial. The outcome of interest was metabolic acidosis defined as an umbilical cord-artery blood pH below 7.05 combined with a base deficit calculated in blood above 12 mmol/L. We used multiple imputation techniques for missing data. We developed prediction models both before and during labour using multivariable logistic regression. To correct for overestimated regression coefficients, the models were (internally) validated by bootstrapping techniques and shrinkage. We used calibration and receiver operating characteristic (ROC) analysis (*c*-statistic) to assess model performance.

Results

In the trial, 119 neonates of 5667 women had metabolic acidosis (2.1%). Antepartum predictors associated with an increased risk of metabolic acidosis were increased gestational age, nulliparity, a previous caesarean delivery and maternal diabetes. Intrapartum factors that increased the risk of metabolic acidosis were a spontaneous onset of labour and epidural anaesthesia, whereas ruptured membranes for more than 24 hours with or without maternal fever decreased this risk. Predicted probabilities of the final extended model ranged from 0.2 to 10.4% with an acceptable calibration and a *c*-statistic of 0.64 (95% CI 0.59-0.69).

Conclusion

In women with a high-risk cephalic positioned singleton term pregnancy, patient characteristics both before and during labour influence the a priori probability of neonatal metabolic acidosis at birth. This information could potentially be used in obstetric clinical management.

Introduction

The ultimate goal of fetal surveillance during labour is the prevention of perinatal asphyxia. Perinatal asphyxia is associated with several short- or long-term complications, varying from mild hypoxic ischemic encephalopathy (HIE), to cerebral palsy (CP) and death.[1-5]
In the cascade from labour and perinatal outcome to long-term consequences, there has been a strong focus on the association between adverse outcome in the perinatal period and long-term cerebral injury or death, and on univariable associations between single factors and adverse outcomes. However, in clinical practice it is important to identify women with a high(er) risk of developing adverse neonatal outcome as early as possible, e.g. at entrance in the hospital or even antenatally. Clinical practice is always multivariable: no prognosis is set by a single factor.[6] Timely prognostication may lead to more effective decision making during labour, in specific with respect to the type of fetal monitoring that is offered, as well as the interpretation of fetal heart rate patterns.
Fetal surveillance during labour is performed with cardiotocography (CTG), fetal blood sampling (FBS) or ST-analysis of the fetal electrocardiogram (ECG). However, these tests are often applied and interpreted in isolation, without taking into account other factors that may influence the probability of an adverse outcome at birth.
The aim of the present study was therefore to identify which factors measured both before and during labour could be used in a multivariable way to adequately predict neonatal metabolic acidosis at birth. For this purpose we used data from a large multicentre trial in which labouring women with a high-risk vertex singleton pregnancy beyond 36 weeks of gestation were studied.[7]

Methods

Setting

In a recently finished randomised clinical trial in The Netherlands, labouring women with a high-risk vertex singleton pregnancy beyond 36 weeks of gestation were randomly allocated to either intra partum monitoring by cardiotocography (CTG) plus ST-analysis of the fetal electrocardiogram (ECG; STAN®) or CTG only, using a strict protocol for performance of FBS. The design and main results are presented elsewhere.[7]
In The Netherlands, pregnant women at low-risk are monitored by midwives or general practitioners at home or in hospital (primary care), whereas pregnant women at high-risk are monitored by gynaecologists in hospital (secondary care). High-risk pregnancies are those that are complicated by pre-existing maternal disease, complicated obstetric history, hypertensive disorders, intrauterine growth restriction, ruptured membranes for more than 24 hours, a post date gestational age, failure to progress, need for pain relief, meconium stained amniotic fluid or non-reassuring fetal heart rate at intermittent auscultation by a midwife.

Outcome

The primary outcome in the original trial was metabolic acidosis based on a base deficit (BD) calculated in the extracellular fluid compartment (BDecf). However, in the present study, the primary outcome was metabolic acidosis defined as an umbilical cord-artery pH below 7.05 and a BD calculated in blood (BDblood) above 12 mmol/L. There were two reasons for using the latter outcome. First, most cord blood analysers calculate and report BDblood instead of BDecf, which makes multivariable analysis for metabolic acidosis based on BDblood more applicable to daily clinical practice. Second, a practical reason was the higher incidence of metabolic acidosis calculated in blood, allowing for more statistical power to identify possible predictors.

Predictors under study

We selected candidate predictors for metabolic acidosis based on literature and clinical reasoning. Selected candidate predictors were divided in two categories. The first category contained only antenatal variables: maternal age, fetal gender, gestational age, parity, previous caesarean delivery, maternal diabetes mellitus and antenatal estimated fetal weight. The latter was defined as a dichotomous variable using actual birthweight below tenth percentile according to birthweight reference curves of the Perinatal Registration in the Netherlands (PRN).[8] Maternal diabetes mellitus was defined as both pregestational type 1 and 2 as well as gestational diabetes mellitus. This first set of variables was used to develop an antenatal baseline risk model (model 1).

The second category contained variables obtained during labour i.e. onset of labour, ruptured membranes > 24 hrs with or without intrapartum fever (≥ 37.8 °C), failure to progress, oxytocin augmentation, meconium stained amniotic fluid and epidural anaesthesia.

This set of characteristics was added to model 1, to determine their added predictive value and to develop a final extended model containing predictors measured both before and during labour (model 2).

Data analysis

Univariable associations between the candidate predictors and metabolic acidosis were estimated with logistic regression analysis. Pre-selection of predictors for inclusion in the multivariable analyses was not done, since such selection based on univariable statistics often results in unstable prediction models.[9-12]

Maternal and gestational age were analysed as continuous variables. Linearity of their association with the outcome was assessed using cubic spline analyses.[10] All other variables, including the outcome, were dichotomous. To correct for the allocated intervention followed by randomisation in the original trial, we also included this intervention variable in the multivariable analysis of model 1 and 2.

The final predictors of both multivariable models were identified by backward stepwise selection using Akaike's Information Criterion, which is similar to selection based on a p-

value of 0.157 if the predictor is modeled with one regression coefficient as for e.g. dichotomous predictors.[10,11]

The ability of the two models to discriminate between women with and without metabolic acidosis was studied with the area under the Receiver Operating Characteristic (ROC) curve (*c*-statistic). Calibration was assessed by comparing the predicted probabilities with the observed frequencies of metabolic acidosis. The agreement between the observed proportions of metabolic acidosis and the predicted risks, was studied with a calibration plot.[10,13,14] This plot also provides additional insight in the distribution of the predicted outcome incidences.

As the number of cases was relatively low, there was a chance of finding spurious predictors and overestimated regression coefficients.[10,11,15] Such overfitted models will yield too extreme and optimistic predictions when applied in new patients. To adjust for this we (internally) validated the models with bootstrapping techniques. This yielded a shrinkage factor for the regression coefficients and for the *c*-statistic, to adjust both for optimism.

For variables with missing values, which ranged from 0.2 to 11.9%, multiple imputation (ten times) was used to obtain unbiased data, without loss of power.[16-18] All analyses including the multiple imputation were performed in S-plus 6.1 (Insightfull Corp, Seattle, Washington, USA).

Results

Between January 2006 and July 2008, 5681 women were randomised.[7] After randomisation 14 women were excluded, because they did not meet the inclusion criteria. In the remaining 5667, metabolic acidosis occurred in 119 neonates (incidence of 2.1%). Descriptive characteristics of the entire study population are presented in Table 1.

Variables related to metabolic acidosis in univariable analysis were gestational age (odds ratio (OR) 1.14 per week), multi parity (OR 0.63), neonatal female gender (OR 0.78), maternal diabetes (OR 3.03), induced onset of labour (OR 0.67), ruptured membranes > 24 hrs with or without intrapartum fever (OR 0.43), oxytocin augmentation (OR 1.52), meconium stained amniotic fluid (OR 1.58) and epidural anaesthesia (OR 1.51) (Table 2).

In model 1, four variables before labour were identified to independently predict metabolic acidosis: gestational age (OR 1.12 per week), multi parity (OR 0.57), previous caesarean delivery (OR 1.86) and maternal diabetes mellitus (OR 2.82) (Table 3). The model's *c*-statistic corrected for optimism was 0.61 (95% CI 0.56-0.66).

After adding all predictors obtained during labour to the variables of model 1, backward stepwise selection yielded that induced onset of labour (OR 0.75), ruptured membranes > 24 hrs with or without intrapartum fever (OR 0.49) and epidural anaesthesia (OR 1.28) showed added predictive value to the predictors of model 1 (Table 3). The *c*-statistic corrected for optimism of model 2 was significantly higher at 0.64 (95% CI 0.59-0.69).

Table 1 Characteristics of the entire RCT study population (N=5667)
Data are presented as mean ± standard deviation or n (%)

Characteristic	
Antenatal	
Maternal age (y)	32.0 ± 4.8
Gestational age (wks)	40.2 ± 1.4
Multi parity	2431 (42.9)
Previous caesarean delivery	716 (12.6)
Neonatal female gender	2668 (47.1)
Birthweight below tenth percentile	519 (9.2)
Maternal diabetes mellitus	169 (3.0)
During labour	
Induced onset of labour	2341 (41.3)
Ruptured membranes > 24 hrs	692 (12.2)
Failure to progress	406 (7.2)
Oxytocin augmentation	2044 (36.1)
Meconium stained amniotic fluid	1471 (26.0)
Epidural anaesthesia	2389 (42.2)
Intrapartum fever (≥ 37.8 °C)	470 (8.3)
Outcome (RCT)	
Metabolic acidosis	119 (2.1)

Calibration of both models is shown in figures 1 and 2. At first glance these models seem to calibrate poorly, but to enhance the interpretation the axes have been adjusted based on the a priori low observed (and thus predicted) outcome incidences. For model 1, the predicted probabilities ranged from 0.5 to 7.1% (Figure 1) and for model 2 from 0.2 to 10.4% (Figure 2). For model 1 calibration was good for the group with predicted probabilities below 2%. Some underestimation was seen for predicted risks between 2 and 5% and some overestimation at higher risks (Figure 1). In the final model 2, for the group with predicted probabilities below 5% calibration was good. At higher risks, there was some overestimation, which was largely due to the low number of cases in this group (Figure 2).

Table 2 Univariable associations between candidate predictors and metabolic acidosis*
Data are presented as mean ± standard deviation or n (%)

Predictor	Metabolic acidosis			
	Present N=119	**Absent N=5548**	**Odds Ratio (95% CI)**	**P value**
Antenatal				
Maternal age (y)	31.5 ± 5.1	32.0 ± 4.8	0.98 (0.94-1.02)†	0.32
Gestational age (wks)	40.4 ± 1.4	40.2 ± 1.4	1.14 (0.99-1.33)‡	0.08
Multi parity	38 (32.3)	2393 (43.1)	0.63 (0.41-0.97)	0.04
Previous caesarean delivery	19 (15.6)	697 (12.6)	1.28 (0.73-2.23)	0.39
Neonatal female gender	48 (40.6)	2620 (47.2)	0.78 (0.52-1.18)	0.25
Birthweight below tenth percentile	14 (11.5)	505 (9.1)	1.27 (0.67-2.40)	0.47
Maternal diabetes mellitus	10 (8.3)	159 (2.9)	3.03 (1.45-6.36)	0.00
During labour				
Induced onset of labour	38 (32.3)	2303 (41.5)	0.67 (0.44-1.04)	0.07
Ruptured membranes > 24 hrs and/or intrapartum fever	11 (9.4)	1078 (19.4)	0.43 (0.21-0.85)	0.02
Failure to progress	12 (10.4)	394 (7.1)	1.51 (0.78-2.93)	0.22
Oxytocin augmentation	55 (45.8)	1989 (35.9)	1.52 (1.01-2.28)	0.04
Meconium stained amniotic fluid	42 (35.4)	1429 (25.8)	1.58 (1.04-2.42)	0.03
Epidural anaesthesia	62 (52.1)	2327 (42.0)	1.51 (1.01-2.27)	0.05

* Absolute numbers (%) in this table are based on the mean of ten imputations. † Odds ratio per year. ‡ Odds ratio per week.

Table 3 Multivariable logistic regression models for the prediction of metabolic acidosis*

Predictor	**Model 1**			**Model 2**		
	OR (95% CI)	**Beta**	**P value**	**OR (95% CI)**	**Beta**	**P value**
Antenatal						
Gestational age (wks)**	1.12 (0.96-1.31)	0.11	0.04	1.13 (0.96-1.33)	0.12	0.06
Multi parity	0.57 (0.32-0.99)	-0.57	0.01	0.57 (0.32-1.02)	-0.57	0.01
Previous caesarean delivery	1.86 (0.91-3.80)	0.62	0.02	1.71 (0.82-3.57)	0.54	0.06
Maternal diabetes mellitus	2.82 (1.30-6.10)	1.03	0.00	3.22 (1.47-7.07)	1.17	0.00
During labour						
Induced onset of labour	-	-	-	0.75 (0.48-1.18)	-0.29	0.11
Ruptured membranes > 24 hrs and/or intrapartum fever	-	-	-	0.49 (0.24-0.99)	-0.72	0.01
Epidural anaesthesia	-	-	-	1.28 (0.84-1.97)	0.25	0.14

* All analyses are adjusted for original RCT randomisation allocation. Presented betas are shrunken.
** Odds ratio (OR) per week.

Figure 1 Calibration plot for the antepartum model 1 for prediction of metabolic acidosis

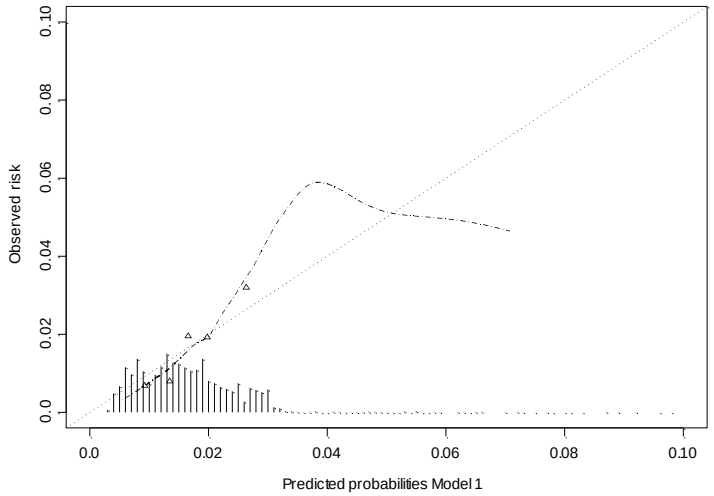
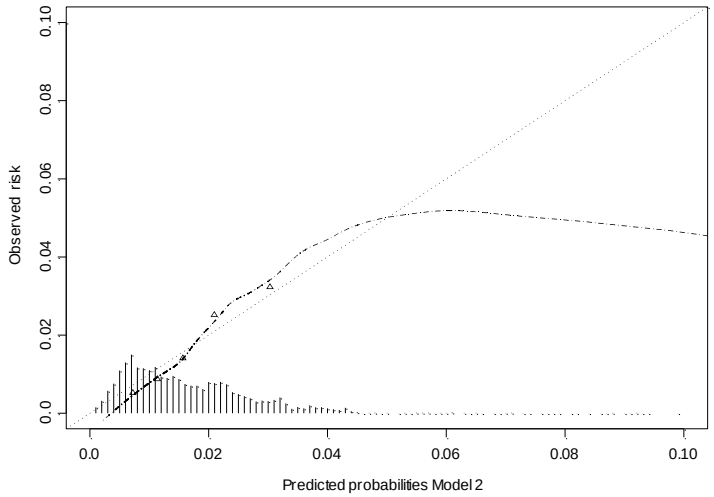


Figure 2 Calibration plot for the final extended model 2 for prediction of metabolic acidosis by characteristics obtained both before and during labour



Note figures 1 and 2: To enhance interpretation the axes have been adjusted to a scale from 0.0 to 0.10, based on the low observed and predicted outcome incidences. Vertical bars (histogram) indicate the frequencies (number of patients) across the predicted probabilities.

