

VII. SWEDISH RANDOMIZED CONTROLLED TRIAL

This section contains a complete report of the clinical trial including statistical analysis of results and case report forms.

The trial was conducted in Sweden and, therefore, no IDE was submitted. The trial was conducted according to internationally recognized clinical trial guidelines. Institutional approval was obtained prior to study start and patient informed consent was given by all study participants

The original study protocol is included in **Appendix VII-B**. Institutional approvals and the Informed Consent Form are included as appendicies to the protocol.

Copies of the references cited in the discussion can be found in Section X of this PMA.

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Attachment VII-1: Neonatal Outcome in the CTG+ST Group

Attachment VII-2: Neonatal Outcome in the CTG Group

Appendices

Appendix VII-A: STAN S21 Technical Problems During SRCT

Appendix VII-B: Randomized Controlled Trial (RCT) Protocol

A. Summary

Background

Previous studies indicate that analysis of the ST waveform of the fetal ECG provides information on the fetal response to hypoxia. In a multicenter randomized controlled trial, the hypothesis was tested that intrapartum monitoring with Electronic Fetal Monitoring combined with automatic ST waveform analysis results in an improved perinatal outcome as compared with EFM alone.

Methods

At three Swedish labor wards, 4969 women with term fetuses in cephalic presentation entered the trial during labor after a clinical decision had been made to apply a fetal scalp electrode for internal CTG recording. They were randomized to monitoring with CTG plus ST-analysis or CTG only. Clinical action was guided by the study protocol.

Results

The CTG+ST group showed a 61 % reduction in the number of cases with umbilical artery metabolic acidosis (pH < 7.05 and base deficit > 12 mmol/L) (p=0.01), a 78 % reduction in cases with metabolic acidosis admitted to neonatal intensive care unit (p=0.04), and there were 27% fewer operative deliveries for fetal distress (p=0.004), as compared with the CTG only group. The rates of operative interventions for failure to progress did not differ between the two groups. The enhanced experience of the staff in the second half of the trial led to a still more pronounced reduction in cord metabolic acidosis (75 %) and operative deliveries for fetal distress (44 %).

Conclusion

Intrapartum monitoring with CTG combined with automatic ST waveform analysis increases the ability of obstetricians to more appropriately intervene in cases of a non-reassuring fetal status during labor.

B. Introduction

Since the introduction of intrapartum electronic fetal monitoring (EFM), intrapartum death has become a rare event and the method has been shown to reduce neonatal morbidity as manifested by neonatal seizures. However, little benefit has been proven regarding long-term outcome and there is still much concern about clinical management of labor based on the information available from EFM. Moreover, the method has been claimed to cause an unnecessarily high rate of cesarean deliveries. Although most cases of fetal asphyxia are preceded by EFM abnormalities, similar abnormalities are not uncommon in cases with normal outcome, and misinterpretation of EFM traces is often a contributing factor in cases of asphyxia. Fetal blood sampling (FBS) can be used to assist in the interpretation of the cardiotocogram (CTG), but it requires additional intervention and expertise, which leads to a tendency to manage labor without this support. Maintaining calibrated systems for scalp pH and blood gas determinations must also meet federal guidelines for quality control and user qualifications. This makes such systems impractical for all but the largest volume tertiary centers. As the EFM did not live up to its initial expectations, there is continuous interest in developing new methods for intrapartum fetal surveillance.

Analysis of the ST waveform of the electrocardiogram (ECG) provides valuable information on how the adult myocardium responds to an increased workload during exercise. Similarly, experimental research into the fetal ECG has shown that ST waveform patterns are related to the ability of the fetal myocardium to react to hypoxia. An elevation of the ST segment and T wave, quantified by the ratio between T wave and QRS amplitudes (T/QRS), identifies fetal myocardium responding to hypoxia by a catecholamine surge, beta adrenoceptor activation and myocardial glycogenolysis. An ST segment depression may indicate a situation in which the myocardium is now incapable of a healthy response to hypoxia.

For more information on experimental studies, see Module M002 and Section V.A. of this PMA.

These experimental observations initiated development of a CTG+ST waveform analyzer (STAN[®]). In a previous randomized controlled trial, intrapartum monitoring with CTG alone was compared with CTG in combination with ST waveform analysis in 2400 cases. A 46% reduction in operative interventions for fetal distress occurred when ST analysis was applied. The study also highlighted two other issues: the need for technical improvements of the ST waveform analyzer to enable clear identification of an ST segment depression that may be overlooked if only the T/QRS ratio is calculated, and the importance of staff training.

Consequently, a new CTG+ST waveform recorder was developed utilizing digital signal processing techniques and automatic assessment of ST changes. After evaluation in observational clinical studies, the new system was validated in the present multicenter randomized controlled trial. The aim was to test the hypothesis

that intrapartum monitoring of term fetuses with CTG and automatic ST waveform analysis results in a reduced rate of both operative deliveries for fetal distress (ODFD) and newborns with metabolic acidosis, as compared with CTG alone. Staff training was improved with the use of multimedia technique with a simulator function allowing staff to experience recordings obtained from cases of intrapartum hypoxia.

For more information on prior clinical studies, see Section VI of this PMA.

C. Material and Methods

The trial was conducted during 18 months (December 1, 1998 to June 4, 2000) at three major labor wards in Sweden: University Hospital Lund (in 1999: 2829 deliveries, perinatal mortality 8.2 per 1000, cesarean section rate 12.5 %), University Hospital Malmö (3220, 4.0 per 1000, and 13 %, respectively), and Sahlgrenska University Hospital, Gothenburg (4229, 6.5 per 1000, and 14.7 %, respectively). Education and two months of using a prototype STAN[®] S 21 fetal heart monitor preceded the trial. The education consisted of lectures, written information, and multimedia-based teaching, including a simulator module displaying previously recorded cases with ST-analysis. At each center, a research midwife was appointed half time to conduct the training, to support the staff during the trial and to verify the data entries into a computerized database. The regular labor ward staff (in all more than 300 obstetricians and midwives) managed all women included in the trial. Research Ethics Committees at the respective University approved the trial. All participating women gave their informed consent before entering the study.

Entry criteria for the study included women in active labor at more than 36 completed gestational weeks, with singleton fetuses in cephalic presentation, and who were felt to require (on clinical grounds) a fetal scalp electrode for continuous internal CTG recording. At all three centers, clinical grounds that prompted internal monitoring as the preferred method of surveillance in high-risk pregnancies included women with suspicious or abnormal external CTG, induced or oxytocin augmented labor, meconium stained amniotic fluid, or epidural analgesia.

The labor wards were equipped with a total of 25 STAN[®] S 21 prototypes. The STAN S 21[®] is based on a Pentium class personal computer, including signal amplification and analogue-to-digital data conversion at 500 Hz. Signal processing and 15" screen data presentation are based on dedicated software using a real-time operating system (Phar Lap Software Inc, Cambridge, MA). Fetal heart rate, uterine activity (recorded as either external or internal tocogram), and fetal ECG ST waveform changes (T/QRS ratio and biphasic ST) were continuously displayed on screen and printed out on a paper (**Figure VII-1**). Fetal ECG signals for identification of ST waveform changes were sampled via a unipolar lead from a single spiral fetal scalp electrode. A skin electrode placed on the maternal thigh was used as reference.

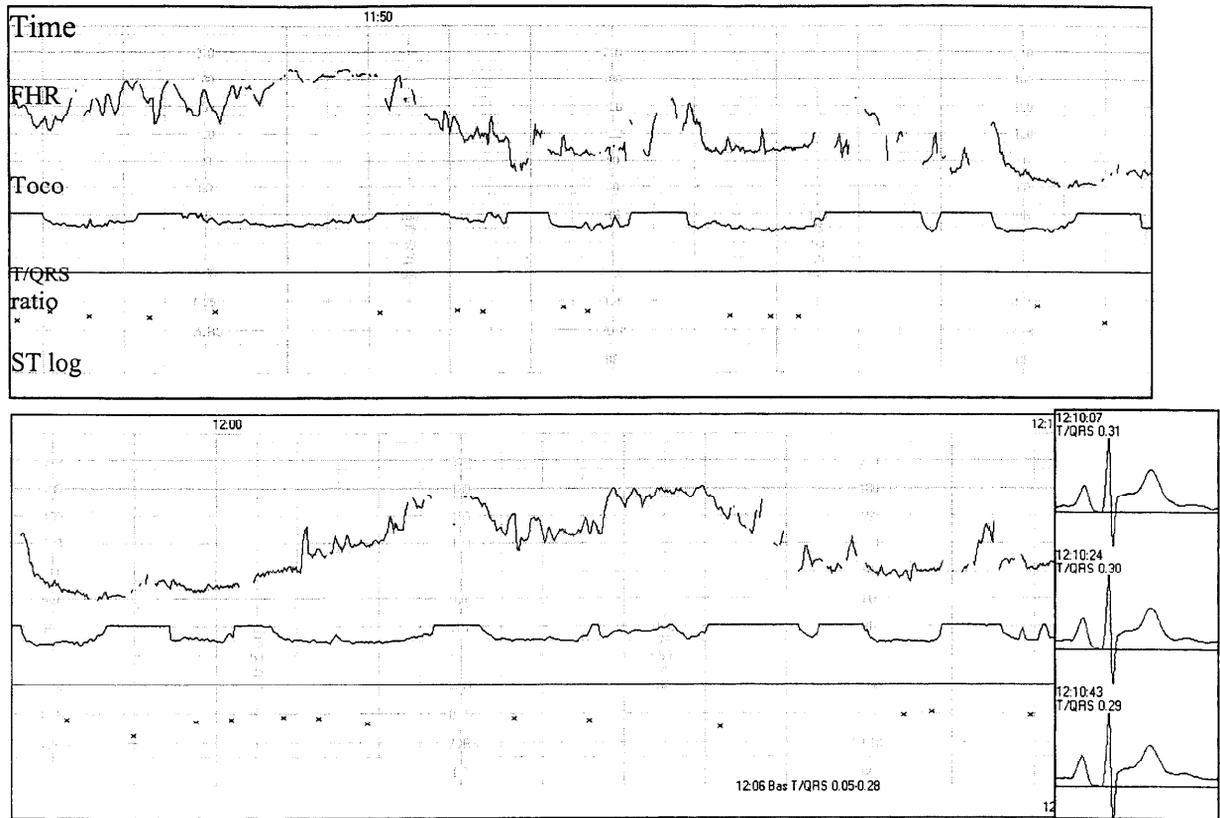


Figure VII-1: Cardiotocogram (CTG) and ST waveform analysis recording from a baby with metabolic acidosis at delivery subsequently admitted to the Neonatal Intensive Care Unit. The panels above show fetal heart rate (FHR), uterine activity (toco) and the T/QRS ratio plot with ST log statements. The CTG shows a fluctuating baseline, maintained fetal heart rate variability and variable decelerations. The T/QRS ratio rises steadily to >0.25 . The right panel shows ECG elevated ST segment and T/QRS ratios between 0.29 and 0.31. The baby was delivered with forceps for fetal distress at 12:49 h with a cord artery pH of 6.88, base deficit of 14.9 mmol/L and Apgar score of 4 at 1 min and 8 at 5 min.

1. Randomization Procedure

Parturients included in the study were randomly allocated by the computer, contained in the prototype STAN[®] S 21, at power-on to either CTG (CTG group) or CTG with ST waveform analysis (CTG+ST group) monitoring. At power on, the computer software addressed the first figure available from a table that consisted of a list of figures chosen at random by a computerized random generator. Each computer was equipped with such a table. Once a figure had been utilized, it was no longer available for further use. These numbers, even or uneven, decided to what extent ST information would be displayed or not.

To avoid the problem of the STAN[®] unit being turned off and on again, thereby changing the allocated mode, two hours had to pass with the recorder turned off before a new number would be chosen by the same machine. No ST

information was available in the CTG group. In both trial arms, fetal ECG signals were automatically stored in digital form for future analysis.

The clinical management in the CTG group was guided by the CTG interpretation according to FIGO (International Federation of Gynecologists and Obstetricians) guidelines (**Table VII-1**), with an option of fetal blood sampling (FBS) left to the discretion of the obstetrician. In cases with persistently abnormal CTG, intervention was suggested. Depending on the clinical circumstances, the intervention could be delivery, FBS, or alleviation of a possible cause of fetal distress, e.g., uterine hypertonus or maternal hypotension. In cases with scalp blood pH <7.20 or preterminal CTG, immediate delivery was always recommended.

Table VII-1: Interpretation of the cardiotocogram (CTG). Modified from the FIGO guidelines

CTG Classification	CTG characteristics		
	Baseline heart rate	Variability, reactivity	Decelerations
Normal	110 - 150 bpm	5 - 25 bpm accelerations present	early decelerations uncomplicated variable decelerations with duration < 60 s and loss < 60 bpm
Suspicious	100 - 110 bpm 150 - 170 bpm short episode of bradycardia < 100 bpm	> 25 bpm without accelerations < 5 bpm for > 40 min	uncomplicated variable decelerations with duration < 60 s and loss > 60 bpm
Abnormal	> 170 bpm persistent bradycardia < 100 bpm combination of several characteristics of suspicious CTG	< 5 bpm for > 60 min sinusoidal pattern	complicated variable decelerations with duration > 60 s
Preterminal	total lack of variability and reactivity with or without decelerations and/or bradycardia		

bpm: beats per min

In the CTG+ST group the clinical management was guided by CTG interpretation supported by ST waveform assessment (ST log[®]) according to the trial protocol (Table VII-2). The ST log automatically informed if any of the ST events listed in the study protocol occurred. Intervention, as described above for the CTG group, was indicated at the occurrence of preterminal CTG regardless of ST change, or in instances of abnormal or intermediate CTG patterns with ST events as listed in the protocol. No intervention was recommended if the CTG was normal irrespective of the ST waveform. The CTG+ST clinical guidelines combine visual analysis of the CTG with automatic analysis of ST waveform changes. Visual CTG assessment is known to vary between experts. Data from the Plymouth randomized trial showed that with the additional support of ST, the ability of the staff to identify a normal CTG pattern increased significantly. In the CTG only arm, 2.7% of those with a normal CTG on retrospective analysis had had an operative intervention. The corresponding figure for CTG+ST was 0.3%. Thus, members of staff improved in their capacity to correctly identify a normal CTG in cases where they obtained support from a likewise normal ST waveform. During the second stage of labor, immediate delivery was recommended if ST changes appeared.

