

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Obstetric Data Analyzer

Device Trade Name: STAN[®] S31 Fetal Heart Monitor

Applicant Name and Address: Neoventa Medical AB
Ågatan 32
SE-431 35 Mölndal
Sweden

United States Representative:
M Squared Associates, Inc.
719 A Street, NE
Washington, DC 20002

Date of Panel Recommendation: June 23, 2005

Premarket Application (PMA) Number: P020001

Date of Notice of Approval to Applicant: November 1, 2005

II. INDICATIONS FOR USE

The STAN[®] S31 Fetal Heart Monitor (STAN S31) is indicated as an adjunct to fetal heart rate monitoring to determine whether obstetrical intervention is warranted when there is increased risk of developing metabolic acidosis.

This device is intended for use in patients with

- planned vaginal delivery;
- >36 completed weeks gestation;
- singleton fetus;
- vertex presentation; and
- ruptured amniotic membranes.

III. CONTRAINDICATIONS

Use of the STAN S31 monitor fetal electrocardiogram (FECG) analysis function is contraindicated in the following situations:

- Non-reassuring, Grade 2 Fetal Heart Rate (FHR) classification (as defined in the STAN S31 Training Materials). When fetal asphyxia has been severe and long lasting, the ST waveform returns towards normal, reflecting a markedly reduced ability by the fetus to respond. **A change over time can not be expected, therefore, reliance on ST event signals in this situation may lead to serious adverse neonatal outcome.**
- In patients for whom use of a fetal scalp electrode is contraindicated such as
 - HIV;
 - infectious hepatitis;
 - active herpes simplex virus; and
 - known or suspected fetal coagulation disorder.
- Patients with fetal bleeding disorders. Chronic fetal bleeding (e.g., due to partial placental abruption), leading to loss of fetal blood volume, may result in a reduction in the margin of safety or time that the fetus can successfully respond to hypoxia.
- Monitoring initiated in the second stage of labor, since time may be insufficient to establish the baseline fetal ECG data required for automatic ST event signals.
- Patients experiencing precipitous labor, as rapid labor may preclude acquisition of necessary baseline fetal ECG data.
- Patients receiving Transcutaneous Electrical Nerve Stimulation (TENS) for analgesia during labor because TENS may interfere with acquisition of the fetal ECG signal.
- Patients requiring immediate delivery as in the following situations:
 - conditions that preclude vaginal delivery such as documented or suspected placenta previa;
 - cord prolapse; and
 - need for immediate delivery unrelated to fetal heart rate or fetal ECG, such as active maternal or fetal bleeding.

IV. WARNINGS AND PRECAUTIONS

The WARNINGS and PRECAUTIONS can be found in the STAN S31 monitor Fetal Heart Monitor labeling.

V. DEVICE DESCRIPTION

The STAN[®] S31 Fetal Heart Monitor Fetal ECG Analysis System (STAN S31) is a fetal heart monitoring system used during labor and delivery to measure, display, and analyze the fetal ECG (FECG) waveform. The STAN System provides this ST waveform analysis as an adjunct to standard Electronic Fetal Monitoring (EFM).

Device Components

The STAN S31 consists of a Main Unit, which physically consists of two modules, a Display Unit (DU) and Patient Interface Box (PIB), that are interconnected mechanically and by cabling. The system also includes patient sensors and embedded application software.

FECG and FHR are measured continuously via a scalp electrode placed on the fetal vertex and connected via a legplate connecting cable to the PIB.

The legplate provides a connection for a skin electrode on the maternal thigh. This electrode provides a reference which is essential in obtaining the FECG waveform.

Uterine activity is measured either by an external transducer [tocodynamometer (TOCO)] placed on the abdomen of the mother or by an intrauterine pressure catheter (IUPC) connected via an adapter cable. The STAN S31 monitor can measure FHR (but not ST) using an ultrasound transducer. **A spiral fetal scalp electrode is needed whenever FECG is to be recorded for the ST waveform analysis.**

The STAN S31 is designed for use with commercially available disposable single-spiral electrodes that are compatible with STAN S31 monitor. The TOCO, IUPC, ultrasound transducer and spiral electrodes are provided with the device, additional supplies must be purchased separately.

General Technical Description and Principle of Operation

The operator interface for the STAN System is a touch-screen. This screen also displays EFM and ST information in real-time. Patient information and clinical notes (e.g., dilatation and effacement) can be entered using a keyboard. FHR and uterine activity signals are presented onscreen as with traditional EFM.