Discussion

To date, this study is the first to gain quantitative insight into the predictive capacity of combinations of obstetric characteristics obtained before and during labour for metabolic acidosis of the newborn at birth. Previous studies mainly focused on the prediction of longer-term outcomes, such as HIE, cerebral palsy and death and frequently applied a univariable approach. From a recent systematic review and meta-analysis it is known that a low cord pH at birth is highly associated with clinically important neonatal and long-term outcomes.[19] Hence, prevention of a low cord pH at birth also prevents cases with long-term adverse outcomes. Early knowledge of a woman's individual risk of developing such adverse outcome, preferably at an early stage, enhances the possibilities to anticipate the intrapartum monitoring, decision and management process.

Our results show that before the start of labour in high-risk singleton term vertex pregnancies, nulliparity, higher gestational age, a history of caesarean delivery and diabetes increase the risk of metabolic acidosis already threefold (7.1%), as compared to the a priori risk (overall observed incidence of 2.1%). Factors during labour, such as a spontaneous onset and epidural anaesthesia, may increase this risk even further. Our results may allow clinicians to avoid unnecessary interventions in low-risk women and may influence decisions during labour regarding the interpretation of fetal heart rate patterns and the application of additional techniques for fetal monitoring, such as ST-analysis of the fetal ECG or FBS.

Although the aim of prognostic research is purely to predict,[6] the results of our study show that expected causal relations turn out to be different in our analysis. In advance, one would expect women with an induced onset of labour, ruptured membranes for more than 24 hours and/or intrapartum fever to be at higher risk for metabolic acidosis at birth. However, in our analyses these factors had a protective effect, which may be explained as follows. First, despite analysing data from a very large randomised multicentre trial, model development is still based on a selection of labouring women with high-risk pregnancies. Some women started labour in secondary care, but a large part of women was admitted to secondary care during labour. In the latter group, all women had a spontaneous onset of labour, and probably a higher incidence of metabolic acidosis, which leads to a seemingly protective effect of factors like induction of labour and prolonged ruptured membranes.

Second, the unexpected effect of ruptured membranes above 24 hours with or without intrapartum fever is likely to be explained by interaction or effect modification. However, in our data there was only one case of metabolic acidosis with both prolonged ruptured membranes and intrapartum fever. Preferably, we would have included clinically relevant interaction terms in our multivariable analysis, but due to the small number of the study outcome this was impossible.

Finally, a troublesome aspect of all prognostic studies in labouring women is an obstetrician's decision to perform an intervention which may disturb the baseline prognostic associations between predictor and outcome. In our study, operative vaginal deliveries or caesarean sections for other reasons than suspected fetal distress, may have caused such an interference

with the development of metabolic acidosis. Possibly, the predictive effect of prolonged ruptured membranes with or without intrapartum fever was masked, because these factors by themselves triggered the performance of an operative delivery. This leads to a seemingly protective effect on metabolic acidosis. This is also supported by the finding that in all five cases with both metabolic acidosis and intrapartum fever an operative delivery was performed.

Another striking result of our study was that neither meconium stained amniotic fluid nor oxytocin augmentation appeared to be a risk factor for metabolic acidosis. In the Netherlands, these characteristics substantially contribute to the number of admissions from primary to secondary care, in order to continuously monitor the fetus. The results of our study imply that other obstetric characteristics more importantly contribute to the prediction of metabolic acidosis. Again, one should keep in mind that the models were developed in a high-risk population.

To appreciate the present results, a final aspect needs to be addressed. As a biochemical derivative of asphyxia often metabolic acidosis is used, which is the combined presence of both a low umbilical cord-artery pH and BD. Several cut-off values for pH and BD are being used, although a consensus statement has reported pathological acidosis to occur at an umbilical cord-artery pH below 7.00 and a BD above 12 mmol/L.[20] However, in various papers often a slightly more liberal definition is used: umbilical cord-artery pH below 7.05 and a BD above 12 mmol/L.[21] In our study, the use of the latter definition, consisting of substantially more cases than for an umbilical cord-artery pH below 7.00, made the identification of predictors more powerful.

Our work shows that there is a strong variation in the antenatal baseline risk for acidosis, and this risk may even be adjusted with factors that occur during labour. At present, however, such information is hardly used in clinical practice. It should be noted that our study only aimed to determine which variables are independently predicting the occurrence of metabolic acidosis. Despite our internal validation procedure, further steps of model development and validation are surely needed before a model can be introduced in clinical practice.[11,12] Specific attention should be paid to applicability of the models to new labouring women, thereby remarking that the antepartum model was actually developed by using data on women that were in labour already at the moment of entering the trial.

As figures 1 and 2 show, the predicted risk of acidosis is below 1% in about 10% of women and between 1% and 2% in about 50%, and highly agreed to the observed risks. For the extended model, even until predicted risks of 5% this agreement was high. From a clinical viewpoint it is of minor importance that at higher risks the calibration of our models is less good, because with a risk above 2% women will anyway be categorised in the highest risk group and managed as such. The variation in predicted risks is of the utmost importance, as this is guiding both in the type of fetal surveillance that is offered, as well as in its interpretation.

In summary, in women with a high-risk cephalic positioned singleton term pregnancy, factors both before and during labour influence the a priori probability of developing metabolic

acidosis of the newborn at birth. The identified predictors were internally validated by bootstrapping techniques. After external validation and proof of generalisability, this information should be used in obstetric clinical management, with a specific focus on the type of fetal monitoring that is offered and its interpretation.

Acknowledgements

We thank all research nurses and midwives of the Dutch Obstetric Consortium, as well as the staff of the labour wards of the participating centres for their invaluable contributions to the study. The trial, of which data were used for the present study, was funded by a grant from ZonMW, the Dutch Organization for Health Research and Development (Grant number: 945-06-557).

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11

Summary, conclusions and general discussion

Summary and main conclusions

In this thesis studies on intrapartum fetal monitoring by ST-analysis of the fetal electrocardiogram (ECG; STAN®) are presented, with respect to its effectiveness, limitations, cost-effectiveness, clinical implications and guidelines. The following questions addressed in this thesis, as posed in **Chapter 1**, were:

1) What is the existing evidence regarding effectiveness of ST-analysis of the fetal ECG?
2) What are limitations and drawbacks of ST-analysis of the fetal ECG in clinical practice?
3) Is a strategy of fetal monitoring by ST-analysis of the fetal ECG more cost-effective than monitoring by cardiotocography (CTG) only?
4) To what extent does correct adherence to clinical guidelines for a strategy of fetal monitoring by ST-analysis prevent cases with adverse neonatal outcome, as compared to monitoring by CTG only?
5) Which patients still need fetal blood sampling (FBS) in addition to monitoring by ST-analysis of the fetal ECG?
6) Can neonatal metabolic acidosis at birth be predicted by characteristics both before and during labour?

As outlined in the introduction, it is the aim of intrapartum fetal monitoring to timely identify a distressed fetus, to decide on management (interventions) for preventing asphyxia related neonatal and long-term morbidity and mortality. To serve this purpose, CTG has been introduced in the 1970's, without its diagnostic accuracy and clinical effectiveness having been thoroughly investigated. Nevertheless, CTG has been widely used since then. Interpretation of the intrapartum CTG is difficult, since non-reassuring CTG traces are not specific enough to identify the compromised fetus. Furthermore, there is a large inter- and intra-observer variation on CTG classification.

Additional intrapartum fetal monitoring

To prevent unnecessary interventions for suspected fetal distress, fetal information in addition to non-reassuring CTG traces is crucial. In **Chapter 2** two techniques for obtaining complementary fetal information during labour, i.e. FBS and ST-analysis of the fetal ECG, are reviewed.

1.1. Fetal blood sampling (FBS)

Although by performing FBS direct information on the fetal acid-base state is obtained, its use is limited to only few countries. One of the reasons is that FBS only provides a result at a specific point in time and that with a persistent non-reassuring CTG it should be repeated. Moreover, the decision to obtain FBS depends on the subjective and often inadequate interpretation of the CTG. In addition, FBS is invasive, technically difficult and patient-

unfriendly. In at least 10% of the attempts, FBS is unsuccessful and needs to be repeated making it a time-consuming procedure. Finally, the relatively large quantity of blood that is required to determine the pH is also mentioned as a disadvantage of FBS.
A survey among all Dutch obstetric clinics revealed that FBS is performed in 88% of the clinics. In 60% of these clinics, FBS is always or usually performed in case of a non-reassuring CTG. This survey also showed that in many hospitals proper logistics for determination of results of FBS are lacking.

1.2. ST-analysis of the fetal ECG

Experimental animal research has shown that changes in the ST-segment of the ECG are correlated with fetal hypoxia during labour. Since the 1990's, it has been possible to record not only the fetal heart rate but also the fetal ECG signal, in particular the ST-segment, through a scalp electrode. This has led to the development of intrapartum fetal monitoring by ST-analysis of the fetal ECG (STAN® method).
The STAN® concept is based on a combined interpretation of CTG and ST-changes of the fetal ECG. The relevance of ST-changes depends on the visual assessment of the CTG, classified according to the STAN® clinical guidelines as normal, intermediary, abnormal or (pre)terminal. These guidelines also indicate in which situations intervention is recommended (Appendix A).
A meta-analysis based on four randomised trials comparing fetal monitoring by ST-analysis of the fetal ECG to CTG only has shown a reduction in metabolic acidosis (RR 0.73; 95% CI 0.49 to 1.09), in total operative deliveries (RR 0.92; 95% CI 0.86 to 0.98), in FBS (RR 0.65; 95% CI 0.59 to 0.72) and in neonatal encephalopathy (RR 0.37; 95% CI 0.14 to 1.00) in favour of ST-analysis of the fetal ECG.

2. Limitations of monitoring by ST-analysis of the fetal ECG

In the visual assessment of the CTG, on which the STAN® methodology is based, lie two problems. First, the large inter- and intra-observer variation that is associated with classification of the CTG, logically also plays a role in monitoring by STAN®. In **Chapter 3** the inter- and intra-observer agreement, following STAN® guidelines (Appendix A), on classification of the intrapartum CTG and subsequent decisions to intervene, were quantified. STAN® recordings of 73 labouring women with a high-risk term pregnancy were assessed by six observers. They decided if and when they would suggest an intervention. Results of this study showed that inter-observer agreement for the normal and (pre)terminal CTG was reasonable to good (Kappa), but decreased when the CTG was intermediary or abnormal. Observers agreed better on the decision to intervene than on the decision to perform no intervention, a finding which was confirmed by other studies. This study suggests that addition of information regarding fetal ECG, especially in case of intermediary or abnormal CTG traces, results in a more standardised decision to intervene or otherwise.

A second potential limitation of the STAN® method, also in part caused by the reliance on visual CTG assessment, is that of human failures and inconsistent adherence to clinical guidelines. In **Chapter 4** we describe three cases in which infants with severe acidosis (umbilical cord-artery pH < 7.00) were born despite monitoring by ST-analysis of the fetal ECG. These cases illustrate several limitations of the STAN® methodology in the prevention of perinatal metabolic acidosis. Poor signal quality, difficulties in correct interpretation of CTG patterns, compliance to the STAN® clinical guidelines and our, as yet, incomplete knowledge of intrapartum fetal pathophysiology (eg. in the situation of maternal fever), may still result in unexpected unfavourable outcomes. Chapter 4 ends with the recommendation that STAN® clinical guidelines should include more detailed instructions regarding the correct identification of 'difficult cases' , with suggestions for adequate management interventions based on ST-analysis results. In 2007 a consensus meeting of European STAN® experts in Utrecht (the Netherlands) resulted in adjustment of the guidelines (Appendix A).

3. Effectiveness of monitoring by ST-analysis of the fetal ECG versus CTG

In 2006 controversy in the literature led to the start of a large pragmatic multicentre randomised clinical trial to quantify the cost-effectiveness of monitoring by ST-analysis of the fetal ECG compared to CTG only, using a strict protocol for performance of FBS. The trial was set up within the Dutch Obstetric Consortium, which is a collaboration of obstetric clinics in the Netherlands (www.studies-obsgyn.nl/stan). Three Dutch academic and six non-academic teaching hospitals participated in the trial.

Chapter 5 provides a detailed description of the study protocol. Labouring women aged 18 years or older with a singleton high-risk pregnancy, a fetus in cephalic presentation, a gestational age of more than 36 weeks and an indication for internal electronic fetal monitoring were randomly assigned to either monitoring by ST-analysis of the fetal ECG (index group) or CTG only (control group). Performance of FBS in the index group was restricted to three situations: 1) start of STAN® registration with an intermediary or abnormal CTG trace; 2) abnormal CTG trace for more than 60 minutes during first stage without ST-events; and 3) poor ECG signal quality in the presence of an intermediary or abnormal CTG trace. Further management was guided by the STAN® clinical guidelines (Appendix A).

Primary outcome was metabolic acidosis defined as umbilical cord-artery pH below 7.05 combined with a base deficit calculated in the extracellular fluid compartment (BDecf) of more than 12 mmol/L, according to the Siggaard-Andersen acid-base chart algorithm.

Secondary outcomes were metabolic acidosis according to pH and base deficit calculated in blood (BDblood), Apgar scores below four and seven at one and five minutes, total neonatal admissions, admissions to a neonatal intensive care ward (NICU), number of newborns with moderate to severe hypoxic ischemic encephalopathy (HIE), operative deliveries, number of cases with FBS and costs.

In total, 5200 women had to be randomised to reduce the risk of metabolic acidosis (based on BDecf) from 3.5 to 2.1%. Multiple imputation was used to handle missing values in the data.

Analyses were performed by intention-to-treat. Relative risks (RR) with 95% confidence intervals (CI) were estimated, adjusted for the stratified randomisation by centre and parity.