Table VII-2
Management guidelines for the CTG+ST group: ST changes indicating clinical intervention. In cases of preterminal CTG an intervention is indicated irrespective of ST waveform.

	CTG	
	Suspicious	Abnormal
ST changes:		
Episodic T/QRS rise (duration < 10 min)	increase > 0.15 from baseline	increase > 0.10 from baseline
Baseline T/QRS rise (duration 10 min)	increase > 0.10 from baseline	increase > 0.05 from baseline
Biphasic ST*	continuous (> 5 min) or > two episodes of coupled biphasic ST	continuous (> 2 min) or > one episode of coupled biphasic ST

*Biphasic ST: ST segment depression with a component of the ST segment below the baseline of ECG

2. Data Collection

A research midwife was employed at each site to oversee data collection and to provide local monitoring. The data collection system was based on that used by the Swedish Board of Health and Welfare which has operated nationally for many years. The research midwife transferred data from the national data collection system to the trial case record form checking for any data inconsistency. The identity of the mother and child was changed to the specific trial identity number created by the STAN[®] unit at onset of recording.

According to the protocol, all patients that entered the study would have the umbilical cord artery and vein acid-base status assessed at delivery. Cord acid-base was used to provide a marker of the hypoxic process. The levels chosen were the same as in the Plymouth trial. Metabolic acidosis is only a soft measure of the quality of labor ward care but it serves the purpose of providing an alarm before the baby gets into major problems and it also gives immediate feedback. The cord should be double-clamped before or at time of first breath. An alternative was to puncture the artery and vein directly at delivery. Acid-base analysis should be made within 30 minutes.

Main indications of obstetric intervention were noted. This was done prospectively with order of priority of indications stated.

Primary outcome

Metabolic acidosis at birth was assigned the main outcome variable, defined as a cord artery blood pH <7.05 and a base deficit in the extracellular fluid compartment (BD_{ecf}) >12.0 mmol/L, using the Siggaard-Andersen Acid Base Chart algorithm.¹

Secondary outcome

The secondary outcome variable was the rate of operative deliveries (cesarean sections, forceps or ventouse deliveries) for fetal distress (ODFD). In addition, the neonatal morbidity was evaluated in terms of Apgar scores at 1 and 5 minutes and admissions to the special care baby unit (SCBU or NICU).

3. Assessment of Neonatal Data

A pediatrician blinded for which of the study groups the neonate belonged to assessed all pediatric notes for babies admitted to NICU, and classified whether there had been any signs of neonatal encephalopathy according to Sarnat & Sarnat² or if there had been other signs of intrapartum hypoxia, i.e. umbilical cord metabolic acidosis. In case of no cord data being available, arterial acid

¹ Siggaard-Anderson O. An acid base chart for arterial blood with normal and pathophysiological reference areas. *Scand J Clin Lab Invest* 1971;27:239-45.

² Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. *Arch Neurol* 1976;33:696-705.

base and lactate data obtained within the first hour were also used to verify signs of intrapartum hypoxia.

Assessment of the central nervous system followed the guidelines presented by Low et al³ and included evidence of neonatal encephalopathy, defined as follows: minor - with irritability and jitteriness, moderate - with profound lethargy or abnormal tone and severe - with coma or abnormal tone and seizures. Cases with moderate and severe encephalopathy have an increased risk of long-term sequelae.

All cases admitted to NICU had their recordings assessed according to the CTG+ST clinical guidelines. This was done without knowledge of which study group the case belonged to.

4. Analysis According to Adequate Recordings and According to Intention-to-Treat

According to the protocol, analysis was made with the exclusion of neonates with severe malformations and inadequately monitored cases - those monitored for less than 20 min and cases where the monitoring was interrupted more than 20 min before delivery. This analysis of adequate recordings was done on the following basis; the device needed at least 20 min to establish a baseline T/QRS-ratio. Also, cases with severe malformations and those without monitoring during the last period before deliveries were considered to obscure possible associations between monitoring and outcome. An analysis of outcome was also done strictly according to intention-to-treat, i.e. without any exclusions. Intention-to-treat analysis is a standard when it comes to drug trials. Medical device testing with strict documentation of how to apply the technology is somewhat different in that action is dependent on the attitude of a user. Thus, it is logical to analyze both according to intention-to-treat and according to adequate recordings. In fact, the latter would be more unbiased and give a truer picture related to the impact of the device as such.

5. Power and Interim Analysis

Based on data from the CTG only arm of the Plymouth trial, power analysis indicated a requirement of 3200 cases to demonstrate a 70 % reduction in the number of newborns with cord artery metabolic acidosis, assuming an incidence of 1.3%, $\beta = 0.20$ and $\alpha = 0.05$. The current trial protocol included an interim analysis after enrollment of 1600 cases in order to assess the true incidence of umbilical cord artery metabolic acidemia. As a result of the interim analysis, a low incidence was found (0.65%) and a second power analysis was performed to assess the necessary number of additional cases to show a reduction in ODFD without an increase in the incidence of metabolic acidosis. This number was $n =$

³ Low JS. Intrapartum fetal asphyxia: Definition, diagnosis, and classification. Am J Obstet Gynecol 1997; 176:957-9.

2160. A new study deadline was determined, taking into account the previous recruitment rate. The low incidence found initially is difficult to explain unless this was a finding related to the “Hawthorn” effect. However, it was clear from the interim data analysis that CTG+ST provided information that, when used according to the protocol, would improve outcome both according to primary and secondary outcome measures and it was decided to continue.

The interim analysis also revealed protocol violations. These included disregarding the recommendation to intervene according to CTG+ST guidelines and intervention delayed or done without regard to the guideline recommendation. As a result, retraining was conducted. The “violation” cases were discussed along with other cases from the trial. The trial committee decided that the trial would continue throughout the retraining. It was also decided that an additional analysis of the data would be done that included before and after retraining.

The results were statistically evaluated with the Medcalc[®] statistical software (version 5). χ^2 or Fisher’s exact tests were used for discrete variables and the odds ratios (OR) with 95% confidence intervals (CI) were given. P-values < 0.05 were considered significant.

6. Patient Informed Consent

The mothers were informed about the trial taking place on the labor wards and its general objectives as part of their antenatal information.

Before admission to the study, all patients were informed of the nature of the study, its purpose, procedures and the benefits and risks involved in study participation. Each patient was given the opportunity to ask questions and was informed about the fact that they were free to withdraw from the study at any time. Withdrawal happened in two cases because of discomfort with the fetal scalp electrode.

D. Results

A total of 4966 parturients entered the trial between December 1998 and June 2000, of whom 2447 were randomized to the CTG only group and 2519 to CTG+ST. The total number of included patients, the number with available acid-base data, and the number of cases with adequate monitoring in each group are shown in **Figure VII-2**, **Table VII-3** and **Table VII-4**. The numbers of women recruited for the study at each center correspond to 36 %, 31 % and 33 % of all women delivered during the study period in Lund, Malmö and Gothenburg, respectively.

Figure VII-2

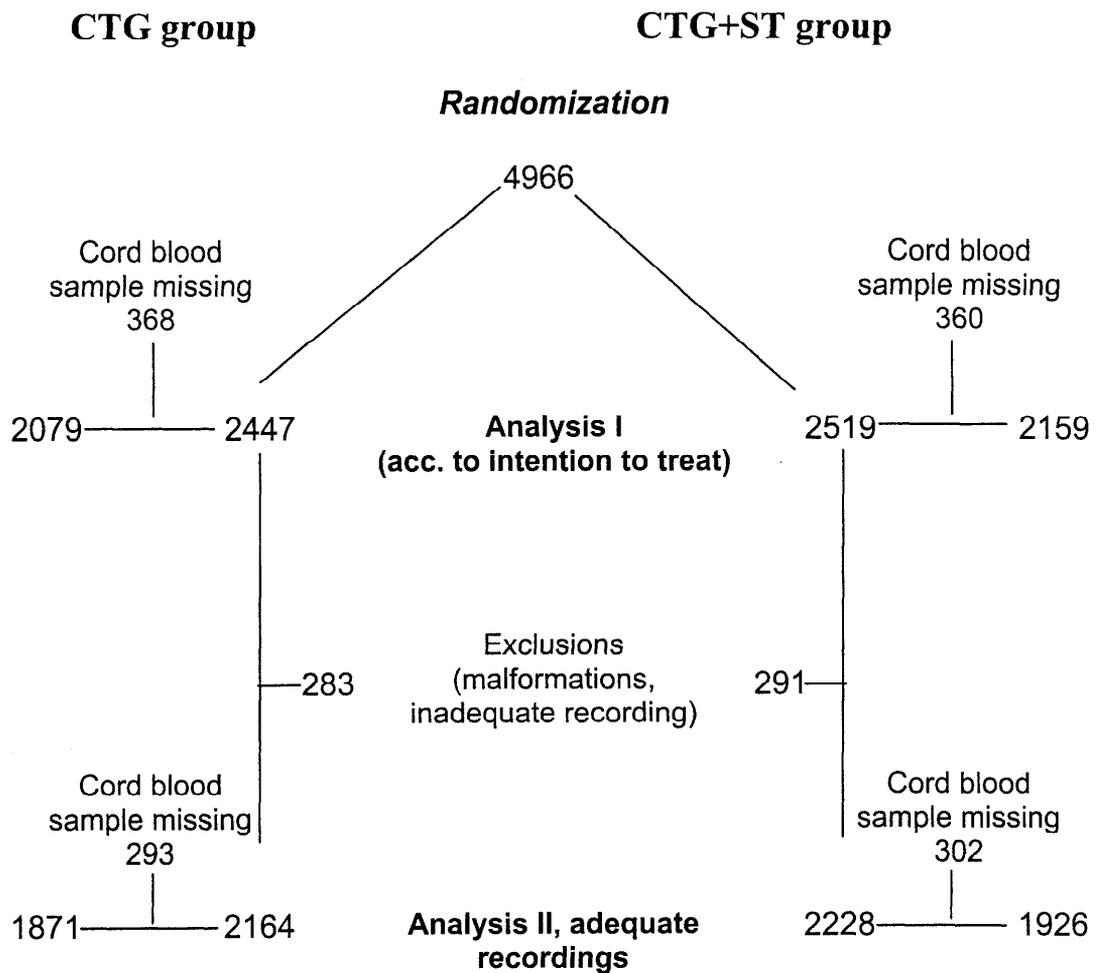


Figure VII-2: Flow chart of trial exclusions. Inadequate recordings comprise cases with recording shorter than 20 min, delivery > 20 min from the end of recording, poor ECG signal quality, technical failure, and other causes specified in the text. In cases with cord blood sample missing, the base deficit could not be calculated. The results of analyses I and II are given in Tables VII-3 and VII-4, respectively.

Operative interventions	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, total	2447		2519				
Operative delivery for fetal distress	227	9.28	193	7.66	0.81	0.66-0.99	0.047
Cesarean section for fetal distress	97	3.96	87	3.45	0.87	0.64-1.18	0.38
Ventouse or forceps for fetal distress	130	5.31	106	4.21	0.78	0.60-1.02	0.08
Operative delivery for other indications	273	11.16	261	10.36	0.92	0.77-1.11	0.39
Cesarean section for other indications	125	5.11	123	4.88	0.95	0.73-1.24	0.76
Ventouse or forceps for other indications	148	6.05	138	5.48	0.87	0.69-1.11	0.29
Operative deliveries total	500	20.43	454	18.02	0.86	0.74-0.99	0.034
Cesarean sections total	222	9.07	210	8.34	0.91	0.74-1.12	0.38
Ventouse/forceps total	278	11.36	244	9.69	0.84	0.69-1.01	0.06
Midcavity ventouse/forceps for fetal distress	56	2.29	39	1.55	0.68	0.44-1.04	0.07
Outlet ventouse/forceps for fetal distress	74	3.02	67	2.66	0.88	0.62-1.24	0.49
Midcavity ventouse/forceps for other indications	66	2.70	75	2.98	1.11	0.78-1.57	0.61
Outlet ventouse/forceps for other indications	82	3.35	63	2.50	0.74	0.52-1.05	0.09
Midcavity ventouse/forceps total	122	4.99	114	4.53	0.9	0.69-1.18	0.48
FBS number of cases	261	10.67	234	9.29	0.86	0.71-1.04	0.116
FBS number of samples	440		406		0.88	0.75-1.02	0.08
Demographic data							
Nulliparous	1510	61.71	1552	61.61	1	0.89-1.12	0.96
Prolonged pregnancy	255	10.42	240	9.53	0.91	0.75-1.09	0.31
Induction of labor	405	16.55	439	17.43	1.06	0.92-1.24	0.43
Epidural analgesia	989	40.42	942	37.40	0.88	0.79-0.99	0.03
Meconium stained amniotic fluid	562	22.97	574	22.79	0.99	0.87-1.13	0.9
Oxytocin augmentation	1521	62.16	1518	60.26	0.92	0.82-1.04	0.18
Birth weight <2500	42	1.72	51	2.02	1.18	0.77-1.82	0.48