When FECG is recorded with a spiral electrode, changes in the T wave and the ST segment of the FECG are automatically identified and analyzed by the application software. The analysis is displayed in the lower section of the screen as a series of data points (T/QRS crosses) and event markers. The ST analysis identifies patterns and changes in the T wave and ST segment, and displays events based on the analysis of those changes. All events are stored in the Event Log.

The STAN System provides intrapartum information about two aspects of fetal myocardial physiology (Ref. 3,7,11):

1. **The rate of utilization of stored sugar (glycogen).** Myocardial glycogenolysis is the key source of energy when oxygen is lacking and the fetal heart must perform. Glycogenolysis is triggered by increases in circulating epinephrine, the primary stress hormone, which is liberated in large quantities during labor-induced hypoxia. Potassium ions are liberated from myocardial cells into extracellular space as glycogen is utilized. T waves increase in amplitude with this release of potassium, resulting in an increased T/QRS ratio.
2. **Reduced myocardial function.** In any clinical situation where there is a reduction in the ability of the myocardium to maintain its own perfusion and contractile performance, such as during acute reduction in oxygenation, a sudden reduction in blood volume returning to the heart, tissue immaturity, or as a consequence of infection, biphasic ST waveforms result. These indicate that the myocardial function is depressed and the contractile strength is reduced.

When these changes occur in association with non-reassuring FHR patterns during labor, the clinician has additional information about the working conditions of the fetal heart. (This is analogous to stress testing in the adult for coronary insufficiency.) The STAN System helps the clinician to determine when the stress of labor on a fetus has progressed to a point where intervention is warranted.

Algorithms and Software

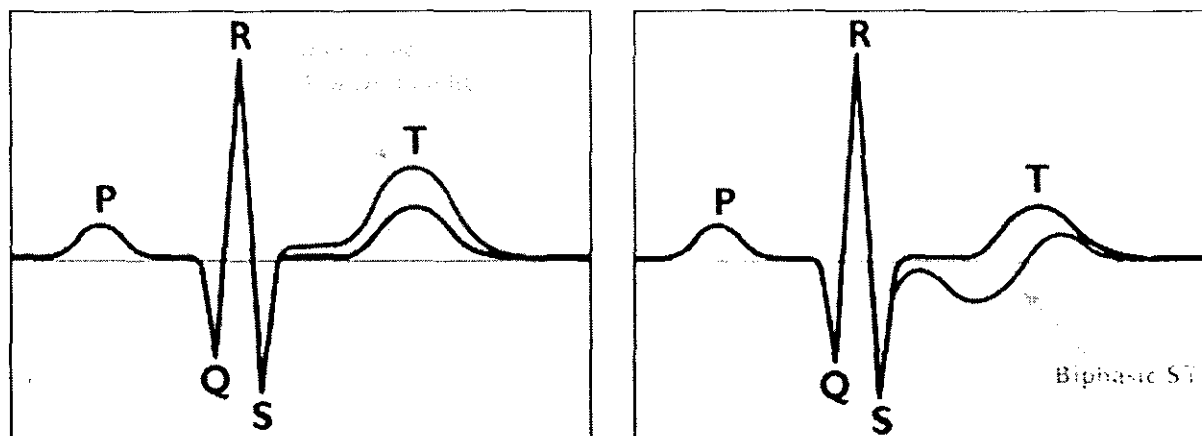
The STAN System Application Software controls the data handling during a recording. The two major components of the Application Software are

1. the Main Software running on the CPU in the Display Unit which handles high-level signal processing, user interaction, data presentation, and system control; and
2. the DSP Software running on the Digital Signal Processor on the DSP Board in the PIB which handles digital filtering.

The main function of the STAN S31 monitor is addressed by the graphical user interface of the Main Software running on the Display Unit. Data are displayed continuously on screen and also on paper, if a local printer is connected. External ultrasound recording displays only the FHR, while internal recording, using a spiral electrode, can also show the fetal ECG wave-form.

Fundamentally, the STAN S31 acquires and analyzes the QRS and ST segments of the fetal ECG (Figure 1).

Figure 1. T/QRS waveform. T-wave increase and Biphasic ST



The STAN algorithms use two signal characteristics derived from the FECG to determine events: ST segment slope differences and T/QRS amplitude differences. The algorithms generally operate by comparing the latest sample (either an ST segment or a T/QRS value) to an established baseline to identify a change.