Results of this trial are presented in **Chapter 6**. From January 2006 to July 2008, 5681 women were randomised. 2832 women were assigned to the index and 2849 to the control group. After randomisation, 14 women were excluded (five in the index group, nine in the control group), because they did not meet the inclusion criteria. Data for 5667 women (2827 in the index and 2840 in the control group) were analysed according to intention-to-treat.
The FBS rate was 10.6% in the index group versus 20.4% in the control group (RR 0.52; 95% CI 0.46 to 0.60). The incidence of the primary outcome was 0.7% in the index group versus 1.1% in the control group (RR 0.70; 95% CI 0.38 to 1.28). When metabolic acidosis was analysed according to BDblood, these rates were 1.6% and 2.6%, respectively (RR 0.63; 95% CI 0.42 to 0.94). The number of operative deliveries, low Apgar scores, neonatal admissions and newborns with moderate to severe HIE was comparable in both groups. There were five cases of perinatal death (three in index and two in control group), of which three were due to lethal congenital disorders. The remaining two cases in the index group are described in Appendix B.
From these results we conclude that addition of ST-analysis of the fetal ECG to surveillance with CTG during labour reduces the number of newborns with (metabolic) acidosis, without an effect on Apgar scores, neonatal admissions, moderate to severe HIE or operative deliveries.

4. Adverse neonatal outcome

In chapter 6 we describe that in both deliveries monitored by ST-analysis of the fetal ECG as well as CTG only, infants with unfavourable outcome are born. To assess to what extent these adverse outcomes are related to either type of fetal monitoring, a subgroup analysis of the above mentioned randomised trial including all cases with adverse neonatal outcome, is described in **Chapter 7**. Three observers independently assessed all cases with adverse neonatal outcome, identified by (one of) the following criteria: 1) cord-artery metabolic acidosis (pH < 7.05 & BDecf > 12 mmol/L); 2) cord-artery pH < 7.00; 3) perinatal death; and/or 4) moderate or severe HIE.
61 (1.1%) cases with adverse neonatal outcome were identified (26 index and 35 control group). In these cases with adverse outcome monitored by ST-analysis of the fetal ECG (index group), the total number of operative deliveries was 23 (88.5%) versus 20 (57.1%) in the cases monitored by CTG only (control group) (p=0.01). Observer evaluation showed that there was an indication to intervene for suspected fetal distress in 23 (88.5%) and 19 (57.6%) cases, respectively (p=0.01). The number of cases with an indication to intervene more than 20 minutes before delivery were 13 (50.0%) and 11 (33.3%), respectively (p=0.20). In the cases with adverse outcome in the index group, indications were based on significant ST-events (52.2%) as well as (pre)terminal CTG traces (39.1%), whereas in cases in the control group this was mainly on a (pre)terminal CTG (73.7%). STAN® guidelines or the study

protocol were violated in 11 (42.3%) and 13 (39.4%) cases of the index and control group, respectively. Correct adherence to these guidelines, leading to earlier intervention, would probably or certainly have led to better neonatal outcome in 6 (23.1%) and 4 (12.1%) cases, respectively.

These data indicate that monitoring by ST-analysis of the fetal ECG is more specific and comprehensive, regarding the aim to detect and deliver compromised fetuses, than monitoring by CTG only. Correct adherence to STAN® guidelines may increase the detection rate even further. However, in 50% of cases with adverse outcome monitored by ST-analysis there were no clear signs of fetal distress more than 20 minutes before birth, indicating that these could still not have been prevented.

5. Fetal blood sampling in addition to monitoring by ST-analysis of the fetal ECG

Since the existing STAN® guidelines are consensus rather than evidence based, in **Chapter 8** a study is described in which we aimed to evaluate these guidelines, with specific focus on recommendations for situations that may require FBS in addition to ST-analysis of the fetal ECG. Further analysis of the trial data, as described in chapter 6, was performed on deliveries monitored by CTG plus ST-analysis of the fetal ECG (index group) in which at least one fetal blood sample was taken. Three observers assessed the STAN® recordings, to examine whether FBS was performed according to the trial protocol, which allowed FBS in three situations, as previously described in chapter 5. Furthermore, pH results were related to indications for performance of FBS and to ST-waveform analysis.

Of 301 deliveries, 224 STAN® recordings were complete for analysis. A total of 296 fetal blood samples was performed. For 112 of 172 (65.1%) samples performed according to the trial protocol, the reason was an abnormal CTG of more than 60 minutes without ST-events. In 10 (8.9%) of these cases, fetal acidosis (pH<7.20) was present. 18 (10.5%) samples were performed because of an abnormal CTG at start, nine (5.2%) because of an intermediary CTG at start and 33 (19.2%) because of poor ECG signal quality. Two, none and four samples revealed fetal acidosis, respectively. 124 samples (41.9%) were not performed according to the trial protocol, of which 10 (8.1%) samples indicated fetal acidosis. In one of these cases there had been no ST-events.

From these results we conclude that the consensus based recommendation in the STAN® guidelines to additionally check fetal condition by FBS in case of an abnormal CTG of more than 60 minutes without ST-changes, has been effective for early identification of fetal acidosis. However, given the high number of non-hypoxic FBS results, extending the duration of abnormal CTG from 60 to 90 minutes may be considered. Consequent adherence to the STAN® guidelines may further decrease the necessity for FBS in addition to ST-analysis of the fetal ECG.

6. Cost-effectiveness of ST-analysis of the fetal ECG versus CTG

As the use of ST-analysis of the fetal ECG is an effective strategy to prevent acidosis compared to CTG only, it is important to assess the economic consequences of its

introduction. In **Chapter 9** the results are described of the short-term cost-effectiveness analysis, which was performed alongside the above mentioned trial, described in chapter 6. This analysis was primarily based on clinical trial results, of which metabolic acidosis according to pH and BDecf (primary outcome in trial) was used as measure of effectiveness. For the analyses a health care perspective was used and costs and effects were compared from the moment of randomisation to hospital discharge of both mother and child. Total costs per patient were calculated by multiplying resource use per patient by unit costs. Incremental cost-effectiveness ratios (ICER) were calculated by dividing the difference in costs by the difference in effectiveness. Sensitivity analyses were performed to explore the impact of different assumptions and alternative unit-cost estimates on the results of the costs analysis.
Mean costs per patient in the index group were €1.345 (95% CI: €1.013 to €2.115) and €1.316 for the control group (95% CI: €978 to €2.080). Costs per patient appeared to be only €29 (95% CI: -€9 to €77) higher in the index group compared to the control group. This was mainly because of the more expensive STAN® equipment and training.
With an estimated difference in incidence of metabolic acidosis between the two groups of 0.4% in favour of ST-analysis, and a mean difference in costs per patient of €29 in favour of CTG only, the ICER is €7.250 per prevented case of metabolic acidosis. Sensitivity analyses showed that monitoring by ST-analysis of the fetal ECG becomes more cost-effective at a decreasing number of training hours and an increasing difference in the incidence of metabolic acidosis, compared to monitoring by CTG only.
From these results we conclude that the additional costs of monitoring by ST-analysis of the fetal ECG are very limited when compared to CTG only and very low compared to the total costs of labour. Therefore, monitoring by ST-analysis of the fetal ECG appears to be a cost-effective strategy.

Neonatal outcome

Since the goal of intrapartum fetal monitoring is to prevent perinatal asphyxia and long-term adverse neurological outcomes, it is important to identify women with a high(er) risk of developing adverse neonatal outcome as early as possible, e.g. at admission to the hospital or even antenatally. Timely prognostication may lead to more effective decision making during labour, in specific with respect to the type of fetal monitoring that is offered, as well as the interpretation of fetal heart rate patterns.
In **Chapter 10** a study is presented, which aimed to quantify factors measured both before and during labour to predict neonatal metabolic acidosis at birth. We studied labouring women with a high-risk singleton pregnancy in cephalic position at more than 36 weeks of gestation, which were included in the above mentioned trial. The outcome of interest was metabolic acidosis defined as an umbilical cord-artery blood pH below 7.05 combined with a base deficit calculated in blood above 12 mmol/L. We used multiple imputation techniques

for missing data. We developed prediction models both before and during labour using multivariable logistic regression. To correct for overestimated regression coefficients, the models were (internally) validated by bootstrapping techniques and shrinkage. We used calibration and receiver operating characteristic (ROC) analysis (c-statistic) to assess model performance.
In the trial, 119 neonates of 5667 women had metabolic acidosis (2.1%). Antepartum predictors of metabolic acidosis were higher gestational age, nulliparity, a previous caesarean delivery and maternal diabetes. Intrapartum predictors that increased the risk of metabolic acidosis were a spontaneous onset of labour and epidural anaesthesia, whereas ruptured membranes for more than 24 hours with or without maternal fever decreased this risk. Predicted probabilities of the final extended model ranged from 0.2 to 10.4% with an acceptable calibration and a c-statistic of 0.64 (95% CI 0.59-0.69).
From these results we conclude that in women with a high-risk singleton term pregnancy and a fetus in cephalic position, factors both before and during labour can clearly increase and decrease the prior probability of neonatal metabolic acidosis at birth. After external validation and proof of generalisability, these predictors may be used in obstetric clinical management.

Main conclusions of this thesis

- The intrapartum CTG alone, is not specific enough to identify the fetus with an abnormal adaptation to the process of labour. Intrapartum use of the CTG in isolation therefore leads to unnecessary interventions due to false-positive CTG results.
- FBS provides fetal information in addition to the CTG. However, besides practical limitations, the decision whether or not to perform FBS is subjective and therefore often inefficient and even inadequate. Moreover, in the Netherlands, the application of FBS is inconsistent.
- ST-analysis of the fetal ECG also provides additional fetal information, in a continuous, automatic and less-invasive way compared to FBS. However, interpretation of ST-analysis of the fetal ECG in clinical practice is hampered by poor visual assessment of the CTG and human failure to consequently follow clinical guidelines.
- In women with a term singleton fetus in cephalic position, intrapartum monitoring by ST-analysis of the fetal ECG compared to CTG only:
  - reduces the number of newborns with acidosis by 30 to 44%, depending on its definition
  - reduces the need to perform FBS by 50%
  - has no effect on the number of newborns with low Apgar scores
  - has no effect on the number of total neonatal admissions or NICU admissions
  - has no effect on the number of newborns with moderate to severe HIE
  - has no effect on the number of total operative deliveries
  - has very limited additional costs and therefore is a cost-effective strategy

- Although monitoring by ST-analysis of the fetal ECG does not prevent all cases with adverse neonatal outcome, it is more specific and comprehensive regarding the aim to detect and deliver compromised fetuses, than monitoring by CTG and - if indicated - FBS. Monitoring by ST-analysis of the fetal ECG with strict adherence to the STAN® clinical guidelines may further increase the detection rate of compromised fetuses, thus preventing subsequent adverse outcome.
- A major advantage of monitoring by ST-analysis of the fetal ECG as compared to CTG is the substantial decrease by at least 50% in the need to perform FBS. Monitoring by CTG plus ST-analysis therefore is less-invasive than monitoring by CTG only. Strict following of the STAN® guidelines, with the application of FBS only in recommended situations, may further reduce the rate of FBS performed in addition to ST-analysis of the fetal ECG.
- In women with a high-risk singleton term pregnancy with a fetus in cephalic position, factors both before and during labour influence the a priori risk of the development of neonatal metabolic acidosis at birth. This information should be used in obstetric clinical management.

General discussion

For almost 40 years, intrapartum fetal monitoring by CTG has been used, without an optimal balance between the number of operative deliveries for suspected fetal distress and neonatal or long-term outcome.[1-8] Without any doubt, the cause of this imbalance lies in the poor specificity and the difficult interpretation of the CTG.
Non-reassuring CTG traces do not provide sufficient specific information to identify compromised fetuses. Given the high number of non-reassuring CTG traces during labour, especially during second stage, clinical management based on monitoring by CTG alone inevitably leads to many false-positive results and unnecessary interventions.
Furthermore, it has been reported that obstetricians agree on normal CTG patterns, but when normality disappears there is a high inter- and intra-observer variation in grading and classification of such anomalous CTG traces.[9-12] Due to the problematic interpretation of the intrapartum CTG, its isolated use is limited. Techniques to obtain fetal information in addition to the CTG should therefore be used. However, even when other techniques are applied, screening of fetal condition by CTG still remains the first step in the process of intrapartum fetal monitoring.

ST-analysis of the fetal ECG

Although visual and subjective assessment of the CTG is a clear disadvantage of the STAN® method, this may be compensated by the fact that with the use of STAN®, CTG abnormalities may be neglected less easily, compared to monitoring by CTG only. Since the use of ST-analysis of the fetal ECG requires frequent consultation of the STAN® clinical guidelines and the so-called 'ST-log' to classify the CTG and interpret ST-waveform changes, obstetricians are likely to be more alert to the presence of (initial) CTG abnormalities. As a consequence, a more accurate interpretation of the CTG may by itself lead to a more efficient screening of fetal condition during labour, which is a major advantage of the STAN® method. Moreover, it has been reported that obstetricians and midwives prefer the continuity of monitoring by ST-analysis of the fetal ECG to traditional surveillance by CTG plus FBS.[13]
In addition to a more consistent and profound interpretation of the CTG, monitoring by ST-analysis of the fetal ECG has also been found to be more effective in the prevention of adverse neonatal outcome. Both the results of a meta-analysis on four previous trials and the trial described in this thesis indicate that the use of ST-analysis of the fetal ECG reduces the incidence of acidosis, at least in settings in which FBS is being used.[14-18] Table 1 provides an overview of the results of all five trials that have been performed until now.

Table 1 Overview of main outcome measures of five randomised clinical trials comparing intrapartum fetal monitoring by ST-analysis of the fetal ECG to CTG (N=15.338).
Data are presented as n (%) or as relative risk (95% CI), as reported in the published papers.

Author	Total	Metabolic acidosis*	Operative deliveries	FBS
Westgate 1993[14] Relative risk		0.38 (0.14-1.07)	0.90 (0.79-1.01)	0.81 (0.63-1.06)
ST	1219	5 (0.4)	344 (28.2)	93 (7.6)
CTG	1215	13 (1.1)	383 (31.5)	114 (9.4)
Amer-Wahlin 2001[15] Relative risk		0.47 (0.25-0.86)	0.88 (0.79-0.99)	0.87 (0.74-1.03)
ST	2519	15 (0.7)	454 (18.0)	234 (9.0)
CTG	2447	31 (2.0)	500 (20.4)	261 (11.0)
Ojala 2006[16] Relative risk		2.43 (0.86-6.85)	1.03 (0.82-1.31)	0.45 (0.33-0.61)
ST	733	12 (1.7)	117 (15.9)	51 (7.0)
CTG	739	5 (0.7)	114 (15.4)	115 (15.6)
Vayssière 2007[17] Relative risk		1.60 (0.53-4.86)	0.98 (0.86-1.11)	0.44 (0.36-0.52)
ST	399	8 (2.0)	216 (54.1)	108 (27.1)
CTG	400	5 (1.3)	221 (55.3)	248 (62.0)
Westerhuis 2009 Relative risk		0.70 (0.38-1.28)	0.96 (0.87-1.06)	0.52 (0.46-0.59)
ST	2827	20 (0.7)	789 (27.9)	301 (10.6)
CTG	2840	30 (1.1)	822 (28.9)	578 (20.4)
Total				
ST	7697	60 (0.8)	1920 (24.9)	787 (10.2)
CTG	7641	84 (1.1)	2040 (26.7)	1316 (17.2)

* Metabolic acidosis was defined as an umbilical cord-artery pH < 7.05 and BDecf > 12 mmol/L. However, in the trial of Ojala 2006, metabolic acidosis was defined as an umbilical cord-artery pH < 7.05 and BDblood > 12 mmol/L.[16]

From this table, it can be seen that in two large trials without a significant difference in the FBS rate, much lower incidences of metabolic acidosis in the ST-groups were found.[14,15] On the other hand, in two smaller trials reporting significant reductions in the incidence of FBS of more than 50% in favour of the ST-group , no reduction and even an increase in the rate of metabolic acidosis in favour of monitoring by CTG was found.[16,17] The two smaller trials were probably underpowered to adequately assess the effect on metabolic acidosis. Moreover, the population under study in the French trial probably was at higher risk than in the other trials, because only deliveries with meconium stained amniotic fluid and/or abnormal CTG traces were included. Mainly because of these controversies and inconsistent findings, our large trial was performed. We have shown that monitoring by ST-analysis of the fetal ECG

indeed leads to a reduction in acidosis, but its incidence and therefore statistical significance depends on the definition of acidosis. The reduction in acidosis was achieved with a significantly reduced need to perform FBS. The main results of our trial resemble those of the meta-analysis of the four previous trials.[18]

Given the fact that none of the previous trials, including ours, reported an overall increased rate of operative deliveries in labouring women monitored by ST-analysis of the fetal ECG, one must conclude that in addition to the effect of obstetricians being more alert to the CTG, monitoring by ST-analysis of the fetal ECG also is more effective than monitoring by CTG only from a (patho)physiological point of view. This is also supported by the fact that in cases with adverse neonatal outcome in our trial, the operative delivery rate was significantly higher in deliveries monitored by ST-analysis, compared to CTG only. The latter finding may indicate that a strategy of monitoring by CTG and ST-analysis is more directly aimed at the detection and delivery of compromised fetuses, thereby preventing cases with adverse neonatal outcome.