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, total							
excluding lethal malformations	2447		2519				
Apgar 1 min <4	47	1.92	36	1.43	0.74	0.47-1.17	0.21
Apgar 5 min >7	28	1.14	26	1.03	0.9	0.51-1.59	0.81
Apgar 5 min <4	6	0.25	2	0.08	0.32	0.05-1.76	0.17
Admission to SCBU	181	7.40	169	6.71	0.86	0.69-1.07	0.21
Moderate or severe neonatal encephalopathy	8	0.33	1	0.04	0.12	0.01-0.94	0.02
Perinatal death	1	0.04	2	0.08			
Umbilical cord acid base data available	2079		2159				
Cord artery metabolic acidosis	31	1.49	15	0.69	0.46	0.25-0.86	0.02
Admission to SCBU after obstetric intervention	n	%	n	%			
Operative delivery for fetal distress	58	25.6	47	24.4			ns
Cesarean section for fetal distress	30	30.9	30	34.5			ns
Ventouse or forceps for fetal distress	28	21.5	17	16.0			ns
Operative delivery for other indications	42	15.4	26	10.0			ns
Cesarean section for other indications	21	16.8	9	7.3			ns
Ventouse or forceps for other indications	21	14.2	17	12.3			ns
Operative deliveries total	100	20.0	73	16.1			ns
Cesarean sections total	51	23.0	39	18.6			ns
Ventouse/forceps total	49	17.6	34	13.9			ns
Midcavity ventouse/forceps for fetal distress	16	28.6	10	25.6			ns
Outlet ventouse/forceps for fetal distress	12	16.2	7	10.4			ns
Midcavity ventouse/forceps for other indications	11	16.7	12	16.0			ns
Outlet ventouse/forceps for other indications	10	12.2	5	7.9			ns
Midcavity ventouse/forceps total	27	22.1	22	19.3			ns

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, total							
Cases with adverse/complicated neonatal outcome (perinatal death, neuromuscular symptoms, metabolic acidosis + neonatal care)							
	19	0.91%	10	0.46%	0.51	0.22-1.16	0.12
Perinatal death	1		2				
Neuromuscular symptoms	8		3				
Seizures	3		0				
Increased neuromuscular tone + Apgar <4 at 5' or met acidosis (pH<7.05 and BDecf>12 mmol/l)	4		0				
Irritability/Jitteriness only	1		3				
Met acid + other symptoms	10		5				

Operative interventions	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, before	1250		1333				
Operative delivery for fetal distress	104	8.32	114	8.55	1.03	0.77-1.37	0.88
Cesarean section for fetal distress	41	3.28	49	3.68	1.13	0.72-1.75	0.65
Ventouse or forceps for fetal distress	63	5.04	65	4.88	0.97	0.67-1.40	0.91
Operative delivery for other indications	144	11.52	121	9.08	0.77	0.59-1.00	0.047
Cesarean section for other indications	65	5.20	51	3.83	0.73	0.49-1.07	0.11
Ventouse or forceps for other indications	79	6.32	70	5.25	0.82	0.58-1.16	0.28
Operative deliveries total	248	19.84	235	17.63	0.86	0.71-1.06	0.16
Cesarean sections total	106	8.48	100	7.50	0.88	0.65-1.18	0.39
Ventouse/forceps total	142	11.36	135	10.13	0.88	0.68-1.14	0.34
Midcavity ventouse/forceps for fetal distress	26	2.08	24	1.80	0.86	0.48-1.56	0.7
Outlet ventouse/forceps for fetal distress	37	2.96	41	3.08	1.04	0.65-1.67	0.95
Midcavity ventouse/forceps for other indications	34	2.72	38	2.85	1.05	0.64-1.72	0.93
Outlet ventouse/forceps for other indications	45	3.60	32	2.40	0.66	0.41-1.07	0.09
Midcavity ventouse/forceps total	60	4.80	62	4.65	0.97	0.66-1.41	0.93
FBS number of cases	120	9.60	129	9.68	1.01	0.77-1.32	0.99
FBS number of samples	178		213		1.15	0.92-1.43	0.23
Demographic data							
Nulliparous	756	60.48	810	60.77	1.01	0.86-1.19	0.91
Prolonged pregnancy	121	9.68	116	8.70	0.89	0.67-1.17	0.42
Induction of labor	201	16.08	223	16.73	1.05	0.85-1.30	0.69
Epidural analgesia	479	38.32	505	37.88	0.98	0.83-1.15	0.85
Meconium stained amniotic fluid	295	23.60	294	22.06	0.92	0.76-1.11	0.37
Oxytocin augmentation	765	61.20	784	58.81	0.91	0.77-1.06	0.23
Birth weight <2500	18	1.44	32	2.40	1.68	0.91-3.14	0.1

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, before	1250		1333				
Apgar 1 min <4	20	1.60	20	1.50	0.94	0.48-1.82	0.96
Apgar 5 min >7	12	0.96	17	1.28	1.33	0.60-2.98	0.56
Apgar 5 min <4	1	0.08	2	0.15	1.88	0.13-52.28	0.95
Admission to SCBU	84	6.72	98	7.35	1.1	0.81-1.51	0.58
Moderate or severe neonatal encephalopathy	3	0.24	1	0.08	0.36	0.01-3.80	0.63
Perinatal death	1	0.08	1	0.08			
Umbilical cord acid base data available	1064		1157				
Cord artery metabolic acidosis	16	1.50	10	0.86	0.57	0.24-1.34	0.22
Cases with adverse/complicated neonatal outcome (perinatal death, neuromuscular symptoms, metabolic acidosis + neonatal care)	7	0.66%	8	0.69%			
Perinatal death	1		1				
Neuromuscular symptoms	3		3				
Seizures	1		0				
Increased neuromuscular tone + Apgar <4 at 5' or met acidosis (pH<7.05 and BDecf>12 mmol/l)	1		0				
Jitteriness/Irritability only	1		3				
Met acid+ other symptoms	3		4				

Operative interventions	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, after	1197		1186				
Operative delivery for fetal distress	123	10.28	79	6.66	0.62	0.46-0.85	0.00197
Cesarean section for fetal distress	56	4.68	38	3.20	0.67	0.43-1.05	0.081
Ventouse or forceps for fetal distress	67	5.60	41	3.46	0.6	0.38-0.91	0.0145
Operative delivery for other indications	129	10.78	140	11.80	1.11	0.85-1.44	0.4668
Cesarean section for other indications	60	5.01	72	6.07	1.22	0.85-1.77	0.2984
Ventouse or forceps for other indications	69	5.76	68	5.73	0.99	0.69-1.42	0.9776
Operative deliveries total	252	21.05	219	18.47	0.85	0.69-1.04	0.12
Cesarean sections total	116	9.69	110	9.27	0.95	0.72-1.26	0.78
Ventouse/forceps total	136	11.36	109	9.19	0.79	0.60-1.04	0.09
Midcavity ventouse/forceps for fetal distress	30	2.51	15	1.26	0.5	0.25-0.97	0.037
Outlet ventouse/forceps for fetal distress	37	3.09	26	2.19	0.7	0.41-1.20	0.21
Midcavity ventouse/forceps for other indications	32	2.67	37	3.12	1.17	0.71-1.95	0.59
Outlet ventouse/forceps for other indications	37	3.09	31	2.61	0.84	0.50-1.40	0.56
Midcavity ventouse/forceps total	62	5.18	52	4.38	0.84	0.57-1.24	0.41
FBS number of cases	141	11.78	105	8.85	0.73	0.55-0.96	0.022
FBS number of samples	262		193		0.69	0.56-0.86	0.0005
Demographic data							
Nulliparous	754	62.99	742	62.56	0.98	0.83-1.16	0.86
Prolonged pregnancy	134	11.19	124	10.46	0.93	0.71-1.21	0.6
Induction of labor	204	17.04	216	18.21	1.08	0.87-1.35	0.48
Epidural analgesia	510	42.61	437	36.85	0.79	0.66-0.93	0.0046
Meconium stained amniotic fluid	267	22.31	280	23.61	1.08	0.89-1.31	0.47
Oxytocin augmentation	756	63.16	734	61.89	0.95	0.80-1.12	0.55
Birth weight <2500	24	2.01	19	1.60	0.8	0.42-1.52	0.55

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Intention to treat, after	1197		1186				
Apgar 1 min <4	27	2.26	16	1.35	0.59	0.30-1.15	0.1314
Apgar 5 min >7	16	1.34	9	0.76	0.56	0.23-1.36	0.2367
Apgar 5 min <4	5	0.42	0	0.00			0.0622
Admission to SCBU	97	8.10	71	5.99	0.72	0.52-1.00	0.052
Moderate or severe neonatal encephalopathy	5	0.42	0	0.00			0.075
Perinatal death	0	0.00	1	0.08			
Umbilical cord acid base data available	1015		1002				
Cord artery metabolic acidosis	15	1.48	5	0.50	0.33	0.11-0.98	0.045
Cases with adverse/complicated neonatal outcome (perinatal death, neuromuscular symptoms, metabolic acidosis + neonatal care)							
	12	1.18%	2	0.20%	0.17	0.03-0.79	0.017
Perinatal death	0		1				
Neuromuscular symptoms	5		0				
Seizures	2		0				
Increased neuromuscular tone + Apgar <4 at 5' or met acidosis (pH<7.05 and BDecf>12 mmol/l)	3		0				
Jitteriness/Irritability only	0		0				
Met acid+ other symptoms	7	0.69%	1	0.10%	0.14		0.038

Table VII-4

Operative interventions	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, total	2164		2228				
Operative delivery for fetal distress	173	7.99	132	5.92	0.72	0.57-0.92	0.009
Cesarean section for fetal distress	63	2.91	43	1.93	0.66	0.44-0.97	0.04
Ventouse or forceps for fetal distress	110	5.08	89	3.99	0.78	0.58-1.03	0.1
Operative delivery for other indications	242	11.18	227	10.19	0.9	0.74-1.11	0.31
Cesarean section for other indications	110	5.08	103	4.62	0.91	0.68-1.20	0.52
Ventouse or forceps for other indications	132	6.10	124	5.57	0.91	0.70-1.17	0.49
Operative deliveries total	415	19.18	359	16.11	0.81	0.69-0.95	0.008
Cesarean sections total	173	7.99	146	6.55	0.81	0.64-1.02	0.07
Ventouse/forceps total	242	11.18	213	9.56	0.84	0.69-1.02	0.08
Midcavity ventouse/forceps for fetal distress	47	2.17	30	1.35	0.61	0.38-1.00	0.048
Outlet ventouse/forceps for fetal distress	63	2.91	59	2.65	0.91	0.62-1.32	0.66
Midcavity ventouse/forceps for other indications	61	2.82	69	3.10	1.1	0.77-1.59	0.64
Outlet ventouse/forceps for other indications	71	3.28	55	2.47	0.75	0.51-1.08	0.12
Midcavity ventouse/forceps total	108	4.99	99	4.44	0.89	0.66-1.18	0.43
FBS number of cases	225	10.40	196	8.80	0.83	0.68-1.02	0.08
FBS number of samples	370		316		0.8	0.68-0.95	0.008
Demographic data							
Nulliparous	1349	62.34	1390	62.39	1	0.89-1.13	0.99
Prolonged pregnancy	218	10.07	208	9.34	0.92	0.75-1.13	0.43
Induction of labor	357	16.50	384	17.24	1.05	0.90-1.24	0.54
Epidural analgesia	889	41.08	834	37.43	0.86	0.76-0.97	0.02
Meconium stained amniotic fluid	490	22.64	489	21.95	0.96	0.83-1.11	0.6
Oxytocin augmentation	1378	63.68	1359	61.00	0.89	0.79-1.01	0.07
Birth weight <2500	33	1.52	38	1.71	1.12	0.68-1.84	0.72

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, total	2164		2228				
Apgar 1 min <4	38	1.76	23	1.03	0.58	0.34-1.01	0.055
Apgar 5 min >7	21	0.97	17	0.76	0.78	0.39-1.55	0.56
Apgar 5 min <4	6	0.28	2	0.09	0.32		0.173
Admission to SCBU	151	6.98	132	5.92	0.84	0.66-1.07	0.18
Moderate or severe neonatal encephalopathy	7	0.32	0	0.00			0.007
Perinatal death	0	0.00	0	0.00			
Umbilical cord acid base data available	1871		1926				
Cord artery metabolic acidosis	27	1.44	11	0.57	0.39	0.19-0.79	0.01

Admission to SCBU after obstetric intervention	% of op interv		% of op interv		
Operative delivery for fetal distress	39	22.5	28	21.2	ns
Cesarean section for fetal distress	17	27.0	15	34.9	ns
Ventouse or forceps for fetal distress	22	20.0	13	14.6	ns
Operative delivery for other indications	36	14.9	21	9.3	ns
Cesarean section for other indications	19	17.3	7	6.8	ns
Ventouse or forceps for other indications	17	12.9	14	11.3	ns
Operative deliveries total	75	18.1	49	13.6	ns
Cesarean sections total	36	20.8	22	15.1	ns
Ventouse/forceps total	39	16.1	27	12.7	ns
Midcavity ventouse/forceps for fetal distress	12	25.5	7	23.3	ns
Outlet ventouse/forceps for fetal distress	10	15.9	6	10.2	ns
Midcavity ventouse/forceps for other indications	6	9.8	10	14.5	ns
Outlet ventouse/forceps for other indications	11	15.5	4	7.3	ns
Midcavity ventouse/forceps total	18	16.7	17	17.2	ns

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, total							
Cases with adverse/complicated neonatal outcome (perinatal death, neuromuscular symptoms, metabolic acidosis + neonatal care)							
	17	0.79%	3	0.13%	0.17	0.04-0.61	0.003
Perinatal death	1		0				
Neuromuscular symptoms	7	0.323%	1	0.045%	0.14		0.036
Seizures	2		0				
Increased neuromuscular tone + Apgar <4 at 5' or met acidosis (pH<7.05 and BDecf>12 mmol/l)	4		0				
Irritability/Jitteriness only	1		1				
Met acid + other symptoms	9		2		0.21		0.06