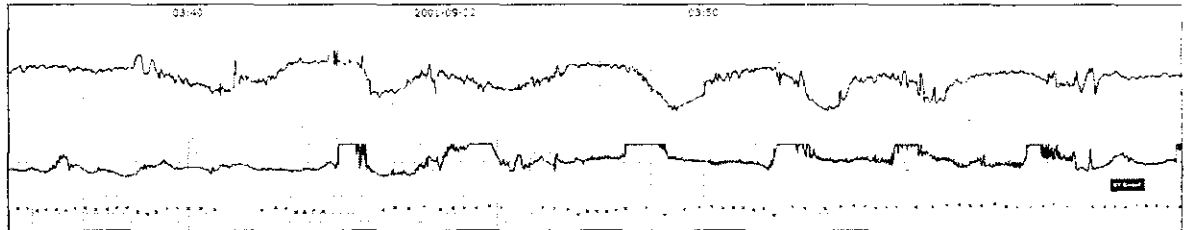
The STAN system calculates an average ECG waveform from the FECG channel (scalp-to-skin lead). Every fetal heartbeat generates an FECG complex, which is assessed by STAN S31 monitor against strict quality criteria. The FECG complexes satisfying the quality criteria qualify for the subsequent analysis. The averaging is performed over 30 consecutive qualified FECG complexes. The device uses the average ECG waveform to process the T/QRS ratios, the ratio between the T-wave amplitude and the QRS-complex amplitude. A T/QRS baseline is computed every minute and monitored for multiple characteristics, contributing to a determination of a T/QRS difference and the identification of a significant event. The initial 20 minutes are used to collect T/QRS baseline data to allow for a robust determination of starting values used by the processing algorithms for event detection.

The ST analysis software conditions and analyzes the raw ECG signal to identify additional characteristic parameters of the T wave and QRS complex used in decision making. The decision algorithm evaluates these parameters looking for the 3 types of events: (1) episodic T/QRS rise, (2) baseline T/QRS rise; and (3) biphasic ST. STAN defines Biphasic as a condition where the slope of the ST segment has become negative, which the decision algorithm uses as an indicator of fetal abnormality. Biphasic events are further classified into category 1, 2, or 3 indicating that the slope is above baseline, crossing the baseline, or below baseline, respectively.

There are 2 modes of clinical operation: recording and signal mode. The Recording mode is used to record data; and the Signal mode is used to check FECG signal quality. There are also two non-clinical modes: review and demonstration mode. The Review mode is used to review previously recorded data; and the Demonstration mode is used for simulating a patient recording.

In summary, using the fetal ECG information, the STAN S31 calculates the ratio of the amplitudes of the T wave and QRS complex and displays this ratio as an “x” on a tracing below the standard uterine activity tracing. (See Figure 2 below.) The STAN 31 also displays an “ST event” message on the lower tracing if there is a significant increase in T/QRS ratio or in the presence of abnormal ST waveforms. With a prompt by the clinician, the monitor provides additional detail about the nature of the ST event.

Figure 2. STAN 31 tracing



VI ALTERNATIVE PRACTICES OR PROCEDURES

- Electronic fetal heart rate monitoring with the data presented on a strip chart recorder
- Auscultation of the fetal heart beats and palpation may also be used to assess the fetus during labor
- Intermittent fetal scalp pH
- Fetal oxygen saturation
- Fetal scalp stimulation

VII. MARKETING HISTORY

Over 500 STAN monitors have been sold worldwide. This includes approximately 350 model S21 devices and more than 150 model S31 devices (see section IX. Summary of Preclinical Studies for a description of the S21 model).

The device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A previous version of the device, the STAN ESST fetal heart monitor, was evaluated in a prospective, randomized, controlled clinical trial of nearly 5000 patients (Swedish Randomized Controlled Trial or SRCT). There were 29 clinically significant adverse outcomes in that study:

- peripartum death (3);
- mild/moderate/severe encephalopathy (with or without metabolic acidosis) (11); and

- neonates admitted to Special Care Baby Unit (SCBU) with metabolic acidosis and other symptoms (15)

There is only partial overlap between the above cases and the total number of cases in the study in which metabolic acidosis was documented (46). The incomplete overlap is explained by the fact that 31 of the infants with umbilical cord metabolic acidosis were clinically normal, vigorous neonates with normal Apgar scores. These infants were not included as adverse events. Alternately, 15 infants with normal cord blood, or unavailable cord blood, showed evidence of intrauterine hypoxia and/or asphyxia. These infants were included in the adverse events category (see Table 1.)