Interestingly, in our trial there was a discrepancy between biochemical and clinical neonatal outcomes. The effect of monitoring by CTG plus ST-analysis on the Apgar score and neonatal admissions to a NICU, although not significant, was opposite to the effect on acidosis related outcomes. This discrepancy was even more pronounced in the group of cases with adverse neonatal outcome. We believe that this is due to the much higher number of (vaginal) operative deliveries in cases with adverse outcome in the group monitored by ST-analysis, which may cause a lower Apgar score without affecting fetal acid-base status. Although correlation of the Apgar score with short- and long-term outcomes has shown to be poor,[19,20] we should await results of long-term follow-up studies comparing the effectiveness of intrapartum monitoring by ST-analysis of the fetal ECG with CTG only. Only then will we be able to make a final judgement on the STAN® method. At present, such data are lacking, but are underway from the long-term follow-up of our trial subjects. Short-term neonatal follow-up in the four previous trials, analysed in the above mentioned meta-analysis, has shown a reduction in the number of newborns with encephalopathy in favour of monitoring by ST-analysis of the fetal ECG (RR 0.37; 95% CI 0.14 to 1.00).[18,21] In our randomised trial, this difference could not be reproduced, which might be due to the very small number of newborns with HIE.

Clinical implications

Guidelines and training

This thesis has shown that a very important aspect of effective and safe use of ST-analysis of the fetal ECG is adherence to the STAN® clinical guidelines (Appendix A).[22] Several studies in this thesis showed that in practice obstetric caregivers often fail to follow these guidelines. This may lead to inadequate decisions regarding whether or not to intervene for suspected fetal distress. Since the STAN® guidelines also recommend situations that require the use of

additional techniques such as FBS, in addition to ST-analysis, inconsistent adherence to these guidelines may also lead to incorrect decisions to perform or to refrain from performing FBS. More strict interpretation of both CTG and ST-waveform according to the guidelines may further prevent cases with adverse neonatal outcome and guide efficient use of FBS, aimed at specific situations that need additional fetal information, without redundant invasiveness.
Even when STAN® guidelines are consistently followed, still half of cases with adverse outcome being monitored by ST-analysis of the fetal ECG were identified too late, not allowing for earlier intervention. On the other hand, compared to monitoring by CTG only, the rate of 'false-negative' cases, in which there were no indications to intervene based on guidelines and the trial protocol, is much lower when a more comprehensive strategy of monitoring by ST-analysis of the fetal ECG is used, instead of monitoring by CTG only.
Since the information provided by ST-analysis can only be judged when the CTG is correctly classified, CTG interpretation should (still) be continuously trained, not only in a formal but also in an informal clinical setting. Training should emphasize on the (timely) recognition of in specific (pre)terminal CTG patterns, since in 40% of cases with adverse outcome the latter trace, as incorporated in the STAN® guidelines, is reason to perform an intervention.
Overall, monitoring by ST-analysis of the fetal ECG has shown to be a cost-effective strategy, as compared to monitoring by CTG only. Additional costs for training, which is required for effective and safe implementation of ST-analysis of the fetal ECG, may at first sight be considered as a disadvantage. However, the increased use of the STAN® method has already led to training of labour ward personnel in an informal clinical setting, which in the future may limit the need for official training sessions and thereby additional costs.

Fetal blood sampling

Myocardial anaerobic metabolism and glycogenolysis underlie a rise in T/QRS ratio of the fetal ECG, whereas accumulation of CO_2 and a subsequent increase in free hydrogen ions underlie an acidotic pH obtained at FBS. This means that the information provided by ST-analysis seems more valuable, because it probably better reflects the metabolic fetal compensation to hypoxia. A low pH obtained at FBS is dominated by the respiratory component of fetal acidosis, which is part of normal labour. Despite the fact that the results of both ST-analysis of the fetal ECG and FBS are based on different mechanisms, in some situations their combined use may be necessary to timely identify a compromised fetus.
Although in our trial, as well as in the mentioned meta-analysis,[18] the incidence of FBS was significantly lower in the ST-analysis group, still in 10.6% of deliveries FBS was performed in addition to ST-information (Table 1).[14-18] Recommended situations in which FBS should be performed in addition to ST-analysis of the fetal ECG are outlined in the most recent STAN® clinical guidelines.[22] However, in our trial 40% of FBS in addition to ST-analysis was not performed according these guidelines. Moreover, in this group there were only three cases with metabolic acidosis at birth, which had also been identified by significant ST-events before the moment of FBS. This may indicate that consequent obstetrical management

according to the STAN® guidelines will yield an even lower FBS rate in women monitored by ST-analysis of the fetal ECG.
A strategy of monitoring by CTG plus ST-analysis will not completely rule out the use of FBS. However, the substantial decrease in the need to perform FBS, compared to CTG only, is a favourable outcome, since FBS has several drawbacks. It provides only intermittent information and the decision to perform FBS is based on a subjective interpretation of the CTG. Furthermore, performance of FBS requires expertise, is invasive, often fails and is time-consuming.[23-25] The latter may even cause a serious delay in delivery, especially during the second stage of labour, when FBS is performed to check the significance of CTG and ST-changes.
Recently, measurement of lactate instead of pH in fetal scalp blood has been introduced as a biochemical marker of hypoxia. With respect to operative deliveries or neonatal outcome no differences with pH have been found, but the success rate in lactate sampling was higher.[26]

Definition of neonatal outcome

A general problem of studies on intrapartum fetal monitoring is the definition of a clinically relevant outcome measure. Although it may be discussed whether long-term adverse outcomes are of greatest interest and importance, the choice for a marker of adverse outcome also heavily depends on its prevalence. Since cases with perinatal mortality, cerebral palsy and even encephalopathy are rare, most studies primarily focus on short-term neonatal outcomes, such as perinatal asphyxia. Moreover, it is known that a poor condition at birth is associated with the development of neurological problems and long-term adverse outcome.[27-29]

Defining neonatal asphyxia is complicated. Often its biochemical derivative metabolic acidosis is used, which is the combined presence of both a low umbilical cord-artery pH and base deficit (BD). BD is a calculated value from the measured values pH and pCO2 in umbilical cord blood. This calculation is highly influenced by the choice of fetal fluid compartment (whole blood or extracellular fluid). Moreover, algorithms for calculation of BD vary with different brands of blood gas analysing devices.[30-32] Due to the lack of good evidence on the association of either algorithm with neonatal outcome, there is no consensus regarding which algorithm should be used. This creates clinical difficulties with respect to the definition of acidosis. This is clearly illustrated by our trial, in which the incidence of metabolic acidosis according to the BD in blood was much higher than the incidence of metabolic acidosis according to the BD in extracellular fluid. When cord blood gases are used as outcomes, (in)comparability of study results is also a problem. This is illustrated by the five trials comparing monitoring by ST-analysis of the fetal ECG to CTG only (Table 1). In four of these trials metabolic acidosis was analysed according to pH and BD in the extracellular fluid,[14,15,17] whereas in one trial pH and BD in blood was used.[16] Because of the use of different algorithms for calculation of BD, a straight comparison of the results of these trials, as has been done in the meta-analysis,[18] is impossible. Recalculation of BD values in

the trial of Ojala from blood to extracellular fluid,[16] leads to different study results with a (non-significant) decrease instead of an increase in the rate of metabolic acidosis.[33]
To overcome the problem of different algorithms to be used for 'artificial' calculation of BD, the directly determined parameter lactate may be used instead. Lactate alone, preferably adjusted for gestational age, or in combination with pH, has been shown to be a satisfactory alternative for BD as an indicator for fetal condition at birth.[34,35]
Another problem with respect to neonatal acid-base status, concerns the collection of umbilical cord blood. Although parameters measured in the umbilical cord artery correlate best with the fetal tissue oxygenation and acid-base status, it is recommended to obtain blood from both the umbilical cord artery and vein. In this way it is possible to identify the origin of a sample and insight is provided into the cause and duration of hypoxia and the quantity of an acid-base shift. However, in clinical practice often sampling of the umbilical cord is forgotten or only one sample is available. The latter is then likely to be the (less-informative) venous sample, because the vein is larger and contains more blood than the arteries, especially in case of asphyxia. Furthermore, the timing of cord blood clamping influences acid-base values. Delayed clamping (> 30 seconds after birth) of the umbilical cord leads to a rapid decrease in *P*aCO2, which results in a falsely high BD, thereby affecting the measured values of cord blood acid-base parameters.[36]

Strengths and limitations

There are some strengths and limitations related to the studies in this thesis. A major strength is the large number of women that was recruited in our randomised trial within only two years. Without the infrastructure of the Dutch Obstetric Consortium recruitment and data collection of this large group of women would not have succeeded.[37]
The relevance of this thesis also adds to its strength. Perinatal asphyxia remains an important cause of long-term deficits, and of medico-legal litigations. The results of the studies described in this thesis may guide future obstetric management of high-risk deliveries, aiming at further prevention of neonatal and long-term adverse outcomes.
Although many high-risk deliveries in secondary care were studied in our trial, the metabolic acidosis rate was much lower than expected, which may affect generalisability of our results and power of the study. The low metabolic acidosis rate may be explained by the fact that women diagnosed with acute signs of fetal distress at admission were not approached for participation. Another explanation may be that women included in a trial were being treated with more care and alertness, compared to 'normal' clinical practice.
Another limitation of some studies in this thesis is that the results were based on interpretation of CTG traces by observers. Due to inter- and intra-observer variation, in these specific studies, observer bias may have played a role. However, observers in these studies were experienced in interpreting CTG traces and recordings were independently assessed without knowledge of outcome.

Conclusions and recommendations for clinical practice

The studies in this thesis show that intrapartum fetal monitoring by CTG alone does not provide enough specific information to effectively and safely guide labour in order to prevent adverse outcomes. Fetal monitoring by CTG alone, without the option to obtain additional fetal information, should therefore not be practiced.
FBS may be used, although this method has several limitations. Besides practical issues, the most important limitation is that the decision to perform or to refrain from FBS is subjective. In particular timing of performance of FBS is therefore often inadequate.
From the studies in this thesis and from the literature, we conclude that a strategy of fetal monitoring by CTG plus ST-analysis of the fetal ECG, according to the STAN® clinical guidelines, is more cost-effective, less-invasive and more reliable than monitoring by CTG and FBS. Monitoring by ST-analysis of the fetal ECG, as compared to CTG, leads to a reduction in neonates born with acidosis without an increase in operative deliveries and a substantially decreased need to perform FBS. Furthermore, monitoring by ST-analysis of the fetal ECG identifies compromised fetuses and subsequent adverse outcome better and more specific. Since STAN® users are likely to be more alert to the CTG, the latter is probably interpreted more correctly and consistently. This is a major advantage of the STAN® method, since screening of the fetal condition by CTG is the basis of fetal surveillance in general.
The strong variation in antenatal baseline risk for acidosis, which may be adjusted with factors occurring during labour, provides much more information on a woman's individual risk of developing neonatal metabolic acidosis. We recommend obstetricians to take into account these individual risk factors. In this way a more efficient decision making process during labour will be generated, with respect to the interpretation of fetal heart rate patterns in general and the decision which patients would benefit from monitoring by ST-analysis of the fetal ECG.

Recommendations for further research

- Since heterogeneity played a role in the previously published meta-analysis and since the results of the large Dutch STAN® trial are now available, an additional (cumulative) meta-analysis should be performed, to establish a more definitive answer regarding the effectiveness of monitoring by ST-analysis of the fetal ECG in a setting in which FBS is being used.
- In addition to this meta-analysis on aggregate study data, the results of an individual patient data (IPD) meta-analysis on all randomised clinical STAN® trials would be even more valuable. In this way individual variation between studies can be better explored.
- Such IPD meta-analysis also provides (more) adequate power to quantify the effectiveness of fetal monitoring by ST-analysis of the fetal ECG across specific subgroups of patients, such as maternal diabetes, fetal heart abnormalities and maternal intrapartum fever.

- Since the studies in this thesis provide information on the use of ST-analysis of the fetal ECG in a setting with FBS, it would be interesting to assess the effectiveness of monitoring by CTG plus ST-analysis versus CTG alone, in a setting without the possibility to perform FBS, such as the USA.
- This thesis only provides data on short-term neonatal outcomes. Therefore, follow up studies comparing intrapartum fetal monitoring by ST-analysis of the fetal ECG to CTG in relation to long-term outcomes of children are needed. At present, a two-year follow up study of the Dutch STAN® trial is ongoing.
- Since visual CTG assessment is the basis for intrapartum fetal monitoring, computerised quantification of fetal heart rate patterns, in specific fetal heart rate variability, is likely to contribute to a better interpretation of the CTG during labour. More research in this field is needed, especially to incorporate the results of these (existing) studies in the STAN® guidelines and equipment.
- More research is needed to evaluate the possibilities of trans-abdominal fetal ECG assessment, since in this way non-invasive ST-analysis may also be used in the antenatal period, with intact membranes and in preterm fetuses.
- Since monitoring by ST-analysis of the fetal ECG does not totally rule out performance of FBS, it may be questioned whether measurement of pH in fetal scalp blood is most effective and efficient. More research is needed to study the clinical value and implementation of lactate versus pH measurement in fetal scalp blood, not only with respect to the association with neonatal outcome, but also to logistic and efficiency aspects in clinical practice.
- Given the problems related to the calculation of base deficit, existing evidence on the use of lactate instead of base deficit should be used to set up a study to compare these two parameters, with respect to their association with neonatal outcome and logistic aspects.
- It is known that experience and training in the use of the STAN® method play an important role in its effectiveness. It would therefore be of interest to assess the learning-effect of increasing experience with monitoring by ST-analysis of the fetal ECG, on the number of operative deliveries, FBS and neonatal outcome.
- The study described in chapter 10, aimed to indicate which factors measured before and during labour may be considered as risk factors for the development of neonatal metabolic acidosis. Before these results can be applied to new patients in clinical practice, the models should be externally validated on data of other studies.