Operative interventions	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, before	1115		1174				
Operative delivery for fetal distress	82	7.35	79	6.73	0.91	0.65-1.27	0.61
Cesarean section for fetal distress	29	2.60	23	1.96	0.75	0.42-1.34	0.37
Ventouse or forceps for fetal distress	53	4.75	56	4.77	1	0.67-1.50	0.93
Operative delivery for other indications	127	11.39	105	8.94	0.76	0.58-1.01	0.06
Cesarean section for other indications	56	5.02	41	3.49	0.68	0.44-1.05	0.08
Ventouse or forceps for other indications	71	6.37	63	5.37	0.83	0.58-1.20	0.35
Operative deliveries total	209	18.74	184	15.67	0.81	0.64-1.01	0.058
Cesarean sections total	85	7.62	64	5.45	0.7	0.49-0.99	0.043
Ventouse/forceps total	124	11.12	119	10.14	0.9	0.68-1.19	0.48
Midcavity ventouse/forceps for fetal distress	21	1.88	19	1.62	0.86	0.44-1.67	0.74
Outlet ventouse/forceps for fetal distress	32	2.87	37	3.15	1.1	0.66-1.83	0.78
Midcavity ventouse/forceps for other indications	32	2.87	35	2.98	1.04	0.62-1.74	0.97
Outlet ventouse/forceps for other indications	39	3.50	28	2.39	0.67	0.40-1.13	0.14
Midcavity ventouse/forceps total	53	4.75	54	4.60	0.97	0.64-1.45	0.94
FBS number of cases	107	9.60	102	8.69	0.9	0.67-1.20	0.49
FBS number of samples	163	14.62	158	13.46	0.91	0.71-1.16	0.45
Demographic data							
Nulliparous	682	61.17	722	61.50	1.01	0.85-1.20	0.9
Prolonged pregnancy	101	9.06	101	8.60	0.95	0.70-1.27	0.75
Induction of labor	178	15.96	196	16.70	1.05	0.84-1.33	0.67
Epidural analgesia	436	39.10	449	38.25	0.96	0.81-1.15	0.7
Meconium stained amniotic fluid	260	23.32	255	21.72	0.91	0.75-1.12	0.38
Oxytocin augmentation	693	62.15	702	59.80	0.91	0.76-1.08	0.26
Birth weight <2500	14	1.26	26	2.21	1.78	0.89-3.71	0.11

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, before	1115		1174				
Apgar 1 min <4	15	1.35	15	1.28	0.95	0.44-2.06	0.96
Apgar 5 min >7	8	0.72	9	0.77	1.07	0.38-3.05	0.91
Apgar 5 min <4	1	0.09	2	0.17	1.9	0.14-52.26	0.96
Admission to SCBU	73	6.55	78	6.64	1.02	0.72-1.43	0.99
Moderate or severe neonatal encephalopathy	2	0.18	0	0.00			
Perinatal death	0	0.00	0	0.00			
Umbilical cord acid base data available	963		1022				
Cord artery metabolic acidosis	13	1.35	7	0.68	0.51	0.18-1.37	0.21

Cases with adverse/complicated neonatal outcome (perinatal death, neuromuscular symptoms, metabolic acidosis + neonatal care)					
	n	%	n	%	
	6	0.54%	2	0.20%	
Perinatal death	1		0		
Neuromuscular symptoms	3		1		
Seizures	1		0		
Increased neuromuscular tone + Apgar <4 at 5' or met acidosis (pH<7.05 and BDecf>12 mmol/l)	1		0		
Jitteriness/Irritability only	1		1		
Met acid+ other symptoms	2		1		

Operative interventions	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, after	1049		1054				
Operative delivery for fetal distress	91	8.67	53	5.03	0.56	0.39-0.80	0.00126
Cesarean section for fetal distress	34	3.24	20	1.90	0.58	0.32-1.04	0.0703
Ventouse or forceps for fetal distress	57	5.43	33	3.13	0.56	1.35-0.88	0.0114
Operative delivery for other indications	115	10.96	122	11.57	1.06	0.90-1.41	0.7077
Cesarean section for other indications	54	5.15	62	5.88	1.15	0.78-1.70	0.5206
Ventouse or forceps for other indications	61	5.82	61	5.79	0.97	0.66-1.42	0.948
Operative deliveries total	206	19.64	175	16.60	0.81	0.65-1.02	0.08
Cesarean sections total	88	8.39	82	7.78	0.92	0.67-1.28	0.66
Ventouse/forceps total	118	11.25	94	8.92	0.77	0.57-1.04	0.08
Midcavity ventouse/forceps for fetal distress	26	2.48	11	1.04	0.41	0.19-0.88	0.019
Outlet ventouse/forceps for fetal distress	31	2.96	22	2.09	0.7	0.39-1.26	0.25
Midcavity ventouse/forceps for other indications	29	2.76	34	3.23	1.17	0.69-2.00	0.62
Outlet ventouse/forceps for other indications	32	3.05	27	2.56	0.84	0.48-1.45	0.58
Midcavity ventouse/forceps total	55	5.24	45	4.27	0.81	0.53-1.23	0.34
FBS number of cases	118	11.25	94	8.92	0.77	0.57-1.04	0.08
FBS number of samples	207		158		0.72	0.57-0.91	0.0048
Demographic data							
Nulliparous	667	63.58	668	63.38	0.99	0.83-1.19	0.95
Prolonged pregnancy	117	11.15	107	10.15	0.9	0.68-1.20	0.5
Induction of labor	179	17.06	188	17.84	1.06	0.84-1.33	0.68
Epidural analgesia	453	43.18	385	36.53	0.76	0.63-0.91	0.02
Meconium stained amniotic fluid	230	21.93	234	22.20	1.02	0.82-1.26	0.92
Oxytocin augmentation	685	65.30	657	62.33	0.88	0.73-1.05	0.17
Birth weight <2500	19	1.81	12	1.14	0.62	0.28-1.36	0.27

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, after	1049		1054				
Apgar 1 min <4	23	2.19	8	0.76	0.34	0.14-0.80	0.0108
Apgar 5 min >7	13	1.24	8	0.76	0.61	0.23-1.58	0.3744
Apgar 5 min <4	5	0.48	0	0.00			0.0307
Admission to SCBU	78	7.44	54	5.12	0.67	0.46-0.98	0.036
Moderate or severe neonatal encephalopathy	4	0.38	0	0.00			0.06
Perinatal death	0	0.00	0	0.00			
Umbilical cord acid base data available	908		904				
Cord artery metabolic acidosis	14	1.54	4	0.44	0.28	0.08-0.92	0.032

Neonatal Outcome	CTG		CTG+ST		Odds ratio	95% CI	p
	n	%	n	%			
Adequate recordings, after							
Cases with adverse/complicated neonatal outcome (perinatal death, neuromuscular symptoms, metabolic acidosis + neonatal care)							
	11	1.21%	1	0.11%	0.09	0.00-0.68	0.009
Perinatal death	0		0				
Neuromuscular symptoms	4		0				
Seizures	1		0				
Increased neuromuscular tone + Apgar <4 at 5' or met acidosis (pH<7.05 and BDecf>12 mmol/l)	3		0				
Irritability/Jitteriness only	0		0				
Met acid + other symptoms	7		1				0.07

1. Operative Interventions and Metabolic Acidosis, Intention-to-Treat

The main outcome, analyzed according to intention-to-treat including background obstetric characteristics, is shown in **Table VII-3**. The table also provides outcome and demographic data related to the periods before and after retraining.

A significant reduction was found in the rate of metabolic acidosis at birth: 15 cases occurred in the CTG+ST-group and 31 cases in the CTG-group (OR 0.46, 95%CI 0.25-0.86, $p = 0.02$). There was also a significant reduction in operative deliveries for fetal distress (ODFD)(OR 0.81, 95%CI 0.66-0.99, $p = 0.047$). The rates of operative deliveries for other indications (in most cases failure to progress, ODFTP) did not differ significantly between the two groups. The significant differences in ODFD and metabolic acidosis between the two groups occurred after retraining had taken place and when local cases were discussed on a regular basis, with feed-back and expert opinions obtained, OR 0.62, 95%CI 0.46-0.85, $p=0.002$ and OR 0.33, 95% CI 0.11-0.98, $p=0.045$, respectively.

2. Operative Interventions and Metabolic Acidosis, Eligible Entries with Adequate Recordings

Eight newborns had malformations not known before birth. In 574 cases the duration of the recording was insufficient ($n=215$) or monitoring was interrupted more than 20 min before delivery due to poor ECG signal quality ($n=182$), technical failure ($n=48$), use of electrical transcutaneous nerve stimulation for pain relief ($n=70$) or unspecified reasons ($n=59$). See **Appendix VII-A** for information on the technical failures. These cases were excluded in the second analysis of outcome (**Table VII-4**). Among the excluded cases, there were no significant differences between the two arms of the trial with regard to the number of cases, operative delivery rates, cord artery blood acid base data, and Apgar scores.

Also, after these exclusions the differences remained with significantly fewer cases of metabolic acidosis in the CTG+ST-group than in the CTG group (0.57% vs. 1.44%, $p=0.01$) and of ODFD (5.9% vs. 8.0 %, $p=0.009$), including a significantly lower rate of cesarean sections for fetal distress (1.93 vs. 2.91%, $p=0.04$) (**Table VII-4**). As with intention-to-treat analysis, the improved outcome was significant only after retraining with a 44% reduction in ODFD ($p=0.0013$) and 72% reduction in the number of cases with cord artery metabolic acidosis ($p=0.032$).

3. Overall Neonatal Outcome

No significant differences between the groups were found regarding Apgar scores and admissions to SCBU, although there was a general trend for fewer

cases of adverse outcome in the CTG+ST group. This trend only became significant after retraining had taken place and considering adequate recordings (Table VII-4).

4. Outcome of Neonates Admitted to Special Neonatal Care
(For detailed case presentations, see Attachments VII-1 & VII-2)

Of the 351 cases, 350 newborns corresponding to 7.0% of cases included in the trial, were admitted to special neonatal care. The remaining case died during delivery. The events associated with admission to SCBU are listed in Table VII-5

Table VII-5
Reasons for admission to SCBU

	Number of cases	%
ODFD	103	29%
ODFTP	67	19%
Neonatal distress	8	2%
Hypoglycemia	14	4%
Respiratory distress	46	13%
Clinical signs associated with infections	39	11%
Hyperbilirubinemia	22	6%
General observation	51	15%

Of all ODFD, 25% entered SCBU. The corresponding figure for ODFTP was 13%.

Table VII-6 shows clinical findings associated with the 29 cases with adverse/complicated neonatal outcome (perinatal death, neonatal encephalopathy or metabolic acidosis requiring special neonatal care) related to method of intrapartum monitoring and when during the trial the case was included. (**Table VII-3**)

Table VII-6
Clinical findings associated with adverse/complicated neonatal outcome.

	CTG		CTG+ST	
	Before n =1250	After retraining n = 1197	Before, n = 1333	After retraining, N = 1186
Perinatal death	1 Asphyxia, Neonatal death	0	1 Sepsis, Neonatal death	1 Asphyxia, Intrapartum death,

Outcome of SCBU visit

Neuromuscular symptoms	CTG	CTG	CTG+ST	CTG+ST
Seizures	1	2	0	0
Increased neuromuscular tone	1	3	0	0
Irritability only	1	0	3	0
Met acid+ other symptoms	3	7	4	1
Total	7	12	8	2

The number of live-born with moderate (increased neuromuscular tone) or severe neonatal encephalopathy (neonatal seizures/death) showed a significant decrease from 0.33% to 0.04% in the CTG group and CTG+ST groups, respectively (OR 0.12, 95%CI 0.01-0.94, p=0.02).

Furthermore, during the second phase of the trial, the number of cases with adverse/complicated neonatal outcome was reduced from 12 cases in the CTG group to 2 cases in the CTG+ST group (OR 0.17, 95% CI 0.03-0.79, p 0.017). No significant differences occurred within either the CTG or CTG+ST groups comparing outcome measures before and after retraining.

Table VII-7 provides information related to the type of ST events recorded and the time between onset of events and time of delivery. The median duration of ST events in the CTG group was 79 minutes as compared with 32 minutes in the CTG+ST group (p=0.032). In 18 of 20 cases with ST-abnormalities, these were present for more than 20 minutes before delivery.

Table VII-7
Summary of findings related to individual cases grouped according to
clinical and biochemical findings.