Table 1. Adverse Events

	Study Arm FHR-only	Study Arm FHR + ST
Death (intrapartum)	1	2
Severe Encephalopathy	3	0
Moderate Encephalopathy	4	0
Mild Encephalopathy	1	3
SCBU Admissions	10	5

Of the 3 peripartum deaths in the study, 2 were in the FHR + ST arm and 1 was in the FHR only arm, and the difference between the two arms was not statistically significant. There were no cases of moderate or severe encephalopathy in the FHR + ST arm. Of the 15 babies admitted to the SCBU with metabolic acidosis and "other symptoms" not neurologic in nature (e.g., respiratory problems), all were discharged in good condition without evidence of sequelae.

The STAN S21 was also evaluated in two trials in the United States. The first of these trials was intended to test the training program and did not involve patients. The second trial was intended to study use of the device for clinical management of patients in the United States.

In this second study, 530 patients were enrolled. The protocol identified a case based analysis of all cases with cord artery pH<7.15. Of the 27 cases with pH<7.15, there was one case of metabolic acidosis (pH 6.88, BDecf 14.4 mmol/L), but this infant had an Apgar score of 7 and 8 at 1 and 5 minutes respectively, and was not one of the 8 infants admitted to the NICU.

One of the cases with pH<7.15 had a poor outcome during the neonatal period. Of 4 cases with pH of ≤ 7.05 , one infant (pH 7.05, BDecf 10.3mmol/L, Apgars 6 and 8) was admitted to the NICU for observation due to grunting, maternal fever, and possible sepsis. At 28 hours of age, the infant displayed seizure activity lasting for 1 minute. The initial EEG was abnormal. A MRI, two days later showed "acute infarction involving left anterior brain stem and basal ganglia + portions of left frontal and temporal lobe." There was a protocol deviation in that this subject had a private physician (not an investigator) who managed the labor and delivery. The study

investigator obtained informed consent from the patient and placed the STAN system, but then left the room. This adverse event was not device related.

The one death was an infant that was diagnosed at approximately 28 weeks of gestation with a hypoplastic left ventricle. The infant died at approximately two weeks post partum during corrective surgery. This death was unrelated to the use of the STAN S31 monitor.

IX. SUMMARY OF PRECLINICAL STUDIES

System Verification and Validation Testing

The STAN S31 was validated to assure that it performed its intended functions. Verification and validation consisted of testing, analysis, and inspection activities, as follows:

- System verification, complete system internally verified against requirements for system
- System verification, complete system externally tested against requirements for system
- Sub-system verification of hardware modules, verified against requirements for hardware modules
- Software verification, software verified against requirements for software including software quality assurance (SQA) testing, unit level testing, and integration testing
- Software validation, the software and related development validated against its intended use (to operate as part of the system)

Verification was performed using suites of simulated and recorded signals, using human-scored results as applicable to assess correctness. Extensive test suites were developed to assess the performance of the ECG analysis algorithm and its ability to reliably identify the salient waveform parameters. All testing was consistent with FDA guidance for software at a moderate level of concern.

Risk Management Activities

Risk Management was initiated in the Definition and Requirement phases of product development and conducted throughout the design and development activities for the STAN system. The purpose of the Risk Management activities were to identify and control potential hazards arising from any STAN system. Risk Management involved identifying potential hazards, estimating and evaluating the associated risks, and reducing these risks to acceptable levels. The criteria for risk acceptability were generated using the processes in ISO 14971, Application of risk management to medical devices. FDA found the level of testing to be sufficient.

STAN Models and Testing

While the STAN S31 monitor is the subject of this PMA, clinical testing was conducted using previous models of the device. In particular, the STAN[®] S21 fetal

heart monitor (STAN S21 monitor) was used in the US Bridging studies and the predecessor of the STAN S21, the STAN ESST, was used in the Swedish RCT. The differences between the STAN S21 and the STAN S31 versions pertinent to the PMA functions are as follows:

- human factor enhancements;
- minor hardware enhancements;
- support for connectivity options (USB and Ethernet); and
- external monitoring (ultrasound FHR).