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Appendices

Appendix A: STAN® clinical guidelines

Classification of CTG

The intended use of this CTG classification system is to suggest clinical conditions in which adjunctive use of ST waveform changes may aid the interpretation of specific CTG patterns.

CTG	Baseline heart frequency	Variability Reactivity	Decelerations
Normal	• 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*	• 100-110 bpm • 150-170 bpm • Short bradycardia episode (<100 bpm for ≤3 min)	• >25 bpm (saltatory pattern) • <5 bpm for >40 min with absence of accelerations	• Uncomplicated variable decelerations with a duration of <60 sec and loss of >60 beats
Abnormal	• 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	• Total lack of variability (<2 bpm) and reactivity with or without decelerations or bradycardia		

* A combination of several intermediary observations will result in an abnormal CTG.

ST-analysis

These guidelines may indicate situations in which obstetric intervention[1] is required.

ST Events	Normal CTG	Intermediary CTG	Abnormal CTG	Preterminal CTG
Episodic T/QRS-rise (<10 minutes)	• Expectant management • Continued observation	• >0.15	• >0.10	• Immediate delivery
Baseline T/QRS-rise (≥ 10 minutes)		• >0.10	• >0.05	
Biphasic ST (ST-segment below baseline)		• 3 Biphasic log messages[2]	• 2 Biphasic log messages[2]	

[1] Intervention may include delivery or maternal-fetal resuscitation by alleviation of contributing problems such as over-stimulation or maternal hypotension and hypoxia.
[2] The time span between the Biphasic messages should be related to the CTG pattern and the clinical situation.

Information for use of STAN® clinical guidelines

(These guidelines are adapted after Amer-Wahlin et al BJOG 2007;114:1191-93)

- Intervention depends on the cause of fetal compromise and the stage of labour. It includes qualified assessment of the CTG pattern, alleviation of cause(s) of fetal distress (such as 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.

STAN® clinical guidelines – Checklist

Before using ST-analysis:

- >36+0 gestational weeks
- Ruptured membranes
- No contraindication for scalp electrode
- First stage, no active or involuntary pushing

At onset of ST-analysis:

- Check for reactivity and non-deteriorating fetal state; classify the CTG
- Check for normal ECG waveform with sufficient signal quality
- Check for Event Log message “Baseline T/QRS determined”

Appendix B: Perinatal death case reports

Perinatal death

In the randomised clinical trial, in total there were five perinatal deaths (Chapter 6). Three were caused by lethal congenital malformations: one case with a transposition of the great arteries without possibilities for shunting, one case with an intracranial teratoma and one case with a hypoplastic left heart syndrome. In this Appendix the two other cases of perinatal death (both in index group) will be reported in more detail.

Case report 1

A 35-year-old para 1 with a history of caesarean delivery (fetal distress) had an uncomplicated pregnancy monitored in secondary care. At 39 + 4 weeks she went into spontaneous labour and was admitted to hospital.

Observations during labour
Because of decelerations on external CTG monitoring, membranes were ruptured artificially at 22:30 hrs to apply a scalp electrode for internal fetal monitoring. Dilatation was 3 cm and the CTG showed complicated variable decelerations. Because of persisting abnormal CTG at 02:30 hrs, FBS with pH of 7.38 was performed. For pain relief epidural anaesthesia was administered at 03:30 hrs (dilatation 5-6 cm). At 04:20 hrs FBS was performed with pH 7.33. At 04:40 hrs the STAN® recording was started (Figure 1A). At that time dilatation was 9 cm. At 06:30 hrs FBS was repeated because of an abnormal CTG for more than one hour, without ST-events, with pH of 7.31. At 06:45 hrs a baseline T/QRS rise of 0.06 appeared (Figure 1B). Dilatation was 10 cm, but the head was not sufficiently engaged to start active pushing and perform a vacuum extraction. FBS was therefore repeated at 07:00 hrs, with pH of 7.28. At 07:37 hrs a second significant baseline T/QRS rise of 0.06 arose (Figure 1C). Again, FBS was repeated at 07:48 hrs which showed a pH of 7.27. At 08:00 hrs active pushing and oxytocin augmentation was started. At 08:55 hrs it was decided to perform a vacuum extraction because of failure to progress and fetal distress. At that time maternal hematuria was noted. Also, at 09:00 hrs a third significant ST-event arose, after which the vacuum extraction was started (Figure 1D). Traction during two contractions yielded no progress and an emergency caesarean delivery was performed. At that time the mother indicated pain in the region of the previous caesarean delivery scar, vaginal blood loss was noted and the CTG was (pre)terminal. At caesarean delivery rupture of the uterus appeared to be the cause of distress.

Neonatal outcome
At 09:42 hrs a boy 3380 g in weight was born. Apgar scores were 0, 0 and 3 after 1, 5 and 10 minutes, respectively. Only one umbilical cord sample was available, showing a pH of 6.96 with a base deficit of 22 mmol/L. Lactate within 1 hour postpartum was 13.9 mmol/L. The newborn was resuscitated for 20 minutes, intubated and admitted to the neonatal intensive care unit. One hour postpartum the pH was 6.81. Electro encephalography showed no cerebral activity and the baby died of severe perinatal asphyxia and hypoxic ischemic encephalopathy (Sarnat grade 3) after 1 day.

Case report 2

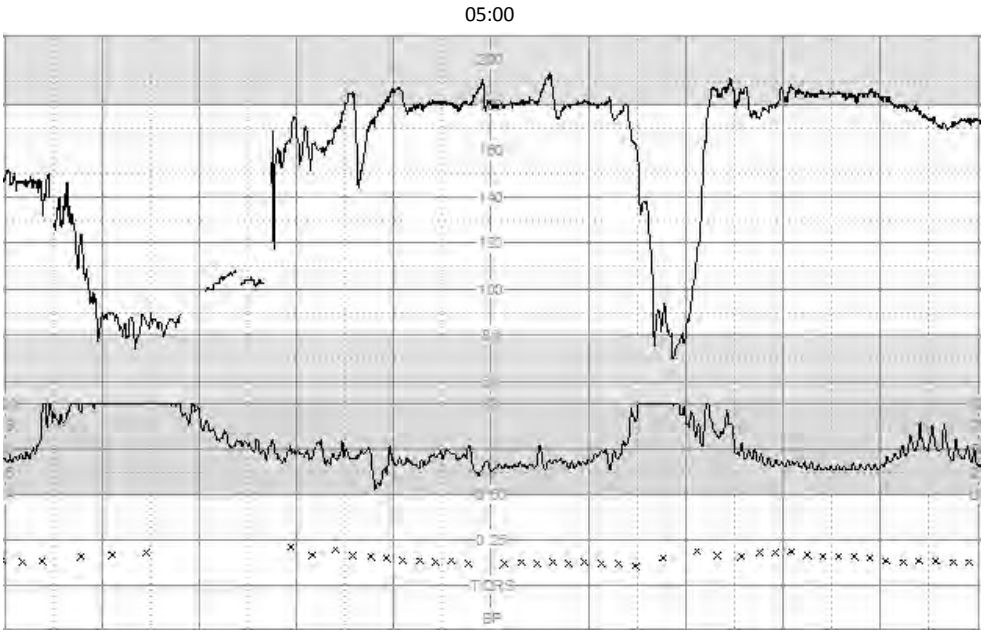
A 35-year-old para 0 had an uncomplicated pregnancy. At 39 + 3 weeks she was admitted to hospital because of ruptured membranes for more than 24 hours.

Observations during labour
At admission external CTG showed a baseline fetal heart rate of 140 with accelerations and good variability. The external CTG recording was ended at 07:49 hrs (Figure 2A). To start induction of labour, at 08:05 hrs a scalp electrode and intra-uterine pressure catheter for internal monitoring was applied and a STAN® recording was started. The CTG showed a (pre)terminal trace directly from the start at 08:09 hrs (Figure 2B), which was acted upon immediately by emergency caesarean delivery. No meconium stained amniotic fluid or blood was noted.

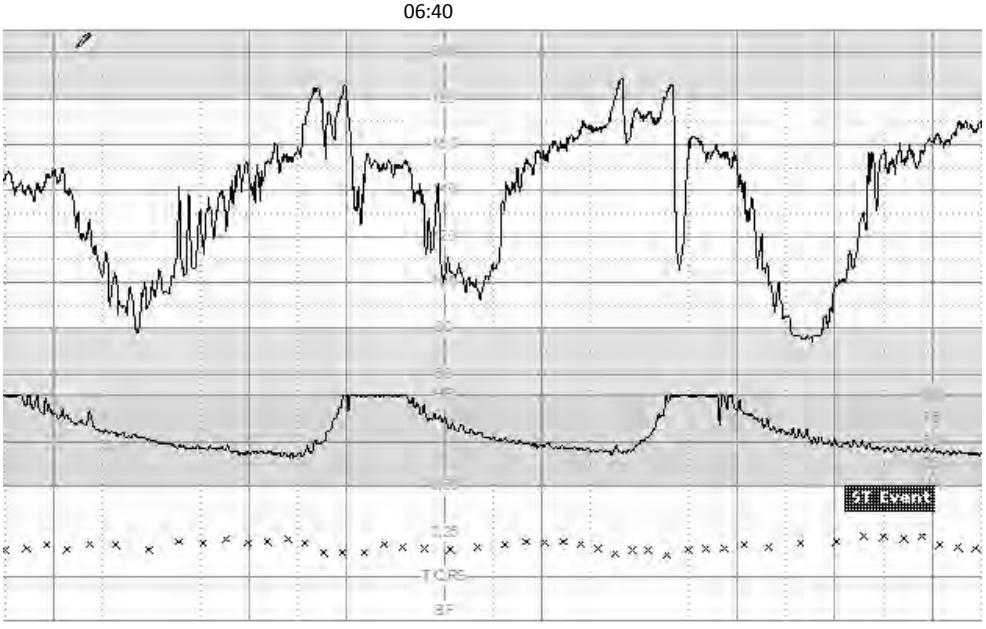
Neonatal outcome
At 08:28 hrs a girl 3260 g in weight was born. Apgar scores were 0 after 1, 5 and 10 minutes. Umbilical cord-artery pH was 6.94 with a base deficit of 13 mmol/L and cord-venous pH was 7.20 with a base deficit of 9 mmol/L. Resuscitation was performed for 15 minutes, without any result. Thorough pathologic and maternal investigation showed no cause for this severe asphyxia.

Figure 1 Subsequent parts of STAN® recording of case 1 (2cm/min)