A. Cases of perinatal death related to intrapartum events

Mode of recording	Case ID and date of recording related to retraining, Apgar scores at 1, 5 and 10 min.	Mode of delivery and reason for operative delivery	Type of ST events and time between onset and delivery	Comments, days in SCBU
CTG	MAB 215, before, 0-2-3	MCV, ODFD	Normal ST at start, no ST data available last 2½h, monitored by CTG recorder.	Norm pregn, 41w, Meconium stained liq. Cord vein metabolic acidosis. Perinatal death after 24h. Labor induced asphyxia
CTG+ST	LDG 245, before, 0-0-0	CS, ODFD	Preterminal CTG, no ST events, no data last 22 min	Norm pregn, 40w, PROM – 21h, maternal pyrexia, chorioamnionitis, GBS, 1 st stage event, Perinatal death after 36h.
CTG+ST	MAE 473, after, 0-0-0	Outlet ventouse, FTP	Baseline T/QRS 38 min before deliv, no data last 27 min.	Norm pregn, myoma uteri, clear liq. 2nd stage event. Intrapartum death

B. Findings related to surviving cases with umbilical cord/immediate neonatal metabolic acidosis

Mode of recording	Case ID and date of recording related to retraining, Apgar scores at 1, 5 and 10 min.	Mode of delivery and reason for operative delivery	Type of ST events and time between onset and delivery	Comments, days in SCBU
CTG	OEK 309, before, 4-6-6	NVD	Baseline T/QRS, 740 min.	Normal pregn, 40w, clear liquor, 1 st stage events, Seizures, 21 days in SCBU. Severe encephalopathy.
CTG	LDA 258, before, 2-5-7	CS, ODFD	Episodic T/QRS, 102 min	Normal pregn, clear liq. 1 st stage events. Increased neuromuscular tone, 9 days. Moderate encephalopathy
CTG	MAA 479, after, 1-3-3	MCV, ODFD	Biphasic ST, 428 min followed by baseline T/QRS last 230 min	Norm pregn. 40w. Meconium stained liquor, maternal pyrexia, 1 st stage events. Increased neuromuscular tone, 5 days. Moderate encephalopathy

Mode of recording	Case ID and date of recording related to retraining, Apgar scores at 1, 5 and 10 min.	Mode of delivery and reason for operative delivery	Type of ST events and time between onset and delivery	Comments, days in SCBU
CTG	MAC 516, after, 3-6-7	NVD	Episodic T/QRS, 149 min followed by baseline T/QRS last 39 min	Normal pregn, 38w, clear liquor, meconium at delivery, maternal pyrexia. 1 st stage events. Increased neuromuscular tone, 14 days. Moderate encephalopathy
CTG	OEK 394, after, 6-9-9	NVD	Baseline T/QRS last 22 min	Norm pregn, clear liq, 40w, 2 nd stage events. Respiratory symptoms, pneumonia, 7 days
CTG	OEJ 330, after, 3-7-8	NVD	Baseline T/QRS last 23 min	Cholestasis in pregn, 38w. clear liq. 2 nd stage events. Respiratory symptoms, 2 days
CTG	LDC 364, after, 1-6-10	CS, FBS pH 7.03	Biphasic ST, 88 min	Norm pregn, 40w, meconium stained liquor, 1 st stage events. General OBS, 6 days
CTG	LDA 275, before, 1-8-9	MCV, ODFD	Baseline T/QRS last 15 min	Norm pregn, 40w, clear liq. 2 nd stage events. Tachypnoea, 1 day
CTG	LDA 298, before, 7-8-8	MCV, FTP	Baseline T/QRS last 23 min	Norm pregn, 40w, clear liq. 2 nd stage events. General OBS, 2 days
CTG	OEF 305, after, 2-3-7	MCV-FBS 7.08	Baseline T/QRS, 2 hour episode starting 440 min before delivery	Post term, clear liq. 1 st stage events. Oliguria, elevated liver enzymes + urea. 10 days in SCBU.
CTG	OEB 363, after, 5-8-8	Outlet Ventouse, ODFD	Baseline T/QRS last 74 min	Norm pregn, 40w, meconium stained liquor. 2 nd stage events. Meconium aspiration syndrome, SGA, 13 days
CTG	OEH 371, after, 3-3-10	NVD	Episodic T/QRS 210 min before delivery followed by baseline T/QRS last 70 min	Norm pregn, 39w, clear liq, 2 nd stage events. General OBS, 2 days
CTG	MAD 342, before, 5-7-8	NVD	Poor signal quality in 2nd stage, no ST events.	Post term, meconium stained liq. 2 nd stage events. Respiratory symptoms, 1 day
CTG	MAD 438, after, 4-6-7	MCV, FTP	No ST information available during the last 60 min.	Post term, oligohydramnios. stage events Respiratory symptoms, 2 days
CTG+ST	OEB 282b, before, 1-3-6	MCV, FTP	Biphasic ST 276 minutes followed by baseline T/QRS for 86 min	Norm pregn, 40w, meconium stained liquor. 1 st stage events. Meconium aspiration syndrome, 12 days in SCBU.
CTG+ST	OEH 330, before, 6-8-8	MCV, ODFD	Baseline T/QRS last 119 min	Norm pregn, 40w, clear liq. 1 st stage events. General OBS, 1 day
CTG+ST	OEB 239, before, 6-8-8	NVD	Baseline T/QRS last 33 min	Pyelonephritis during pregn, 39w, clear liq. 2 nd stage events. Transposition of great arteries, 2+

Mode of recording	Case ID and date of recording related to retraining, Apgar scores at 1, 5 and 10 min.	Mode of delivery and reason for operative delivery	Type of ST events and time between onset and delivery	Comments, days in SCBU
CTG+ST	MAE 251, before, 6-8-9	MCV, ODFD	Normal ST at start, no ST information available last 3h 50 min, monitored by conventional CTG monitor	Norm pregn, 38w, clear liq, maternal pyrexia, suspect events. General OBS, 4 days in SCBU.
CTG+ST	MAD 494, after, 4-9-9	NVD	Baseline T/QRS last 10 min	Norm pregn, 41w, clear liq. 2 nd stage events. Coarctatio aortae, 3 hrs in SCBU

C. Cases of encephalopathy without verified metabolic acidosis

Mode of recording	Case ID and date of recording related to retraining, Apgar scores at 1, 5 and 10 min.	Mode of delivery and reason for operative delivery	Type of ST events and time between onset and delivery	Comments, days in SCBU
CTG	OEH 379, after, 1-2-3	MCV, FBS pH 7.16	Normal ST	Norm pregn, 40w, clear liq. 2 nd stage event Shoulder dystocia, neonatal seizures, subarachn bleed, 20 days in SCBU. Severe encephalopathy
CTG	LDA 23, after, 9-10-10	MCV, ODFD	Biphasic ST, 141 min.	Norm pregn, 41w, clear liq. 1 st stage event Tentorial bleed, neonatal seizures, 18 days in SCBU. Severe encephalopathy
CTG	MAD 408, after, 1-3-5	CS, ODFD	Preterminal CTG, normal ST,	Decreased fetal movements, 39w, oligohydramnios, pre labor events. Increased neuromusc tone, 15 days in SCBU. Moderate encephalopathy
CTG	LDD 263, before, 2-5-7	Outlet ventouse, FTP	No ST events, no ST data last 24 min	Norm pregn, 41w, meconium. 2 nd stage event, Irritability, periventricular bleed, 12 days. Mild encephalopathy.
CTG+ST	MAA 293, before, 3-6-8	CS, ODFD	Baseline T/QRS last 32 min	Proteinurea, 40w, meconium, 1 st stage event. Irritability, respiratory symptoms, 5 days Mild encephalopathy.
CTG+ST	MAC 003, before, 1-7-8	CS, FTP	Bipasic ST 200 min before deliv, no data last 33 min	Hypertension in pregn, 38w, clear liq, PROM – 33h, maternal pyrexia. 1 st stage event. Neonatal irritability and hypoglycemia, 5 days. Mild encephalopathy.

Mode of recording	Case ID and date of recording related to retraining, Apgar scores at 1, 5 and 10 min.	Mode of delivery and reason for operative delivery	Type of ST events and time between onset and delivery	Comments, days in SCBU
CTG+ST	MAC 433, before, 3-8-9	MCV, FTP	Normal ST, no data last 30 min	Norm pregn, 41w, clear liq, 2 nd stage event, large sub galeal haematoma, Irritability due to pain, 9 days in SCBU. Mild encephalopathy.

NVD – normal vaginal delivery, MCV – mid cavity ventouse delivery, ODFD – operative delivery for fetal distress, FBS – fetal blood sample, GBS –group B streptococci infection.

5. Perinatal Mortality and Morbidity

Five perinatal deaths occurred, two due to malformations (combined congenital heart malformation and pulmonary hypoplasia, respectively) and three related to intrapartum events (Table VII-7A).

6. Events in labor associated with perinatal death

Three babies died either during labor or within 36 hours of delivery. One case in the CTG arm (MAB 215, CTG) had a mid cavity forceps for fetal distress, was born with cord metabolic acidosis and low Apgar scores. Unfortunately, no ST data is available for retrospective analysis during the last 171 minutes of labor. The reason for the severe intrapartum asphyxia is unclear with meconium stained liquor as the only finding apart from an abnormal CTG recording. The two cases in the CTG+ST arm allows for a more detailed analysis.

The first case (LDG 245, CTG+ST) was a para 0, uneventful pregnancy with spontaneous onset of labor after 40 weeks gestation, meconium stained liquor. Maternal fever, 39.3 °C treated with i.v. antibiotics in labor. Bacterial culture from the uterine cervix showed streptococci group B and the placental examination showed signs of chorioamnionitis. Figure VII-3 shows the final part of the STAN[®] recording, finishing 22 minutes before delivery by an emergency caesarean section. The baby got Apgar scores of 0-0-0 at 1,5 and 10 minutes and established regular heart rate at 12 min of age. Life supporting treatment was withdrawn at 36 hours of age due to cardiovascular failure.

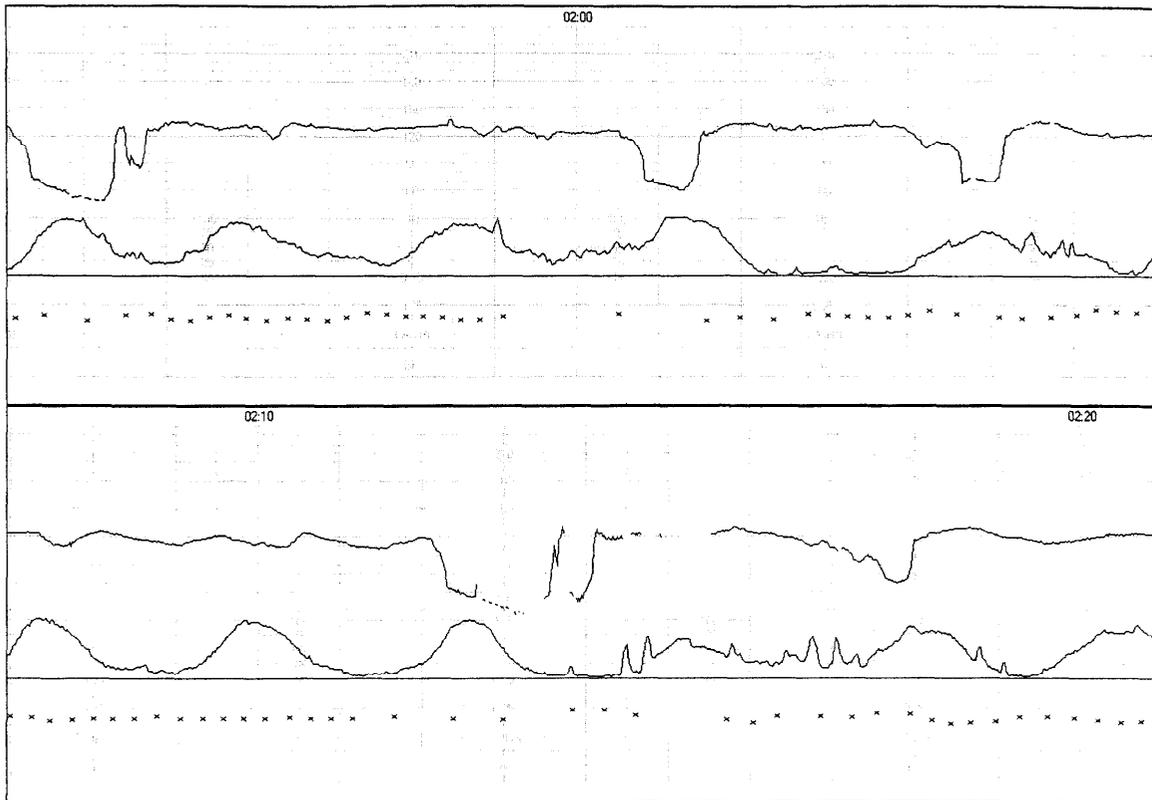
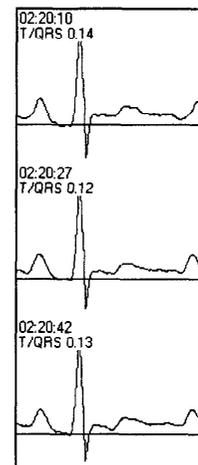


Figure VII-3
Case LDG 245, CTG+ST group. The figure depicts thirty minutes of CTG+ST recording, including a sample of three averaged fetal ECG complexes. Note the FHR trace showing a preterminal pattern with no signs of variability and reactivity. The recording lasted 44 minutes and was preceded by six hours of continuous external CTG monitoring.



The second case (MAE 473, CTG+ST) was a para 0, uneventful pregnancy, and spontaneous onset of labor after 40 weeks gestation, clear liquor. **Figure VII-4** presents the CTG+ST recording obtained prior to disconnecting the fetal scalp electrode. Normal course of labor until 18:40 when the fetus reacted with an increase in baseline FHR from 150 to 170 bpm followed by variable decelerations. At 18:45 the ST log identified an episodic rise in T/QRS from 0.11 to 0.22, which was not noted by the clinician and midwife. Signal quality deteriorated, limiting the possibility to automatically assess further ST events. The T/QRS rise was more persistent from 19:06 onwards. The bradycardia is associated with a change in the configuration of the ST with a negative slope emerging. The scalp clip was disconnected at 19:20 as a vacuum extractor was applied because of failure to progress. According to the staff, the externally recorded CTG showed a fetal heart rate of 120-160 bpm during the 23 minutes

required to deliver the baby. The baby had Apgar scores of 0-0-0 at 1, 5 and 10 minutes and did not respond to resuscitation.