The data acquisition and signal processing devices for the two models (S21, S31) are very similar. The transducers and patient cables for FECG are the same. The S31 uses updated design and construction techniques and has been demonstrated to meet the specifications of the original unit. Testing shows that the S31 hardware and software perform equivalently to the model S21.

Device Safety Testing

Electrical, Thermal, and Mechanical Testing

The device was tested for conformance to the UL Medical Electric Equipment Standard, UL 2601, by a third party test facility. In accordance with the standard, the STAN S31 was evaluated for a variety of safety issues such as electric shock, mechanical hazards, and excessive temperatures. This includes tests such as, but not limited to: leakage current, mechanical strength, and temperature testing. The STAN system was found to be compliant with IEC 60601-1. Additionally, they will be submitting the device to UL/ETL for official testing to gain permission to display the UL/ETL mark prior to marketing the device in the United States.

EMC Testing

The STAN system was evaluated for electromagnetic compatibility including emissions and immunity tests performed by an independent laboratory. The STAN system was found to be compliant with IEC 60601-1-2.

Material Safety/Sterilization

The only components of the system that are patient contacting are accessory components, such as the toco transducer, ultrasound transducer, IUP catheter, and spiral electrode. These components are not manufactured by Neoventa, but are existing device already cleared through 510(k).

Summary of Animal Testing

Eleven animal studies were conducted between 1971 and 1989 that led to the first large-scale clinical investigation using a prototype of the STAN S31 fetal heart monitoring system. These studies were used to obtain a basic understanding of metabolic and neurologic aspects of the physiology of fetal hypoxia and asphyxia and to evaluate FECG changes in response to hypoxia.

Basically, two types of experiments were performed in animals. The first type of study used animal fetuses (guinea pig, cat, and lamb) that were acutely exteriorized. The second type of study left the animal fetuses (lamb) in utero with subcutaneous electrodes for FECG. Both studies induced hypoxia in the fetus.

A summary of these preclinical studies is provided in the following charts.

Table 2. "Changes in the fetal heart rate and ECG during hypoxia."

Reference: Rosén KG, Kjellmer I.¹

Date	Animals	Number of animals	Method of evaluation	Results
1971 - 1973	Guinea-pig fetuses Cat fetuses Lamb fetuses Anaesthetized term fetuses, acutely exteriorized and subjected to graded hypoxia.	20 3 3	<p>Objectives To investigate the vagal influence on the fetal hypoxic bradycardia and to identify changes in the fetal ECG during graded hypoxia.</p> <p>Study outline The vagal influence of the fetal hypoxic bradycardia was tested by comparing the time for onset of bradycardia, with or without vagal activity.</p> <p>Precordial ECG was continuously recorded and used for FHR measurement and for identification of changes in the ECG waveform during graded hypoxia.</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (3-10% O₂)</p>	<p>There was no indication of any vagal component in the fetal hypoxic bradycardia. Bradycardia is therefore to be regarded as a sign of myocardial hypoxia and failing fetal circulation.</p> <p>The ECG showed that the fetal bradycardia initially is an AV-block, type II.</p> <p>The data also showed that there are progressive changes in the ST interval as an early sign of hypoxia. Both an increase in the T wave amplitude, S-T elevations and negative T waves were recorded.</p>

Table 3. "Alterations in the fetal heart rate and ECG correlated to glycogen, creatine phosphate and ATP levels during graded hypoxia."

Reference: Rosén KG, Isaksson O.²

Date	Animals	Number of animals	Method of evaluation	Results
1974	Guinea-pig fetuses Anaesthetized term fetuses, acutely exteriorized and subjected to graded hypoxia.	40	<p>Objectives To investigate how the depletion of glycogen, creatine phosphate and ATP in the fetal heart, liver and brain correlates with FECG changes during graded hypoxia.</p> <p>Study outline The depletion of glycogen, creatine phosphate and ATP in the fetal heart, liver and brain, were analyzed in biopsy samples.</p> <p>ST interval changes were graded in a FECG scoring system, with an eight-graded scale, according to severity.</p> <p>The first fetus of each litter was immediately biopsied and served control for its littermates.</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (8% O₂)</p>	<p>A strong linear correlation was found between the FECG scoring system and the depletion of heart glycogen and creatine phosphate. ATP was unaffected until glycogen was severely affected.</p> <p>Bradycardia was strongly associated with failing myocardial metabolism.</p>

19

Table 4. "Myocardial metabolism in relation to electrocardiographic changes and cardiac function during graded hypoxia in the fetal lamb."