A



B

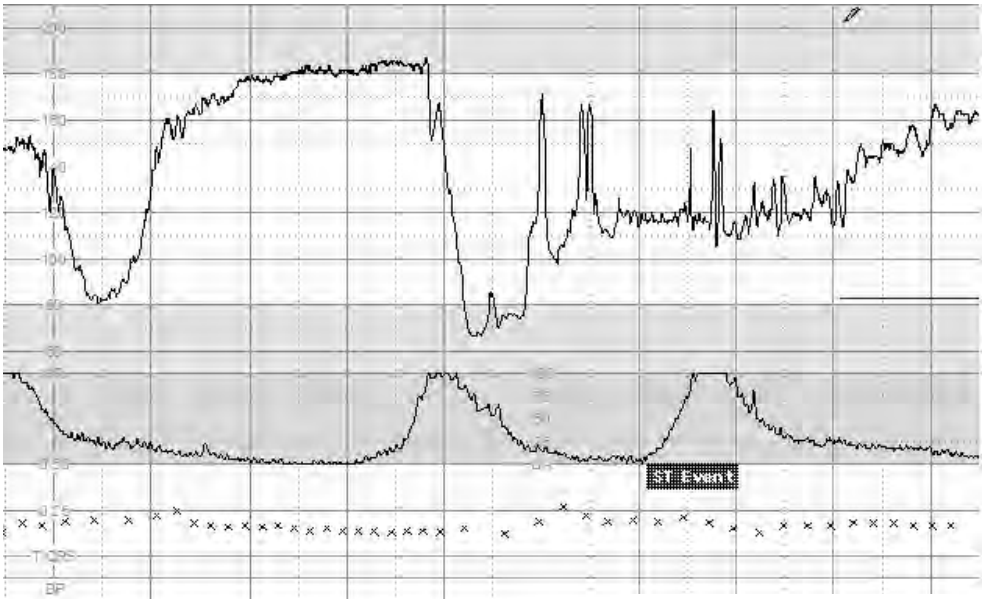


06:45 baseline T/QRS rise 0.06

Figure 1 Continued

C

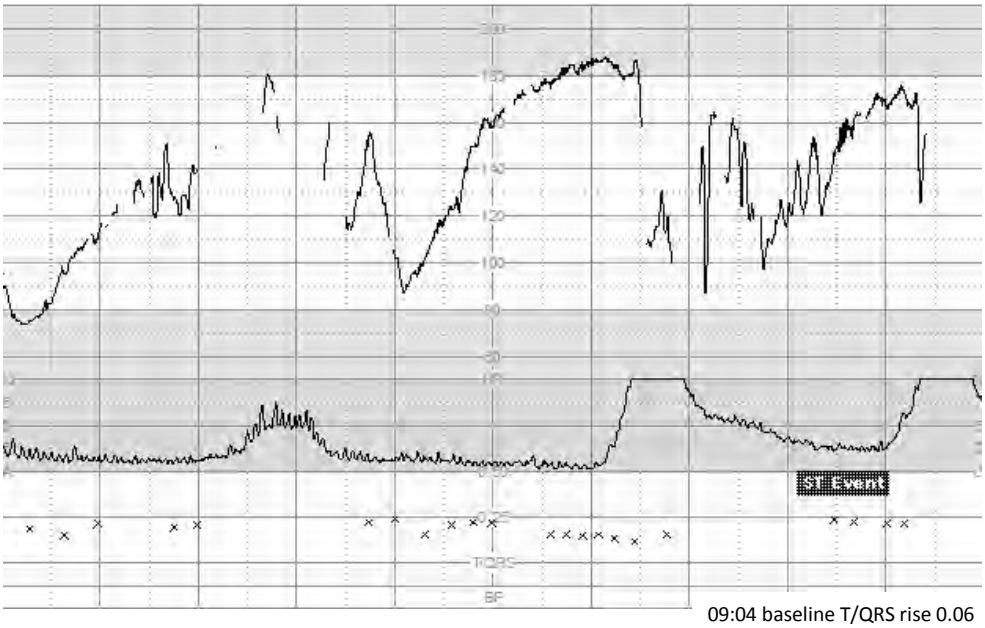
07:30



07:37 baseline T/QRS rise 0.06

D

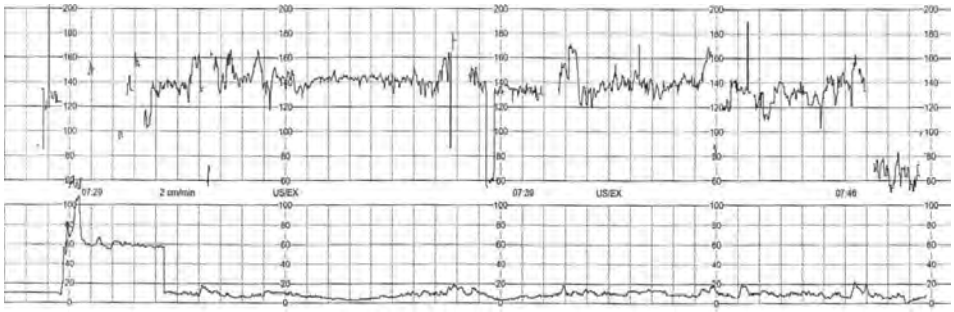
09:00



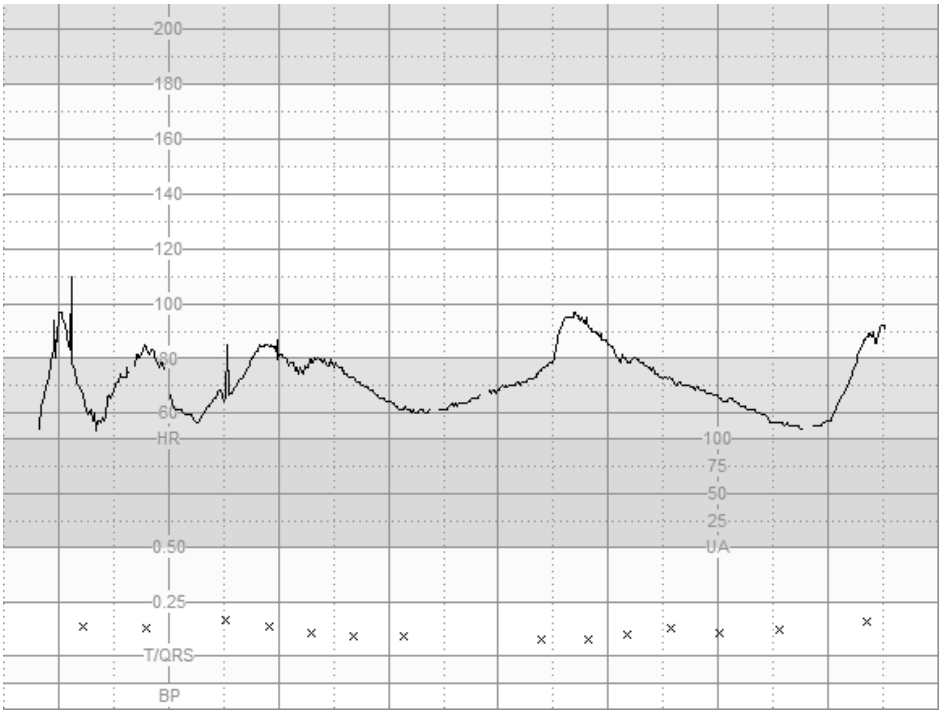
09:04 baseline T/QRS rise 0.06

Figure 2 CTG (A) and STAN® (B) recording of case 2 (2cm/min)

A



B



Nederlandse samenvatting

Summary in Dutch

Introductie

Dit proefschrift gaat over intrapartum foetale bewaking door middel van ST-analyse van het foetale electrocardiogram (ECG; STAN®), met betrekking tot de (kosten) effectiviteit, de beperkingen, de klinische gevolgen en de richtlijnen behorende bij deze methode. Het doel van dit proefschrift wordt in **Hoofdstuk 1** uiteengezet aan de hand van de volgende onderzoeksvragen:

1) Wat zegt de bestaande literatuur over de effectiviteit van ST-analyse van het foetale ECG?
2) Wat zijn de beperkingen en nadelen van ST-analyse van het foetale ECG bij gebruik in de klinische praktijk?
3) Is een strategie als foetale bewaking door middel van ST-analyse van het foetale ECG kosteneffectiever dan bewaking door alleen cardiotocografie (CTG)?
4) In welke mate worden gevallen met ongunstige neonatale uitkomst voorkomen wanneer de klinische richtlijnen behorende bij bewaking door ST-analyse van het foetale ECG correct gevolgd worden? Dit alles in vergelijking met bewaking door alleen het CTG.
5) Bij welke patiënten is het verrichten van microbloedonderzoek (MBO) in aanvulling op bewaking door ST-analyse van het foetale ECG nodig?
6) Is het mogelijk om aan de hand van factoren zowel voor als na de bevalling neonatale metabole acidose bij de geboorte te voorspellen?

Het doel van intrapartum foetale bewaking is het tijdig opsporen van een foetus met dreigend zuurstofgebrek, om lange termijn schade als gevolg van asfyxie te voorkomen. Met dit doel is in de jaren zeventig van de vorige eeuw het CTG geïntroduceerd, zonder dat de diagnostische nauwkeurigheid, laat staan de effectiviteit op patiëntuitkomsten, grondig werd geëvalueerd. Toch wordt het CTG op grote schaal toegepast. De interpretatie van het intrapartum CTG is lastig, omdat afwijkende CTG patronen niet specifiek genoeg zijn om een foetus met vermeend zuurstoftekort op te sporen. Ook is er tussen verschillende artsen en verloskundigen een (te) grote variatie in de beoordeling van CTG patronen en dus de foetale conditie.

Aanvullende methoden voor foetale bewaking durante partu

Om onnodige interventies (vaginale kunstverlossingen en/of keizersnedes) voor vermeende foetale nood te voorkomen, is het in geval van een afwijkend CTG van cruciaal belang aanvullende foetale informatie te verkrijgen. In **Hoofdstuk 2** worden twee methoden van dergelijk aanvullend onderzoek, te weten het microbloedonderzoek (MBO) en ST-analyse van het foetale ECG, beschreven.

1.1. Microbloedonderzoek (MBO)

Ondanks dat door middel van het MBO directe informatie over de foetale zuur-basen status kan worden verkregen, is de toepassing van deze techniek toch maar beperkt tot een aantal landen. Een van de redenen hiervoor is dat het MBO alleen informatie biedt op een bepaald moment en dus bij een afwijkend CTG herhaald moet worden. Bovendien hangt de beslissing om een MBO te doen af van de subjectieve en vaak inadequate interpretatie van het CTG. Verder is het verrichten van een MBO invasief, technisch lastig en patiënt onvriendelijk. Tenminste 10% van de MBO pogingen slaagt niet, waardoor het een tijdrovende procedure kan zijn. De relatief grote hoeveelheid bloed die nodig is voor bepaling van de pH wordt ook als een nadeel van het MBO gezien.

De resultaten van een enquete onder alle Nederlandse obstetrische klinieken laten zien dat het MBO verricht wordt in 88% van alle klinieken. In 60% hiervan wordt bij een afwijkend CTG meestal een MBO verricht. In veel klinieken ontbreekt een goede logistiek voor de bepaling van de resultaten van het MBO.

1.2. ST-analyse van het foetale ECG

Experimenteel dieronderzoek heeft aangetoond dat veranderingen in het ST-segment van het ECG corresponderen met foetaal zuurstofgebrek durante partu. Vanaf de negentiger jaren is het mogelijk om niet alleen de foetale hartslag maar ook de rest van het foetale ECG signaal, met name het ST-segment, te registreren door middel van een schedelelectrode. Dit heeft geleid tot de ontwikkeling van intrapartum foetale bewaking door middel van ST-analyse van het foetale ECG (STAN® methode).

Het STAN® concept is gebaseerd op een gecombineerde interpretatie van het CTG en ST-veranderingen van het foetale ECG. De relevantie van ST-veranderingen is afhankelijk van de visuele beoordeling van het CTG, dat geclassificeerd wordt als normaal, suboptimaal, abnormaal of (pre)terminaal, volgens de STAN® klinische richtlijnen. Deze richtlijnen geven ook aan in welke situaties interventie nodig is (Appendix A).

Een meta-analyse gebaseerd op 4 gerandomiseerde onderzoeken toont aan dat bewaking door middel van ST-analyse van het foetale ECG leidt tot een reductie van het aantal neonaten met metabole acidose en/of encefalopathie en het totaal aantal kunstverlossingen.

2. Klinische beperkingen van bewaking door ST-analyse van het foetale ECG

De STAN® methode is gebaseerd op de visuele beoordeling van het CTG, dat twee problemen kent. In de eerste plaats speelt de grote variatie in CTG interpretatie tussen verschillende beoordelaars logischerwijs ook een rol bij bewaking door STAN®. In **Hoofdstuk 3** werd de inter- en intra-observer overeenkomst in de classificatie van het CTG en de overeenkomstige beslissing tot eventuele interventie - volgens de STAN® klinische richtlijnen - gekwantificeerd. De STAN® registraties van 73 a terme hoog risico bevallingen werden door 6 beoordelaars geobserveerd. Voor het normale en het (pre)terminale CTG was de overeenkomst tussen de beoordelaars redelijk tot goed, maar voor het suboptimale en abnormale CTG patroon kwamen de beoordelaars niet goed overeen. De resultaten van deze

studie suggereren dat toevoeging van informatie over het foetale ECG aan het CTG, met name wanneer dit sub- of abnormaal is, leidt tot een gestandaardiseerd besluit om al dan niet een interventie te verrichten.

Een tweede potentiële beperking van de STAN® methode, deels veroorzaakt door de visuele (onbetrouwbare) beoordeling van het CTG, is het inconsistent volgen van de (STAN®) klinische richtlijnen. In **Hoofdstuk 4** worden drie casus beschreven, waarin ondanks bewaking door ST-analyse van het foetale ECG, kinderen met ernstige acidose (arteriële navelstreng pH < 7.00) geboren werden. Deze casus laten zien dat er bij het voorkomen van perinatale metabole acidose in de klinische praktijk, enkele beperkingen bij het gebruik van de STAN® methode naar voren komen. Slechte ECG signaal kwaliteit, moeilijkheden bij de correctie interpretatie van het CTG, het consequent volgen van de STAN® klinische richtlijnen en de tot op heden incomplete kennis over de intrapartum foetale pathofysiologie (bijvoorbeeld in de situatie van maternale koorts), kunnen leiden tot onverwachte en ongunstige uitkomsten. Dit hoofdstuk eindigt met de aanbeveling dat de STAN® klinische richtlijnen gedetailleerdere instructies moeten bevatten, wat betreft de correcte en tijdige identificatie van 'moeilijke casus'. In 2007 leidde een consensusoverleg tussen Europese STAN® experts in Utrecht dan ook tot aanpassing van deze richtlijnen (Appendix A).

3. Effectiviteit van bewaking door middel van ST-analyse versus het CTG

In **Hoofdstuk 5** wordt het studieprotocol beschreven van een grote pragmatische multicenter gerandomiseerde trial, die als doel had de (kosten) effectiviteit van bewaking door middel van ST-analyse van het foetale ECG te vergelijken met bewaking door alleen het CTG. De trial werd uitgevoerd binnen het Verloskundig Consortium (www.studies-obsgyn.nl/stan). Drie academische en zes niet-academische opleidingsziekenhuizen participeerden in de trial.

Vrouwen durante partu, ouder dan 18 jaar, met een hoogrisico aterme zwangerschap van een eenling in hoofdligging werden gerandomiseerd voor bewaking door middel van het CTG met ST-analyse (index groep) of bewaking door middel van het CTG zonder ST-analyse van het foetale ECG (controle groep). Er was een strict protocol voor het verrichten van MBO's, in de index groep beperkt tot drie situaties: 1) start van een STAN registratie met een sub- of abnormaal CTG; 2) abnormaal CTG > 60 minuten zonder ST-events; 3) slechte ECG signaal kwaliteit met een sub- of abnormaal CTG. Het verdere obstetrische beleid werd geleid door de STAN® klinische richtlijnen (Appendix A).

De primaire uitkomst was metabole acidose gedefinieerd als een arteriele navelstreng pH lager dan 7.05 met een basentekort (BD) berekend in de extracellulaire vloeistof hoger dan 12 mmol/L.

Een secundaire uitkomst was metabole acidose gedefinieerd als een arteriele navelstreng pH lager dan 7.05 met een basentekort berekend in bloed hoger dan 12 mmol/L. Overige secundaire uitkomsten waren het aantal pasgeborenen met een Apgar score lager dan vier en zeven na één en tien minuten respectievelijk, het totaal aantal neonatale opnames en opnames

op een neonatale intensive care afdeling (NICU), het aantal pasgeborenen met matige tot ernstige hypoxisch ischemische encefalopathie (HIE) volgens Sarnat, het aantal instrumentele bevallingen, het aantal bevallingen met MBO en de kosten.

De resultaten van deze trial worden beschreven in **Hoofdstuk 6**. In de periode januari 2006 tot en met juli 2008 werden er in totaal 5681 vrouwen gerandomiseerd, waarvan 2832 voor de index and 2849 voor de controle groep. Na randomisatie werden 14 vrouwen geëxcludeerd (vijf in de index en negen in de controle groep), omdat ze niet aan de inclusie criteria voldeden. Data van 5667 (2827 in de index en 2840 in de controle groep) vrouwen werden geanalyseerd volgens het intention-to-treat principe.
Het MBO percentage in de index groep was 10.6% vergeleken met 20.4% in de controle groep (relatief risico (RR) 0.52; 95% betrouwbaarheidsinterval (BI) 0.46 tot 0.60). De incidentie van de primaire uitkomst was 0.7% in de index versus 1.1% in de controle groep (RR 0.70; 95% BI 0.38 tot 1.28). Indien metabole acidose werd geanalyseerd gebaseerd op pH en BD berekend in bloed, waren de respectievelijke incidenties 1.6% en 2.6% (RR 0.63; 95% BI 0.42 tot 0.94). Het aantal instrumentele bevallingen, lage Apgar scores, neonatale opnames en pasgeborenen met matige tot ernstige HIE was vergelijkbaar tussen de groepen. Er waren vijf perinatale sterftes (drie in de index en twee in de controle groep), waarvan drie veroorzaakt werden door een lethale congenitale aandoening. De twee overige sterftes worden beschreven in Appendix B.
Uit de resultaten van deze trial concluderen we dat toevoeging van ST-analyse van het foetale ECG aan bewaking met het CTG durante partu leidt tot een reductie van het aantal pasgeborenen met (metabole) acidose, zonder een effect op de Apgar scores, neonatale opnames, matige tot ernstige HIE of instrumentele bevallingen.