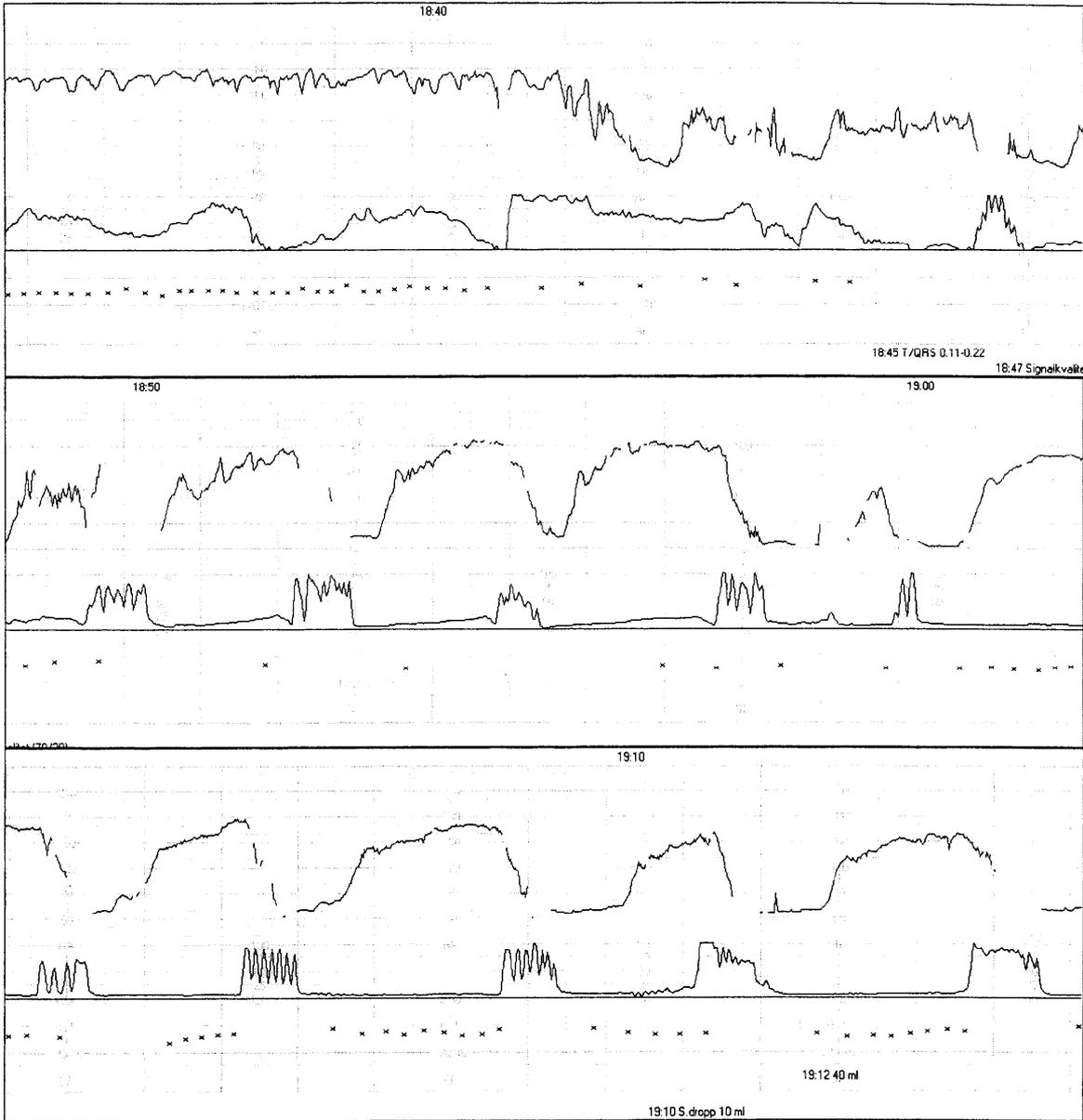


Figure VII-4
Recording obtained at onset of active pushing showing a rise in T/QRS from 0.11 to 0.22. The ST log was not activated further (after the initial message of an episodic rise in T/QRS) due to low signal quality with < 50% of the ECG complexes found to be of a sufficient quality (MAE 473, CTG+ST).

Except for these cases, there were 8 neonates in the CTG-group and 3 in the CTG+ST group with symptoms classified as neonatal encephalopathy. Of these, 7 had signs of moderate/severe neonatal encephalopathy, all in the CTG-arm. (Table VII-7 B, C).

7. CTG and ST findings associated with signs of neonatal encephalopathy, unblinding ST information in the CTG group (Table VII-7 B, C)

Three cases in the CTG group developed neonatal seizures with positive neuroradiological findings. The first case (OEK 309, CTG), on retrospective analysis unblinding the ST information, displayed significant ST events consisting of a baseline T/QRS rise from 0.19 to 0.30 in first stage of labor which by then had lasted 8 hours. The high T/QRS ratio remained until 2nd stage. The second case (OEH 379 - CTG) had a mid cavity ventouse delivery initiated by a scalp pH of 7.16 obtained during active pushing. Severe shoulder dystocia with the shoulders fixed for 8-10 minutes. No ST events were indicated (Figure VII- 5).

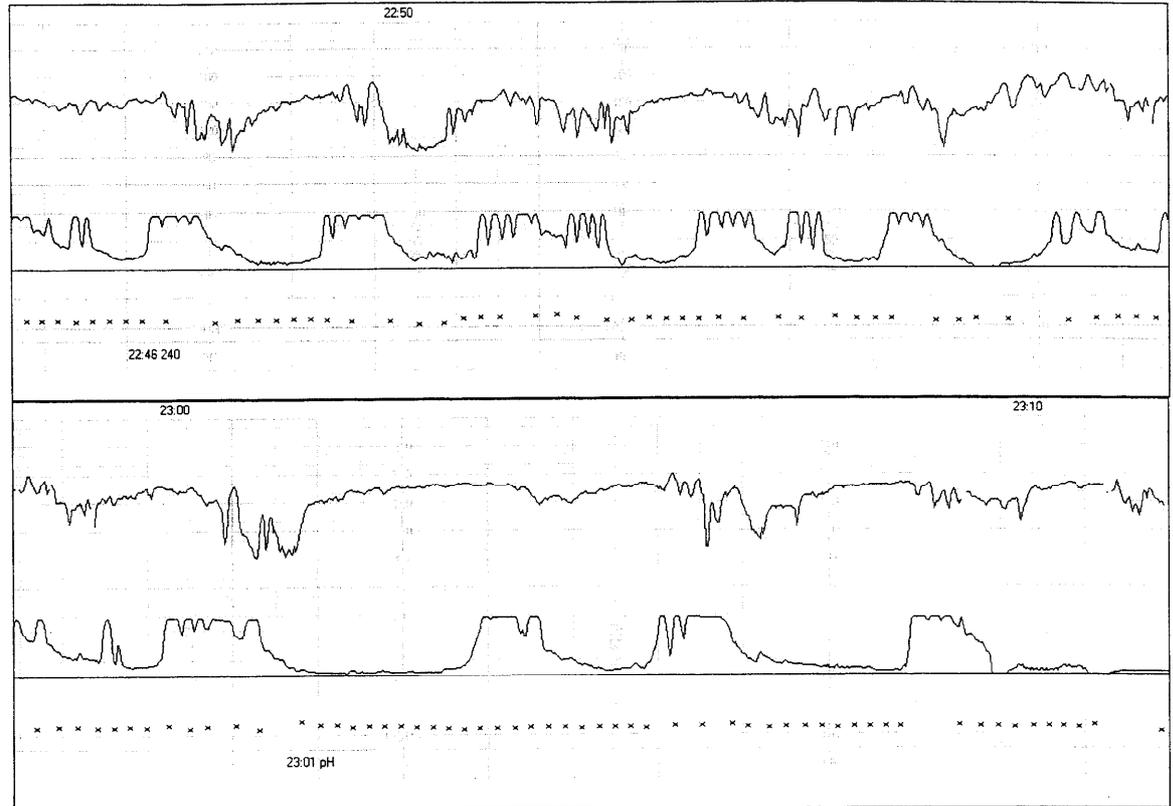
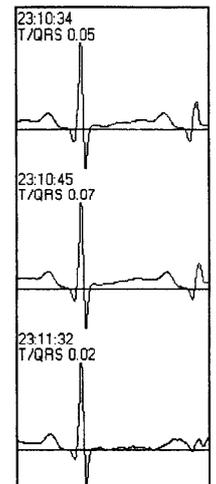


Figure VII-5
Last 30 minutes of recording, including a fetal scalp sample (FBS) of pH 7.16 initiating a mid cavity ventouse with shoulder dystocia and asphyxiated baby. Birth weight 4140g, Apgar scores 1-2-3, cord vein pH 7.14, PCO₂ 9.62 kPa, BDecf 3.7 mmol/l (OEH 379 - CTG).

The third case (LDA 023, CTG) had a complicated mid cavity ventouse delivery for fetal distress and showed a most unusual neuroradiological findings including tentorial bleedings combined with cerebral ischemia related to dissection of the carotid artery and related emboli. **Figure VII- 6** illustrates the STAN[®] recording with biphasic ST waveform changes occurring more then 2 hours before delivery. Thus, in two of the cases CTG+ST clinical guidelines would have indicated a need to intervene and in one case with shoulder dystocia, no intervention was indicated.



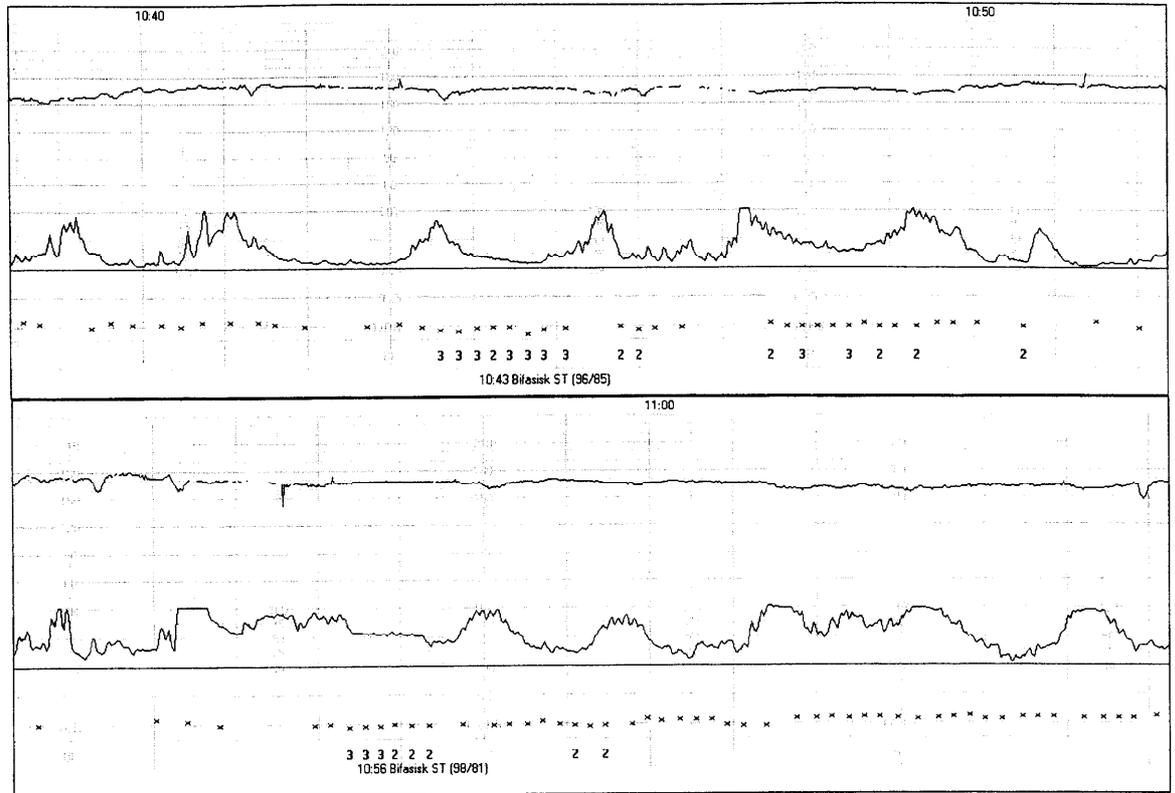
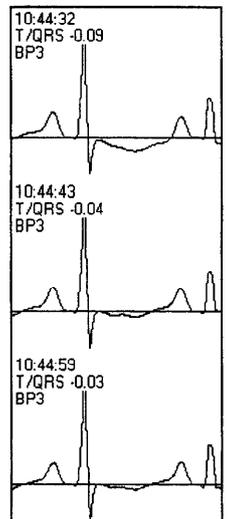


Figure VII-6
CTG+ST patterns recorded 2 hours and 20 minutes before delivery in case (LDA 023, CTG) showing an increase in baseline FHR with reduced variability and repeated episodes of biphasic ST waveform changes. The ECG printout illustrates the negative T waves with ST segment depression.



Five cases in the CTG group and three cases in the CTG+ST group showed signs of increased neuromuscular tone or irritability. Among these eight cases, five showed ST log statements of >30 minutes duration indicating interventions and three did not display any significant ST changes. In the latter group, one case (MAD 408-CTG group) had a history of decreased fetal movements, oligohydramnios and a 32 minutes recording in 1st stage of labor showing a preterminal CTG trace (baseline FHR 150 bpm with no variability or reactivity).

An emergency caesarean section was performed and the baby required assisted ventilation for 25 minutes but no signs of metabolic acidosis and normal neonatal behavior after 4 days. The remaining two cases had ventouse deliveries for failure to progress associated with intraventricular hemorrhage (LDD 263-CTG group) and a subgaleal bleeding (MAC 433-CTG+ST group). Neither of these showed evidence of metabolic acidosis.