Reference: Hökegård KH, Eriksson BO, Kjellmer I, Magno R, Rosén KG.³

Date	Animals	Number of animals	Method of evaluation	Results
1975-1976	Lamb fetuses Anaesthetized fetuses acutely exteriorized and subjected to graded hypoxia.	21	<p>Objectives To analyze the metabolic background of hypoxic FECG changes.</p> <p>Study outline Serial myocardial biopsies in the fetal lambs were analyzed for depletion of glycogen, creatine phosphate and ATP.</p> <p>FECG changes were also correlated to the myocardial performance measured by, FHR, mean arterial blood pressure, combined cardiac output and myocardial contractility (dP/dt).</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (8-15% O₂)</p>	<p>During hypoxia there was a significant relationship between ST changes and depletion of myocardial glycogen. A highly significant correlation was seen between the amount of glycogen available and the increase rate in T wave amplitude. A parallelism was seen between the amount of available glycogen and fetal cardiovascular function.</p> <p>In the absence of acidosis and hypoglycemia, the myocardium showed a remarkable good capacity to regenerate its glycogen stores during periods of adequate oxygenation.</p>

Table 5. "ECG-changes in the fetal lamb during asphyxia in relation to beta-adrenoceptor stimulation and blockade."

Reference: Hökegård KH, Karlsson K, Kjellmer I, Rosén KG.⁴

Date	Animals	Number of animals	Method of evaluation	Results
1976	Lamb fetuses Anaesthetized fetuses acutely exteriorized and subjected to graded hypoxia.	14	<p>Objective To investigate whether beta-adrenoreceptor stimulation and hypoxia exerted additive or potentiating effects of the FECG and several cardiovascular parameters. And to investigate if the hypoxic changes in the FECG could be blocked by beta-adrenoreceptor blocking agents.</p> <p>Study outline FECG changes were quantified according to a scoring system. The grades were then used for correlations with cardiovascular function; measured by FHR, mean arterial blood pressure, end diastolic pressure, blood gases, acid-base status, blood lactate and glucose. Beta-adrenoreceptor stimulation was induced by injection of isoprenaline (0.02 to 0.04 $\mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$).</p> <p>Beta-adrenoreceptor blockade was induced by injection of propranolol.</p> <p>Induction of hypoxia The mother was ventilated with a low oxygen gas mixture (9-15% O_2)</p>	<p>Isoprenaline injection induced the same pattern of changes in FECG as previously recorded during hypoxia.</p> <p>By increasing the isoprenaline dose, an increase in the duration as well as the T wave amplitude were obtained.</p> <p>Propranolol completely abolished the FECG changes induced by isoprenaline as well as by mild hypoxia. During severe hypoxia, the FECG changes could not be abolished by propranolol.</p>

Table 6. "Beta-adrenoceptor agonists and hypoxia in sheep fetuses."

Reference: Dagbjartsson A, Herbertsson G, Stefansson TS, Kjeld M, Lagercrantz H, Rosén KG.⁵

Date	Animals	Number of animals	Method of evaluation	Results
1981 - 1984	Lamb fetuses Anaesthetized fetuses acutely exteriorized and subjected to graded hypoxia.	17 controls 11 in the max group 7 in the 30 µg group 8 in the 10 µg group	Objective To test the influence of maternal beta-mimetic therapy on fetal reactions to hypoxia. Study outline Terbutaline was infused to the mother at three different dosages. In the 10 µg group the terbutaline concentration was in the therapeutical range (11-58 nmol/l). In the max and 30 µg group the terbutaline was (50-748 nmol/l) which is above the therapeutical range. Induction of hypoxia Intermittent complete occlusion of the maternal abdominal aorta.	Fetuses in the max group reacted to moderate hypoxia with excessive responses of heart rate, blood pressure, myocardial contractility and ST waveform changes. The mortality in this group was 50% compared to 12% for the controls. The 10 µg group did not have increased mortality, but the terbutaline caused an increase in myocardial workload and a negative energy balance during severe hypoxia. There was a close correlation between myocardial workload and the T/QRS ratio ($r=0.73$, $P<0.01$).