4. Ongunstige neonatale uitkomst

In hoofdstuk 6 wordt beschreven dat in zowel bevallingen bewaakt met behulp van ST-analyse als met alleen het CTG, kinderen met ongunstige uitkomst geboren worden. In **Hoofdstuk 7** wordt een subgroep analyse van alle casus met ongunstige neonatale uitkomsten in de bovengenoemde trial beschreven. Het doel van deze analyse was te onderzoeken in welke mate deze ongunstige neonatale uitkomsten in relatie staan tot het type intrapartum foetale bewaking (CTG met ST-analyse of alleen het CTG).
Drie beoordelaars onderzochten onafhankelijk alle casus met ongunstige neonatale uitkomsten, die geïdentificeerd werden door (één van) de volgende criteria: 1) metabole acidose in de arterie van de navelstreng (pH < 7.05 & BDecf > 12 mmol/L); 2) arteriële navelstreng pH < 7.00; 3) perinatale sterfte; en/of 4) matige of ernstige HIE.
Er werden 61 (1.1%) casus met ongunstige neonatale uitkomst geïdentificeerd (26 in de index en 35 in de controle groep). In deze casus met ongunstige uitkomsten was het totaal aantal instrumentele bevallingen 23 (88.5%) in de groep bewaakt door middel van ST-analyse (index) versus 20 (57.1%) in de groep bewaakt door middel van alleen het CTG (controle) (p=0.01). De evaluatie door de beoordelaars liet zien dat er in 23 (88.5%) versus 19 (57.6%)

(p=0.01) casus, respectievelijk, een indicatie was om te interveniëren vanwege vermeende foetale nood. Het aantal casus waarbij de indicatie tot interveniëren meer dan 20 minuten voor de daadwerkelijke geboorte optrad, was 13 (50.0%) en 11 (33.3%), respectievelijk (p=0.20). Bij de casus met ongunstige neonatale uitkomst in de index groep waren de indicaties tot interventie met name gebaseerd op significante ST-events (52.2%), terwijl in de controle groep een (pre)terminaal CTG meestal leidde tot een indicatie tot interveniëren (73.7%). Het bleek ook dat in beide groepen de STAN® klinische richtlijnen of het studieprotocol geschonden werden in ongeveer 40% van de bevallingen met een ongunstige neonatale uitkomsten.
Deze resultaten geven aan dat, wat betreft het opsporen van de foetus in nood door gebrek aan zuurstof, bewaking door middel van ST-analyse van het foetale ECG specifieker en veelomvattender is dan bewaking door middel van alleen het CTG. Het correct volgen van de STAN® klinische richtlijnen leidt mogelijk nog tot een hoger detectiepercentage. In de helft van de gevallen met ongunstige neonatale uitkomst, waarbij de bevalling bewaakt was met behulp van ST-analyse, waren er echter geen duidelijke tekenen van foetale nood eerder dan 20 minuten voor de daadwerkelijke geboorte. Deze casus hadden dan ook niet voorkomen kunnen worden.

5. Microbloedonderzoek naast bewaking door ST-analyse van het foetale ECG
Aangezien de bestaande STAN® klinische richtlijnen gebaseerd zijn op consensus door experts, maar niet op 'evidence', wordt in **Hoofdstuk 8** een studie beschreven waarin deze richtlijnen geëvalueerd werden. De aandacht was specifiek gericht op de situaties waarin volgens de richtlijnen en volgens het trial protocol (hoofdstuk 5) aanbevolen wordt een MBO te verrichten naast bewaking met ST-analyse. Voor deze studie werd verdere analyse van de trial data, zoals beschreven in hoofdstuk 6, verricht op de 301 bevallingen die bewaakt werden door middel van ST-analyse met tenminste ook één MBO. Van deze 301 bevallingen waren 224 STAN® registraties compleet voor analyse en evaluatie door drie beoordelaars. In totaal werden er in deze groep 296 MBO's verricht.
Voor 112 (65.1%) van de in totaal 172 MBO's die verricht werden volgens het trial protocol, was de reden een abnormaal CTG langer dan 60 minuten zonder ST-events. In 10 van deze casus (8.9%) was er foetale acidose (pH < 7.20). 18 (10.5%) MBO's werden verricht vanwege een abnormaal CTG bij aanvang van een STAN® registratie, negen (5.2%) vanwege een suboptimaal CTG bij aanvang van een STAN® registratie en 33 (19.2%) vanwege slechte signaalkwaliteit van het ECG. In twee, geen en vier MBO's, respectievelijk, werd er foetale acidose gevonden. 124 (41.9%) MBO's werden niet verricht volgens het trial protocol, waarvan er in 10 (8.1%) MBO's foetale acidose gevonden werd. Slechts in één van deze casus trad er geen ST-event op.
Uit de resultaten van deze studie concluderen we dat de op consensus gebaseerde aanbeveling in de STAN® klinische richtlijnen om in geval van een abnormaal CTG langer dan 60 minuten zonder ST-events de foetale conditie te controleren door middel van een MBO,

effectief geweest is voor het tijdig identificeren van foetale acidose. Echter, gezien het grote aantal niet hypoxische MBO resultaten, is het misschien het overwegen waard om de duur van het abnormale CTG van 60 tot 90 minuten te verlengen, alvorens tot MBO over te gaan. Het consequent volgen van de STAN® klinische richtlijnen kan de noodzaak tot het verrichten van een MBO in aanvulling op ST-analyse van het foetale ECG zo mogelijk nog meer verminderen.

6. Kosten effectiviteit van ST-analyse van het foetale ECG versus het CTG

Aangezien het gebruik van ST-analyse van het foetale ECG vergeleken met alleen het CTG een effectieve strategie blijkt om neonatale acidose te voorkomen, is het belangrijk de economische gevolgen van de introductie van STAN® te onderzoeken. In **Hoofdstuk 9** worden dan ook de resultaten beschreven van een analyse naar de korte-termijn kosteneffectiviteit, die uitgevoerd werd naast de trial, zoals beschreven in hoofdstuk 6. Deze analyse was primair gebaseerd op klinische trial resultaten, waarvan metabole acidose (primaire uitkomst in de trial) als maat van effectiviteit gebruikt werd.

De gemiddelde kosten per patiënte in de index groep waren €1.345 (95% BI: €1.013 tot €2.115) ten opzichte van €1.316 in de controle groep (95% BI: €978 tot €2.080). Per patiënte bleken de kosten in de index groep slechts €29 (95% BI: -€9 tot €77) hoger te zijn dan in de controle groep. Dit kwam met name door de duurdere STAN® apparatuur en de noodzakelijke training. Een geschat verschil in de incidentie van metabole acidose tussen de twee groepen van 0.4% ten gunste van bewaking met ST-analyse, en een gemiddeld verschil in kosten per patiënte van €29 ten gunste van bewaking met alleen het CTG, leveren een incrementele kosteneffectiviteitsratio (ICER) op van €7.250 per voorkomen geval van metabole acidose (primaire uitkomst). Sensitiviteitsanalyses lieten zien dat bewaking door middel van ST-analyse vergeleken met alleen het CTG kosteneffectiever wordt al naar gelang er minder uren nodig zijn voor training en het verschil in de incidenties van metabole acidose tussen beide groepen groter wordt.

Op basis van de resultaten van deze studie concluderen we dat de additionele kosten van bewaking door middel van ST-analyse van het foetale ECG zeer beperkt zijn vergeleken met alleen het CTG, en zeer laag vergeleken met de totale kosten van een bevalling. Bewaking door middel van ST-analyse van het foetale ECG lijkt dan ook een kosten effectieve strategie te zijn.

Neonatale uitkomst

Het doel van intrapartum foetale bewaking is het voorkomen van perinatale asfyxie en ongunstige neurologische consequenties op de lange termijn. Daarom is het belangrijk om vrouwen met een hoger risico op ongunstige neonatale uitkomst zo vroeg mogelijk te identificeren, bij voorkeur op het moment van opname in het ziekenhuis of zelfs voor de start van de bevalling. Tijdige voorspelling leidt mogelijk tot effectievere beslissingen tijdens de

bevalling, niet alleen wat betreft de keuze voor een bepaalde methode van foetale bewaking, maar ook voor de interpretatie van foetale hartslag patronen in het algemeen.
Hoofdstuk 10 beschrijft een studie die als doel had te onderzoeken welke factoren, zowel voor als tijdens de bevalling, neonatale metabole acidose bij de geboorte kunnen voorspellen. De data van vrouwen met een hoogrisico a terme eenling zwangerschap met een foetus in hoofdligging, geïncludeerd in de eerder genoemde trial (hoofdstuk 6), werden bestudeerd. De uitkomst was metabole acidose gedefinieerd als een arteriële navelstreng pH kleiner dan 7.05 met een basentekort in bloed groter dan 12 mmol/L. Met behulp van multipele logistische regressie werden er predictiemodellen gemaakt voor zowel voor als tijdens de bevalling. Om te corrigeren voor een overschatting van de regressie coëfficiënten, werden de modellen (intern) gevalideerd door bootstrapping technieken. De prestatie van de modellen werd onderzocht door middel van calibratie en 'receiver operating characteristic' (ROC) analyses.
In de trial hadden 119 neonaten van de 5667 vrouwen metabole acidose (2.1%). Antepartum predictoren van metabole acidose waren een hogere zwangerschapsduur, nulliparitеit, een keizersnede in de anamnese en maternale diabetes. Intrapartum predictoren die het risico op metabole acidose verhoogden, waren een spontane start van de bevalling en epidurale anesthesie. Langdurig gebroken vliezen met of zonder koorts verlaagden dit risico. In het uiteindelijke uitgebreide model varieerden de voorspelde kansen van 0.2 tot 10.4%, met een acceptabele calibratie en een c-index van 0.64 (95% BI 0.59-0.69).
Uit deze resultaten concluderen we dat bij vrouwen met een hoogrisico a terme eenling zwangerschap in hoofdligging, factoren zowel voor als tijdens de bevalling het a priori risico op neonatale metabole acidose duidelijk kunnen verhogen of verlagen. Na externe validatie en een bewijs van generaliseerbaarheid van onze resultaten, kunnen deze predictoren gebruikt worden in het obstetrisch klinisch beleid.

Belangrijkste conclusies van dit proefschrift

- Het intrapartum CTG alleen is niet specifiek genoeg om de foetus met een abnormale aanpassing aan het proces van de bevalling op te sporen. Om deze reden zal het geïsoleerd gebruik van het CTG vanwege fout positieve resultaten leiden tot onnodige interventies.
- Het MBO verschaft foetale informatie in aanvulling op het CTG. Naast praktische beperkingen is de beslissing om een MBO te verrichten echter subjectief en om deze reden vaak inefficiënt en zelfs inadequaat. Bovendien wordt in Nederland het MBO inconsistent toegepast.
- ST-analyse van het foetale ECG verschaft ook additionele foetale informatie, maar dan op een meer continue en automatische en minder invasieve manier, vergeleken met het MBO. Desalniettemin wordt de interpretatie van ST-analyse van het foetale ECG in de klinische praktijk gehinderd door de slechte visuele beoordeling van het CTG en het inconsequent volgen van klinische richtlijnen.

- Intrapartum bewaking met ST-analyse van het foetale ECG, vergeleken met alleen het CTG, bij vrouwen met een a terme eenling in hoofdligging:
  - leidt tot een 30 tot 44% reductie van het aantal pasgeborenen met acidose, afhankelijk van de definitie
  - leidt tot een 50% reductie van de noodzaak tot het verrichten van MBO's
  - heeft geen effect op het aantal pasgeborenen met een lage Apgar score
  - heeft geen effect op het totaal aantal neonatale opnames of het aantal opnames op een NICU
  - heeft geen effect op het aantal pasgeborenen met matige of ernstige HIE
  - heeft geen effect op het totaal aantal kunstverlossingen en/of keizersnedes
  - leidt tot een zeer beperkte toename in kosten en is om deze reden een kosten effectieve strategie
- Alhoewel bewaking door middel van ST-analyse van het foetale ECG niet alle gevallen met een slechte neonatale uitkomst voorkomt, is deze methode toch specifieker en meer omvattender wat betreft het opsporen van gecompromitteerde foetussen, dan bewaking door het CTG en zo nodig MBO. Strikte toepassing van de STAN® klinische richtlijnen zal de identificatie van gecompromitteerde foetussen waarschijnlijk doen toenemen, waardoor verdere ongunstige neonatale uitkomsten voorkomen kunnen worden.
- Een groot voordeel van bewaking door middel van ST-analyse van het foetale ECG, vergeleken met alleen het CTG, is de substantiële afname van de noodzaak tot het verrichten van MBO's. Om deze reden is bewaking met CTG en ST-analyse minder invasief dan bewaking door alleen het CTG. Het strikt toepassen van de STAN® klinische richtlijnen, waarbij er alleen in de aanbevolen situaties een MBO verricht wordt, zal mogelijk leiden tot een verdere reductie van het aantal MBO's dat verricht wordt in aanvulling op bewaking door CTG met ST-analyse.
- Bij vrouwen met een hoogrisico zwangerschap van een a terme eenling in hoofdligging, beïnvloeden zowel factoren voor als tijdens de bevalling het a priori risico op de ontwikkeling van neonatale metabole acidose bij de geboorte. Deze informatie zou gebruikt moeten worden bij met maken van een obstetrisch klinisch beleid.

List of abbreviations

AS	Apgar score
BD	base deficit
BDecf	base deficit calculated in extracellular fluid compartment
BDblood	base deficit calculated in whole blood
CI	confidence interval
CS	Caesarean section
CO2	carbon dioxide
CTG	cardiotcography
ECG	electrocardiography
FBS	fetal blood sampling
GA	gestational age
HIE	hypoxic ischemic encephalopathy
K	Kappa
MC	medium care ward
NICU	neonatal intensive care unit
NPV	negative predictive value
OI	other indication
OR	odds ratio
OVD	operative vaginal delivery
pCO2	partial pressure of carbon dioxide
pH	hydrogen ion concentration
pHua	pH measured in umbilical cord artery
PPV	positive predictive value
P*s*	proportion of specific agreement
RCT	randomised controlled trial
ROC	receiver operating characteristic
RR	relative risk
S1-S3	Sarnat grade 1 - Sarnat grade 3
SD	standard deviation
SFD	suspected fetal distress
ST	ST-segment of fetal ECG
STAN	fetal monitoring by ST-analysis of the fetal ECG
SVD	spontaneous vaginal delivery

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Westerhuis MEMH, Porath MM, Becker JH, et al. Intrapartum fetal monitoring: identification of cases with adverse neonatal outcome. Submitted.

Westerhuis MEMH, Visser GHA, Moons KGM, et al. Cardiotocography plus ST-analysis of the fetal electrocardiogram versus cardiotocography only for intrapartum monitoring: a Dutch randomised clinical trial. Submitted.

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Dankwoord
Acknowledgements

Een van de belangrijkste lessen uit ruim drie jaar promotietijd: onderzoek doe je niet alleen! Dit proefschrift is dan ook het resultaat van samenwerking met velen, die ik wil bedanken voor hun enthousiaste inzet. Verder wil ik alle vrouwen, die deelgenomen hebben aan de trial, van harte bedanken.