8. Metabolic acidosis and ST events

Table VII-7 B gives a summary of findings related to surviving neonates with metabolic acidosis recorded from cord blood (17 cases) or in case of cord acid base data not being available, neonatal findings indicating intrapartum hypoxia (2 cases). The latter two cases had Apgar scores of 3 at 5 minutes, raised plasma lactate of 11 mmol/l (OEH 371-CTG) or multi organ symptoms (OEF 305-CTG). Out of the nineteen cases, only three (MAD 342-CTG, Mad 438-CTG and MAE 251-CTG+ST) did not display ST events. Also, the recording quality did not allow for ST waveform assessment in two of these three cases. The remaining sixteen cases had all CTG+ST changes that indicated a need for intervention, nine in first stage of labor and seven during active pushing in second stage. **Figure VII-7** shows an example of such a pattern.

Figure VII-7

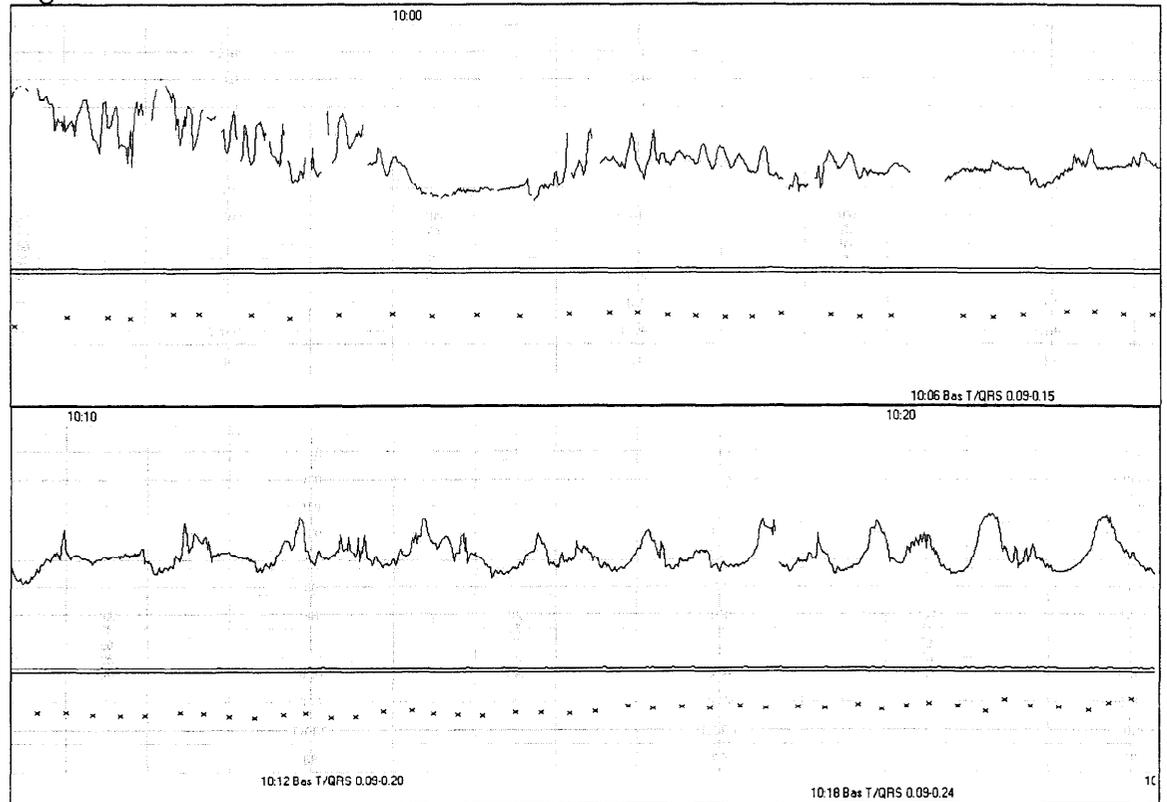
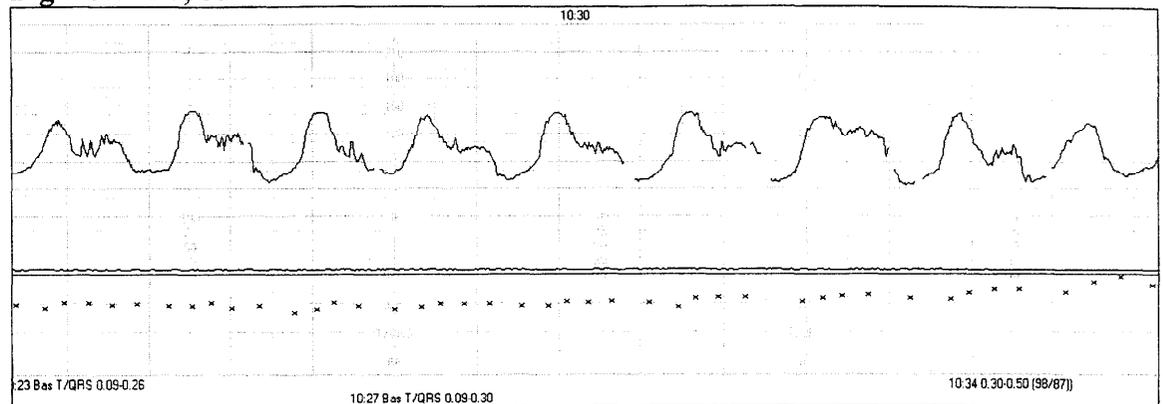
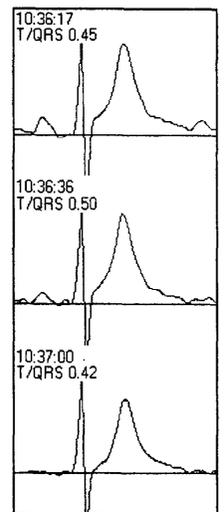


Figure VII-7, cont.**Figure VII-7**

Last 40 minutes of recording (OEB 239-CTG+ST), ending at time of NVD 10:39. Active pushing commenced at 10:00. The first ST log statement of a T/QRS baseline rise was indicated at 10:06. BW 3600g, Apgar 6-8-8, cord art. pH 6.87, PCO₂ 12.6 kPa and BDecf 14.3 mmol/l.



Out of the 29 cases with adverse events defined as perinatal death, neonatal encephalopathy or metabolic acidosis, three cases showed biphasic ST events only. The first case (LDC 364-CTG) showed tachycardia and loss of variability associated with meconium stained liquor and metabolic acidosis. The second case (MAC 003-CTG+ST) showed tachycardia with loss of variability associated with premature rupture of membranes and maternal fever. The third case (LDA 023-CTG, Fig. 6) showed tachycardia with loss of variability but nothing else to indicate an abnormality.

9. Cord artery acid base status and ST events

Cord artery acid base data was obtained from 259 cases out of the 351 cases included in the analysis on neonatal outcome. 207 of these did not display any ST events and the following cord artery data were recorded (mean \pm SD); pH 7.18 \pm 0.09, PCO₂ 7.87 \pm 1.59 kPa, BDecf 5.5 \pm 3.3 mmol/l.

In 52 cases, ST events were recorded. The cord artery acid base status is shown in **Table VII-8**.

Table VII-8
Type of ST waveform changes and cord artery acid base data

	Biphasic ST, n = 11	Biphasic + T/QRS rise, n = 9	T/QRS rise, n = 32
Cord artery pH, (median, range)	7.20 (7.01-7.29)	7.07* (6.73-7.23)*	7.04 (6.78-7.24)
Cord artery BDecf, mmol/l, (median, range)	6.2 (1.0-14.7)	10.2* (5.2-21.8)*	10.2 (1.83-18.4)

*=p<0.05

Table VII-8 gives cord artery acid base data relative to recorded ST events. Fetuses showing a T/QRS rise (n=32) had significantly lower pH and higher BDecf as compared with fetuses displaying biphasic ST only (n=11) or no ST changes (n=207) (p<0.001). The association between a T/QRS rise and the development of metabolic acidosis was also found in cases that initially displayed biphasic ST as their acid base data showed a significantly lower pH and higher BDecf with the rise in T/QRS (p<0.05).

10. Compliance with study protocol

The study protocol provided strict guidance of how to conduct a recording and interpret data. At an interim analysis scheduled after 1600 cases, it was found that five cases with adverse outcome had displayed significant ST events for more than 30 minutes prior to delivery, range 32 - 276 minutes. **Figure VII-8** provides an example of such a case (OEH 330) where the fetal heart rate pattern was thought not to indicate intrapartum hypoxia.

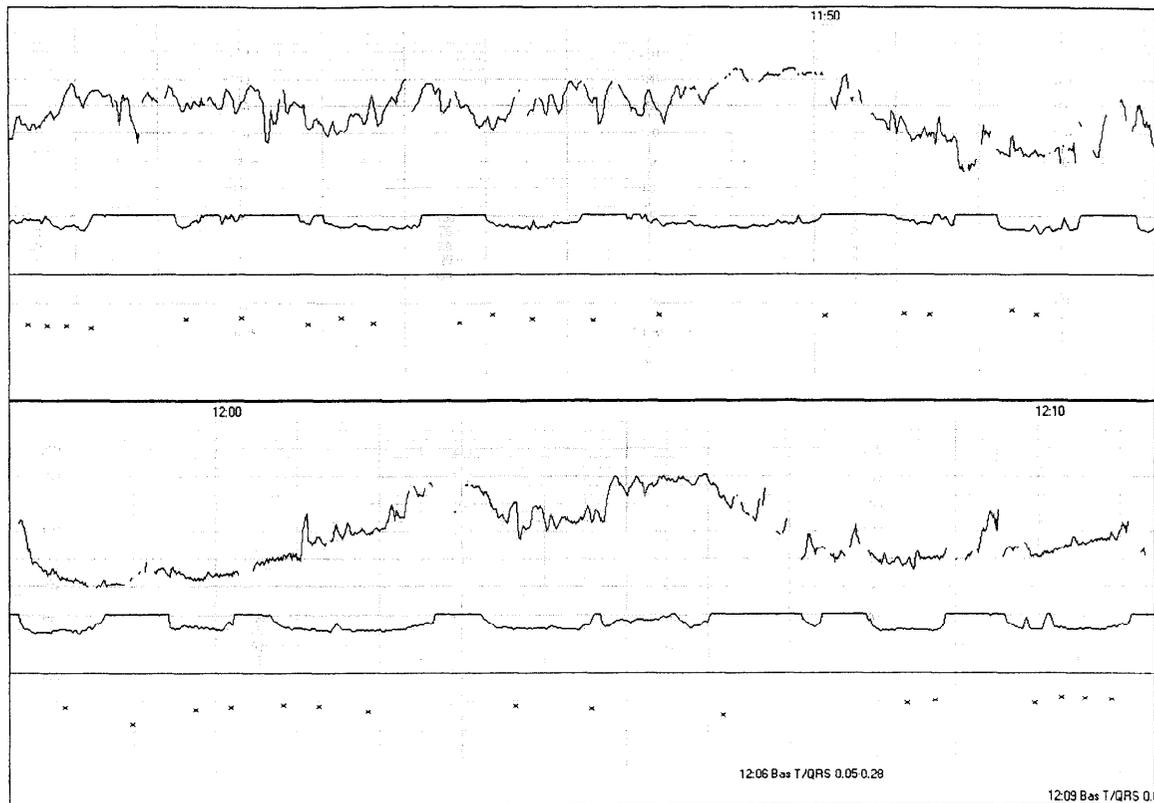


Figure VII-8

A recording obtained during 2nd stage of labor. Normal pregnancy, spontaneous onset of labor after 40w, clear liquor. Mid cavity forceps for threatening hypoxia at 12:49, female 3530g, Apgar 6-8-8, Cord artery: pH 6.88, PCO₂ 11.73 kPa, BDecf 14.9 mmol/l. CTG+ST clinical guidelines would have indicated a need for assisted delivery at 12:00.

After reiterating information about the purpose of the trial and case discussions, the second phase of the trial commenced. During this period, only two cases in the CTG+ST group had an adverse outcome. Apart from the previously described case of intrapartum death (MAE 473), one case (MAD 494) had a baseline T/QRS rise during the last 10 minutes of labor and was kept for three hours in SCBU for general observation. This neonate was later on diagnosed to have a coarctatio aortae.

In cases born within the trial where ST data had been available according to the protocol (adequate recordings), the second phase of the trial showed significant reductions ($p < 0.05$) in the number of neonates with Apgar scores < 4 at one and five minutes (23 cases (2.19%) vs 8 (0.76%) and 5 (0.48) vs 0 in the CTG and CTG+ST groups, respectively). The number of cases with cord artery metabolic acidosis was also reduced from 14 (1.44%) to 4 (0.44%) as was the number of babies admitted to SCBU, 7.44% vs 5.12%.

One reason for the reduction in admissions to SCBU was the decrease in the number of neonates admitted after mid cavity operative vaginal deliveries, 14 out of 26 in the CTG arm as compared to 1 out of 11 in the CTG+ST arm of the trial (p=0.014).

11. Summary of neonatal outcome and ST events

In the CTG+ST group, 45 cases had ST events that were regarded as significant according to CTG+ST clinical guidelines. Of these, 7 cases had adverse or complicated neonatal outcome of which 6 had ST events emerging >30 minutes before delivery, range 32 – 200 min. All these cases occurred during the initial phase of the trial and intervention according to the CTG+ST clinical guidelines should have occurred. These cases were considered as violations of protocol. In the remaining case, recorded during the second phase of the trial, the ST events occurred 10 minutes before delivery.

121 cases had no ST events detected. Out of these, 3 had adverse or complicated neonatal outcome consisting of perinatal death related to group B streptococci septicaemia (preterminal CTG), irritability due to subgaleal bleeding after vacuum extraction and the third case had metabolic acidosis at delivery, normal Apgar scores and had an uneventful neonatal period. In the latter case, no ST data was available for the last 3.5hrs of labor.

In the CTG group, on retrospective analysis, 34 cases displayed significant ST changes and 13 of those were associated with adverse or complicated neonatal outcome. Out of these 13, only one case had ST events emerging <20 minutes before delivery.

151 cases had no significant ST events. Out of these, 6 had adverse or complicated neonatal outcome of which 3 had no ST information available, one had a preterminal CTG, one case showed irritability associated with a periventricular bleeding after vacuum extraction for failure to progress and the remaining case had cord metabolic acidosis and respiratory symptoms neonatally.

12. Analysis of demographic data differences

A significant difference was noted with a 12% reduction in the CTG+ST group in the number of deliveries with epidural analgesia (**Table VII-7 A**). However, this factor did not contribute to the significant differences in primary outcome between the groups, since the frequency of cord artery metabolic acidosis in the CTG+ST group was lower with epidurals than without, 0.42% vs. 0.70%.

13. Fetal blood sampling (FBS)

FBS was performed in 261 patients of the CTG group (10.7%) and in 234 patients (9.3%) of the CTG+ST group (OR 0.86, 95% CI 0.71 – 1.04, p=0.116). During the second period of the trial, the corresponding figures were 11.8% and 8.9%, respectively (OR 0.73, 0.55-0.96, p=0.022).

The study contained six babies with FBS data and metabolic acidosis at delivery. The ST waveform could be assessed in 5 of these six babies, showing abnormalities lasting from 25 to 276 (median 119) minutes before delivery. In one case an abnormal FBS was obtained (pH 7.13). At that point in time, ST events had been recorded for 80 minutes. In the other 5 cases, the scalp pH was normal (>7.20) and not repeated as labor progressed.

E. Discussion

These results demonstrate that monitoring term fetuses with CTG combined with ST waveform analysis lead to a significant improvement in perinatal outcome. This is the first report showing a new fetal monitoring methodology capable of reducing both the risk of babies being exposed to severe intrapartum hypoxia and the number of operative deliveries for fetal distress. Thereby achieving what has recently been required from new developments in EFM.

Our results confirm the experimental research findings that the ST waveform of fetal ECG provides significant information related to fetal hypoxia and myocardial hypoxia in particular. The current study also confirmed the finding in the Plymouth trial that the addition of ST waveform analysis to conventional CTG provided reassurance of fetal state being normal in spite of CTG recorded fetal heart rate changes. This has the effect of reducing the rate of operative deliveries for fetal distress. There was no increase in operative deliveries for other indications in any of these two studies.

The most important finding in the present study was that the rate of metabolic acidosis at birth was significantly reduced with CTG+ST-monitoring, compared with CTG alone as was the number of neonates with signs of moderate/ severe neonatal encephalopathy. In the Plymouth study, there was a similar trend of less babies born with cord metabolic acidosis but the difference was not statistically significant. The current study differed from the Plymouth study in that the STAN[®] system included a computerized interpretation of ST-changes. Another difference was that in the present study the protocol stated that intervention should be performed in cases with a non-reassuring or abnormal CTG if a rise in the T/QRS-ratio occurred and not as in the Plymouth study if the T/QRS-ratio rise exceeded a certain level.

1. Neonatal outcome and ST events

The primary aim of the trial was to test the ability of ST waveform of the fetal electrocardiogram recorded throughout labor to reduce the risk of fetuses being

exposed to significant hypoxia. Metabolic acidosis at birth is the hallmark of intrapartum hypoxia⁴. Low and colleagues at the University of Kingston, Ontario, Canada have studied the relationship between metabolic acidosis and neonatal encephalopathy. In a recent paper⁵, they concluded that the incidence of metabolic acidosis was 2% of total births at term with an incidence of neonatal encephalopathy of 0.3%. In our study, the incidence of cord artery metabolic acidosis with adequate recordings was 1.44 % in the CTG arm and 0.57 % in the CTG+ST arm. We therefore believe that ST-analysis is of value in the prevention of intrapartum asphyxia also in settings with a rather low incidence of metabolic acidosis. The corresponding figures for the Plymouth study were 1.40 and 0.55%, respectively.

Cord artery metabolic acidosis is a marker of active metabolic adaptation to intrapartum hypoxia by anaerobic metabolism. Thus, it should be associated with vigorous neonates as illustrated by the observation that only 7 of the 46 cases in the Swedish RCT with cord artery metabolic acidosis had Apgar scores <7 at 5 minutes and only 4 had an Apgar score <4 at 5 minutes.

The trial result brings the issue of intrapartum events as a cause of neonatal encephalopathy and cerebral palsy (CP) to the fore. Recently, the 8th Swedish population-based cerebral palsy report⁶ was published showing that birth asphyxia was the likely cause of CP in 28% of children born at term, a higher contribution than previously found. In the Western Australian case-control study⁷, the moderate/severe encephalopathy was 3.8/1000 term live births and 29% of term neonates showed signs of moderate/severe encephalopathy related to intrapartum factors. Although intrapartum events may not be the dominant cause of neurological symptoms, still they are of significance as these may be preventable. The significant reduction noted in the current trial of cases with moderate or severe neonatal encephalopathy in surviving infants from 3.3/1000 (8 per 2447 cases) to 0.4/1000 (1 per 2519 cases) in the CTG+ST-arm indicate that a change in obstetric care may improve the situation with regard to adverse neonatal events.

It appears reasonable to assume that the clinical outcome noted in the CTG+ST group should be based on more detailed information provided by ST analysis in relation to the ability of the fetus to handle hypoxia. An increase in the T/QRS ratio provides detailed information on the rate of myocardial glycogenolysis

⁴ Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. *Am J Obstet Gynecol* 1994; 170:1081-7.

⁵ Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. *Am J Obstet Gynecol* 1997;177:1391-4.

⁶ Nagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. *Acta Paediatr* 2001;90:271-77.

⁷ Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998; 317L1549-1553

during experimental hypoxia and there are good reasons to believe that the same mechanisms are involved also during human labor demonstrated by the significant shift of cord acid base towards metabolic acidosis.

The pathophysiology behind biphasic ST waveform changes is less well known. Such patterns have been noted during the initial phase of acute hypoxia, prior to the onset of an increase in T wave amplitude and documented in association with experimental and clinical fetal growth restriction.

Recently, Westgate et al⁸ reported on ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. They found an increase in T/QRS ratio that became more marked when the level of hypoxia was increased by reducing the time between occlusions from 5 to 2.5 minutes. Negative ST waveforms were noticed during basal conditions in four out of eight fetuses. During moderate hypoxia, these four fetuses showed a more marked rise in T/QRS ratio associated with a lower pH, higher base deficit and lactate. The ability of these fetuses to maintain their blood pressure was also somewhat reduced. Fetuses no longer capable of maintaining their cardiovascular response reacted with negative T waves in between occlusions. The authors conclude that an increase in T/QRS ratio indicated hypoxic stress and the appearance of biphasic and negative T waves between contractions may be a useful marker for the development of severe fetal decompensation. Using the same experimental design, the Auckland group⁹ has demonstrated the appearance of subendocardial cell injury associated with fetal decompensation and it appears likely that biphasic ST events with markedly negative T waves recorded during severe fetal decompensation would be the result of a subendocardial cell injury process.

In the current study, of those 29 neonates identified with adverse neonatal events related to delivery, three showed biphasic events only associated with tachycardia and loss of heart rate variability occurring between 88 and 200 minutes before delivery. None of these had signs of neonatal heart failure.

Instrumental vaginal deliveries have been shown to be associated with an increased risk of neonatal intracranial injury. In the current study, two of the cases in the CTG group with seizures (OEH 379 and LDA 023) had mid cavity ventouse deliveries for fetal distress. When examining the potential of ST information retrospectively, in the first case the CTG+ST clinical guidelines did not indicate a need for operative delivery and in the second case indications for an intervention (caesarean section) existed two hours before delivery took place.

⁸ Westgate JA, Bennet L, Brabyn C, Williams CE, Gunn AJ. ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. *Am J Obstet Gynecol*, 2001;184:743-51.

⁹ Gunn AJ, Maxwell L, de Haan H, Bennet L, Williams CE, Gluckman PD, Gunn TR. Delayed hypotension and subendocardial injury after repeated umbilical cord occlusion in near-term fetal lambs. *Am J Obstet Gynecol* 2000; 183:1564-72.

This observation of a potential reduction in complicated vaginal operative deliveries was also demonstrated. After retraining, the rate of mid cavity ventouse/forceps deliveries were significantly reduced from 2.51% to 1.26% in the CTG and CTG+ST groups respectively (OR 0.5, 95%CI 0.25-0.97).

Although intra-cranial trauma may affect perinatal morbidity, intrapartum hypoxia is the main risk factor. This is illustrated by the observation that two of the three cases of perinatal death had acutely emerging hypoxia during last stage of labor. The third case was associated with signs of intrauterine infection. With the information provided by CTG+ST, it was of interest to examine the onset of ST changes among the 17 cases with signs of metabolic acidosis and an adverse or complicated neonatal period. Significant events occurred in 8 cases in 1st stage and in the remaining 9 cases, ST changes appeared in 2nd stage during active pushing. An interesting observation is that the one case where the cause appeared to be antenatal, as indicated by decreased fetal movements and oligohydramnios (MAD 408-CTG), a preterminal CTG pattern was recorded without any ST events. Nor was metabolic acidosis recorded.

Among the 29 cases with adverse or complicated neonatal period, only 13 had any risk factor detected. These consisted of maternal pyrexia during labor (4 cases), growth retardation (1 case), meconium stained liquor (5 cases) and gestational age of >42 completed weeks (3 cases). Among the 17 neonates with metabolic acidosis, only three cases had antenatal risk factors further illustrating the complexity and uncertainty in predicting the outcome of labor.

When testing a new technology, such as CTG+ST, it is important to develop the recommended standards of clinical use. Such standards were well defined in the trial protocol. After exclusion of cases with inadequate monitoring, the differences in primary and secondary outcome parameters between the study groups were more pronounced which supports the benefits of ST analysis.

The successful clinical introduction of any new technology or methodology depends on the acceptance and appropriate application by the users. We are therefore not surprised that in the present trial repeated training and local clinical experience was necessary before full acceptance of the new method was achieved. The lowest rates of metabolic acidosis (0.4%) and of operative delivery for fetal distress (5.0%) were seen in the CTG+ST group following the retraining. This demonstrates the effect of training, feedback and growing experience.

2. Retrospective analysis

The design of the trial included a unique feature in that all data were stored in both arms of the trial so that ST events could be analyzed in the CTG only group. Thus, the following question could be answered: How many cases with adverse or complicated neonatal outcome in the CTG arm could have been

delivered earlier if the ST information had been known and how much earlier could they have been delivered?

Out of the 19 cases in the CTG group with adverse or complicated neonatal period, 17 had ST data available. In 15 of these, intrapartum hypoxia occurred (two cases with neonatal findings related to birth trauma associated with vacuum extractions without signs of intrapartum hypoxia). Out of these 15, 12 had ST events emerging >20 minutes before delivery. Of the remaining 3, 1 case had a preterminal CTG and would not have benefited from ST information and 2 cases had ST events emerging <20 minutes before normal vaginal deliveries. Thus, it appears likely that the reduction of number cases adversely affected by labor seen in the CTG+ST group after retraining could have been achieved in the CTG group as well provided ST information had been available.

3. FBS

The trial design allowed FBS to be used according to the discretion of the clinician. Thus, FBS could be a potentially confounding factor. However, this could not be documented.

4. Continuous process of learning

The issue of education has been recognized ever since the Plymouth trial. In that trial written material together with tutorials formed the basis for the staff learning process. There was also a pilot phase of one month allowing the staff experience with the STAN[®] device.

The current trial had a more ambitious training approach that combined a two-month pilot phase with lectures. The educational material consisted of presentations covering basic physiology, CTG interpretation, ST interpretation and the assessment of the newborn, both in written form and in a multi media based format (CD) for self-training. Furthermore, the CD contained recordings from relevant cases with comments and question/answers. The booklet and CD were distributed to all centers. To secure that everyone had access to the information, a dedicated PC was available on each labor ward.

The study protocol called for an interim analysis after 1600 cases to assess the incidence of metabolic acidosis in the two arms of the trial. During this analysis, it was discovered that in the CTG+ST group, cases of intrapartum hypoxia were missed, i.e. ST events had been indicated by the ST log and no intervention was made. These events were associated with fetal heart rate changes but the staff decided to let labor continue without recommended intervention, thereby delaying an operative intervention or allowing labor progress to a normal vaginal delivery. In these cases, delivery was delayed for > 20 minutes thereby increasing the probability of an acidotic baby being born. The trial was continued but additional training was instituted which included presentation and discussion of actual trial cases. September, 1999, marked the beginning of the

second phase of the trial. This was decided by the monitor in collaboration with the chairman of the trial management group. The only difference between the first and second phase of the trial was the more structured and regular case presentations.

The outcome of fetal monitoring is related to the ability of the staff to interpret and manage specific guidelines. The trial design allowed for comparisons to be made when experience of ST analysis had increased during the second phase of the trial. The data shows an improved outcome provided guidelines were followed.

Considerable effort has gone into the obstetric prevention of birth asphyxia. However, it has been difficult to show that current fetal monitoring techniques reduce the incidence of fetal death or neonatal encephalopathy, and the value of fetal monitoring for predicting events leading to cerebral palsy have been found to be uncertain. The current randomized trial shows that perinatal outcome can be improved not only regarding a reduction in operative interventions but more importantly by reducing the risk of term fetuses being exposed to significant intrapartum hypoxia.

F. Conclusion

The STAN[®] S 21 performs the fetal ECG analysis automatically, but the method still requires the CTG interpretation by the clinician. Intervention must be based on the results of monitoring in the context of the stage of labor and all other available clinical information. For term pregnancies, the present results indicate that using CTG combined with automatic ST waveform analysis substantially increases the ability to detect fetal hypoxia and more appropriately intervene in cases of threatening asphyxia.