Prof. dr. G.H.A. Visser, beste Gerard, mijn eerste echte kennismaking met jou was tijdens mijn co-schap Obstetrie in het WKZ, waarin ik ook betrokken was bij het navelstrengwindingenonderzoek. Tijdens een overleg krabbelde jij in een paar woorden een heel plan van aanpak voor mijn bijdrage aan dat onderzoek op een papiertje. Later, tijdens mijn eigen onderzoek, bleken dat soort krabbels van jou heilig, want ze behelsden altijd de kern van de studie waarmee we bezig waren. Ik ben je zeer dankbaar voor de kans die ik kreeg om bijna 4 jaar fulltime onderzoek te kunnen doen en er ook nog een opleiding tot epidemioloog naast te volgen. Ik vind het echt bewonderenswaardig hoe jij, ook met een overvolle agenda, je zo op een manuscript kan storten dat na jouw aanpassingen alle eerdere onduidelijkheden en problemen eigenlijk als sneeuw voor de zon verdwijnen (zie stelling 9). Dank!

Prof. dr. K.G.M. Moons, beste Carl, jouw begeleiding was echt een verrijking, niet alleen van ons onderzoek, maar ook van mijzelf. Met name dankzij jou heb ik de mogelijkheid gekregen om het Epidemiology Postgraduate programma te volgen. Jouw kritische en analytische blik op mijn manuscripten waren zeer leerzaam. En zonder jouw expertise op het gebied van imputeren, waren we slechts geëindigd met een complete case analyse van de trial data. Ik wil je bedanken voor het feit dat je mij enorm geïnspireerd en geënthousiasmeerd hebt voor de klinische epidemiologie. Ik hoop dan ook in de toekomst nog eens met je te mogen samenwerken!

Dr. A. Kwee, beste Anneke, wat was ik 4 jaar geleden blij toen je me belde om te zeggen dat ik het STAN onderzoek mocht gaan uitvoeren. Daarmee werd ik jouw eerste promovenda! Ik ben je erg dankbaar dat je mij geïntroduceerd hebt in de STAN wereld, wat toch eigenlijk een beetje jouw ‘kindje’ was. Ik vond het erg prettig dat overleg altijd laagdrempelig mogelijk was (niet alleen wat betreft het onderzoek: ik herinner me nog een telefoontje over borstvoeding een paar weken na mijn bevalling…). Met toch wel een beetje pijn in mijn hart draag ik het STAN project nu over, maar ik hoop er in de (nabije) toekomst nog veel aan mee te kunnen werken!

Prof. dr. B.W.J. Mol, beste Ben Willem, jouw motto ‘een dag niet gerandomiseerd, is een dag niet geleefd’ mag niet ontbreken in dit dankwoord. Mede hierdoor was het mogelijk bijna 6000 vrouwen te includeren. Ik heb ontzettend veel bewondering voor jouw meer dan toegewijde drive om nieuwe evidence voor de klinische praktijk te genereren. Ik waardeer het enorm dat je er altijd (maar dan ook echt altijd) was voor overleg en hulp. Jouw vermogen om

mensen te stimuleren, te motiveren en efficiënt samen te laten werken, is zeer bewonderenswaardig.

Drs. N.P.A. Zuithoff, beste Peter, ondanks dat de software je af en toe in de steek liet bij het imputeren van zo'n grote dataset, heb jij het toch voor elkaar gekregen om mij binnen korte tijd te voorzien van de resultaten van de trial. Ik waardeer het enorm dat ik je overal voor kon bellen of mailen en dat je iedere keer de tijd nam me alle statistische stappen en procedures uit te leggen. Natuurlijk ook veel dank voor je hulp bij hoofdstuk 10. Veel succes met het afronden van jouw promotieonderzoek!

Prof. dr. F. van Bel, prof. dr. M.L. Bots, prof. dr. H.W. Bruinse, prof. dr. Y. Jacquemyn en dr. F.P.H.A. Vandenbussche dank ik voor het zitting willen nemen in de beoordelingscommissie.

Alle gynaecologen, arts-assistenten, verloskundigen en verpleegkundigen van het UMC Utrecht, het Diakonessenhuis Utrecht, het St Antonius ziekenhuis Nieuwegein, het TweeSteden ziekenhuis Tilburg, het Jeroen Bosch Medisch Centrum 's Hertogenbosch, het Maxima Medisch Centrum Veldhoven, het VU Medisch Centrum Amsterdam, het OLVG Amsterdam en het MUMC Maastricht, wil ik ontzettend bedanken voor jullie inzet bij de inclusie van patiënten voor de trial.

Alle medewerkers van het Consortium wil ik bedanken. Het is erg bijzonder deel uit te mogen maken van zo'n professionele en inmiddels grote organisatie!

De STAN trial projectgroep (Eline van den Akker, Erik van Beek, Saskia Bijvoet, Thierry van Dessel, Addy Drogtrop, Herman van Geijn, Peppino Graziosi, Jan van Lith, Ben Willem Mol, Carl Moons, Jan Nijhuis, Guid Oei, Herman Oosterbaan, Martina Porath, Robbert Rijnders, Nico Schuitemaker, Lia Wijnberger, Christine Willekes, Maurice Wouters, Annemiek Bolte, Gerard Visser en Anneke Kwee) wil ik bedanken voor de prettige samenwerking.

De researchverloskundigen van de participerende centra, Inge Boot, Coby van Dam, Birgit van der Goes, Corinne van de Griendt, Lidewijde Jongmans, Kim Notten, Louisa Sopacua, Cathy Swarte en Corine Verhoeven, wil ik bedanken voor hun meer dan geweldige inzet bij de organisatie van de trial op lokaal niveau, het includeren van patiënten en het invoeren van de gegevens. Met name dit laatste was een enorme klus, die zonder jullie onmogelijk was geweest!

De Consortium onderzoekers, het zijn er inmiddels te veel om op te noemen, allemaal dank voor de gezellige bijeenkomsten, onderwijsavonden en het uitwisselen van ervaringen. Denise Bijlenga, dank voor het maken van een mooi logo en website. Sylvia Vijgen, wat een werk heb jij verzet om de data compleet en schoon te krijgen! Soms leek het echt ondoenlijk, maar het is gelukt! Natuurlijk ook veel dank voor hoofdstuk 9, een erg belangrijke toevoeging aan

de klinische resultaten.

Dames van het Trialbureau in het AMC, Maya Kruijt en Zelda van Dijk, dank voor al jullie werk en in het bijzonder het bijhouden van de 2-jaars follow-up.

Prof. Dr. Y. van der Graaf, prof. dr. M. Offringa, dr. I. van der Tweel en dr. W.J. van Wijngaarden wil ik danken voor het zitting willen nemen in de Data Safety Monitoring Committee van de STAN trial. Ingeborg, dank voor je hulp en advies bij het opzetten, uitvoeren en analyseren van de trial en het meedenken bij andere STAN deelprojecten.

Dr. F. Groenendaal en dr. M.L. Benders, beste Floris en Manon, heel veel dank voor jullie bereidheid de MC en NICU brieven te beoordelen.

Mariet Haverkamp en Laura Vos wil ik bedanken voor hun enthousiaste (vrijwillige) inzet gedurende de trial.

De (toenmalige) studenten, Nadine van der Burg, Jolijn Groeneweg, Eva van Horen, Chantal Mulkens, Marijke van Polen, Timme Schaap en Sanne Strasser, wil ik ontzettend bedanken voor hun inzet bij verschillende STAN deelstudies en de trial. Zonder jullie was het nooit gelukt om alle gegevens verzameld en ingevoerd te krijgen!

De dames van de 4^{e} etage, Bertina, Lot, Ans, Ineke, Daniëlle en Demelza, wat ontzettend fijn dat jullie altijd direct bereid waren te helpen bij vanalles en nog wat!

Alle dames van het klinieksecretariaat op de 2^{e} etage, ontzettend veel dank voor het verzamelen van alle statussen die ik nodig had voor het compleet maken van mijn database. Het leek af en toe wel een archief op mijn kamer…

Mijn nieuwe collega's en gynaecologen uit het Diakonessenhuis, dank voor de leerzame en leuke start van mijn opleiding. Menstruatie en gynaecologie poli draaien is toch weer een hele andere tak van sport….

Mijn (oud) collega-onderzoekers en kamergenoten, Annemiek, Bas, Deodata, Esther, Helen, Jeroen, Joepe, Karien, Linda, Maarten, Madelon, Margo, Marieke, Marijke, Roel en Ziong, ik heb echt een leuke tijd gehad mede dankzij jullie. De meesten van jullie straks weer collega's in de kliniek! Maarten, een betere kamergenoot had ik me niet kunnen wensen! Altijd bereid te helpen, of het nu te maken had met SPSS of het openen van het zakje met kaas voor op mijn brood. De laatste maanden zaten we in hetzelfde stressige schuitje, en ik wens je dan ook onwijs veel succes met de laatste loodjes en daarna! Als je straks iets meer tijd hebt, spreken we af om bij te praten. Annemiek, dank voor het waarnemen van de trial tijdens mijn

zwangerschapsverlof. Jeroen, we hebben nog een paar maanden samengewerkt en hoofdstuk 8 eruit geperst, waarvoor veel dank. Veel succes met alle andere STAN stukken, dat wordt volgens mij nog een vol boek (en ik ben erg benieuwd naar de kaft)! Helen en Karien, binnenkort buurtborreltje doen voor wat tips en tricks aan deze 1e jaars? Alle onderzoekers van de overkant, dank voor de 'broodjes van de week'! Maartje, David en Joepe, dank voor het overnemen van de consortium pieper 'diensten', researchmobiel en Meander zaken in de laatste fase van mijn onderzoek.

Familie en vrienden, dank voor al jullie steun en interesse de afgelopen jaren!

Lieve Bernard, Poike en Gilles, duizendmaal dank voor alle uren die jullie gestopt hebben in het klussen in ons huis. De zolder is een mooie ruimte geworden, waar ik heerlijk heb kunnen werken en schrijven! Ber, zonder jou was ik een week voor de deadline in grote (computer) problemen geraakt…..

Lieve clubgenootjes, ik heb nu weer tijd om veel meer gezellige dingen met jullie te doen! Dat weekend moet er nu echt van komen binnenkort!

Lieve Ellen, vanaf dag 1 in Utrecht zijn wij een duo ('nee, geen zussen'). Wat hebben we veel meegemaakt samen en wat hebben we gelachen! Ondanks dat we ontzettend verschillen, klikt het zo goed en is onze vriendschap bijzonder. Je staat altijd voor me klaar, ook als we elkaar een tijdje niet gesproken of gezien hebben. Op mijn trouwdag stond je aan mijn zijde en ik ben heel blij dat je ook nu weer naast me staat!

Lieve Carmen, wat ben ik blij met zo'n lieve en attente vriendin! Nadat we elkaar leerden kennen als beginnend geneeskunde studentes, kwamen we ook in dezelfde jaarclub terecht. Vanwege drukte spreken we elkaar soms wat minder, maar onze vriendschap blijft erg dierbaar. Ook gezellig samen met de mannen! Ik vind het heel fijn dat je mijn paranimf bent!

Lieve schoonfamilie, wat een schatten! Jullie oprechte interesse in alles wat ik doe, waardeer ik enorm. Cas en Heleen (en tante Phie!), ontzettend veel dank voor alle dagen dat jullie opgepast hebben op Olivia. Heleen, laten we snel afspreken om te gaan winkelen! Joost en Caroline, een spontaan bezoekje aan het huis in Moray tijdens jullie vakantie, leverde mij een hele bijzondere kaft op! Dank voor jullie hulp hierbij.

Lieve Cecile en Bart, lieve Catherine en Eelco, Siezel en Cathert, allerliefste zusjes! Bij jullie kan ik mezelf zijn en lekker gek doen, jullie zijn mijn allerbeste vriendinnen. Ondanks dat we heel verschillende karakters hebben, is onze band supersterk, hopelijk voor altijd.

Lieve papa en mama, dankzij jullie steun, vertrouwen en stimulatie, sta ik waar ik nu sta. Het is heerlijk bij jullie thuis te komen en ik hoop dat nog heel lang te kunnen doen. Dank voor

alle hulp bij het oppassen, zodat ik mijn boekje af kon maken. Papa, 28 jaar geleden liep ik in een mooi jurkje bij jouw promotie rond, nu doet Olivia dat bij die van mij! Mama, veel dank voor je hulp bij de Nederlandse samenvatting. Vanaf nu hopelijk weer meer tijd voor 'eenpuntskoffietjes' met opgeschuimde melk! Dank voor alles, ik hou van jullie!

Mijn lieve mooie kleine meisje, Olivia, jouw geboorte was het hoogtepunt uit de afgelopen jaren. Als ik naar je kijk, vergeet ik alles om me heen. Vanaf nu geen laptop meer in de buurt, maar lekker veel leuke dingen op 'mama dag'.

Allerliefste Daan, samen met jou voel ik me compleet. Onze liefde is overal tegen bestand, dus ook tegen de afgelopen wat ongezellige tijd waarin ik zo met mijn onderzoek en dit boekje bezig was. Ontzettend veel dank voor al je steun (in huis, maar zeker ook mentaal) en heerlijke cappucino's die je me trouw kwam brengen op zolder als ik aan het schrijven was! Zonder jou had ik het echt niet gered. De avonden in je eentje op de bank zijn nu voorbij (al zul je daar tijdens voetbalwedstrijden misschien nog wel eens met een beetje heimwee aan terugdenken..). Ik verheug me erop samen weer vol te gaan genieten van ons mooie leventje! Je bent mijn allesie, voor altijd.

Curriculum Vitae

De auteur van dit proefschrift werd op 31 maart 1979 te Nijmegen geboren. Zij behaalde in 1997 haar Gymnasium diploma aan het Sint Janscollege te Hoensbroek. In datzelfde jaar begon zij aan de studie Geneeskunde aan de Universiteit van Utrecht. Tijdens haar studie werkte zij mee aan onderzoek op het gebied van kinderhaematologie (Wilhelmina Kinderziekenhuis, dr. T. Révèsc) en verloskunde (Wilhelmina Kinderziekenhuis, prof. dr. G.H.A. Visser). In 2003 ging zij voor het co-schap gynaecologie en verloskunde 3 maanden naar Melbourne, Australië (Box Hill Hospital, prof. dr. G. Kovacs). Na een keuze co-schap bij de afdeling Verloskunde in het Wilhelmina Kinderziekenhuis, behaalde zij in 2004 haar artsdiploma. Hierna startte zij als Agnio gynaecologie en verloskunde in het Sint Elisabeth ziekenhuis te Tilburg. In 2005 startte zij als Agnio op de afdeling Verloskunde van het Wilhelmina Kinderziekenhuis te Utrecht. Hier werd haar interesse gewekt voor de foetale bewaking en in het bijzonder voor ST-analyse van het foetale ECG. In 2006 startte zij dan ook onder begeleiding van prof. dr. G.H.A. Visser, prof. dr. K.G.M. Moons en dr. A. Kwee met het promotie-onderzoek, waarvan het resultaat voor u ligt. Gedurende de onderzoeksperiode volgde zij het Epidemiology postgraduate programma aan de Universiteit van Utrecht, waarvan ze in 2009 het Master diploma behaalde. Zij startte in oktober 2009 met de opleiding tot gynaecoloog in het Diakonessenhuis te Utrecht (opleider dr. P.C. Scholten).

In 2007 trouwde zij met Daan Ebeling Koning en in 2008 werd hun dochter Olivia geboren.