Table 7. "Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxemia."

Reference: Greene KG, Dawes GS, Lilja H, Rosén KG.⁶

Date	Animals	Number of animals	Method of evaluation	Results
1977 - 1979	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterized and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	10	<p>Objectives To study the effect of hypoxia on the ECG waveform in the healthy but chronically instrumented fetal lamb and to explore the possibilities of automatic sampling and quantification of ST waveform changes.</p> <p>Study outline The ST waveform of the fetal ECG in ten chronically instrumented fetal lambs was measured from day 115 to term. Averaged ST waveforms were plotted at 5 min intervals in six fetuses for 2 to 22 days. No diurnal or other rhythms were seen. T wave amplitude was measured in relation to the QRS amplitude as a T/QRS ratio. 20 hypoxia experiments were performed on seven of the fetuses between 120-139 days of gestation.</p> <p>Induction of hypoxia Hypoxia was induced for 1 to 2.5 hours at a time, by administration of a gas mixture of 7% or 9% O₂ and 3% CO₂ in N₂ to the ewe.</p>	<p>The T/QRS ratio was normally <0.30.</p> <p>Persistent T/QRS ratios between 0.32 and 0.65 preceded fetal death by some days in three fetuses and were associated with anaemia and/or hypotension in three other fetuses. In those animals hypoxia caused a further rise in the T/QRS ratio, mean from 0.48 to 0.81 and all died during labor.</p> <p>In the fetuses with normal ST waveforms there were differences in their respectively response to hypoxia, despite a similar drop in PO₂. In eight experiments the T/QRS ratio increased from 0.17 to 0.59 and promptly reverted to normal with normoxia. This was associated with a significant rise in mean arterial blood pressure, plasma lactate, glucose and fall in pH.</p> <p>In four experiments there was a moderate change in mean T/QRS, from 0.19 to 0.25, combined with a moderate increase in plasma lactate.</p> <p>Overall there was a strong correlation between T/QRS ratio and lactate levels.</p>

Table 8. "The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia."

Reference: Rosén KG, Dagbjartsson A, Henriksson BA, Lagercrantz H, Kjellmer I.⁷

Date	Animals	Number of animals	Method of evaluation	Results
1979 - 1982	<p>Lamb fetuses</p> <p>Age during hypoxia experiments was 117-143 days of gestation.</p> <p>During general anaesthesia the mother and the fetus were catheterized and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	7	<p>Objectives To test the hypothesized relationship between the concentration of circulating catecholamines and T wave amplitude.</p> <p>Study outline The ST waveform of the fetal ECG, in seven chronically instrumented fetal lambs, was measured from day 117 to term. Averaged ST waveforms were plotted every 2 min. Blood sampling was done before induction of hypoxia and then every 20 min. 16 one-hour experiments with induced hypoxia were performed. T wave amplitude was measured in relation to the QRS amplitude as a T/QRS ratio.</p> <p>Induction of hypoxia Hypoxia was induced for 1 hour at a time, by administration of a gas mixture of 7% to 9% O₂ and 3% CO₂ in N₂ to the mother.</p>	<p>The response to hypoxia was age-dependent. Fetuses below 126 days of gestation did not react with FECG changes and epinephrine surge, unless acidosis occurred.</p> <p>In more mature fetuses, hypoxia per se induced a surge of epinephrine and ST waveform changes.</p> <p>Overall there was a strong correlation between the T/QRS ratio and the levels of circulating epinephrine ($r=0.765$, $n=95$, $P<0.001$)</p> <p>During normoxia, epinephrine was undetectable (<0.1 nmol/l) in most fetuses, whereas norepinephrine showed an increase at term.</p> <p>The data includes one fetus with chronic ST waveform changes ($T/QRS >0.30$). This was related to a marked increase in plasma epinephrine in spite of normal blood gas values.</p> <p>It was also shown that oxygen concentrations had to decrease by 64% before an adrenaline surge occurred and the T wave increased in amplitude.</p>

24

Table 9. "The relationship between cerebral cardio-vascular and metabolic functions during labor in the lamb fetus and newborn."
Reference: Rosén KG, Lilja H, Hökegård KH, Kjellmer I.⁸

Date	Animals	Number of animals	Method of evaluation	Results
1980 -1982	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterized and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	2	<p>Objectives</p> <p>To compare the different means of fetal surveillance with special emphasis on ST waveform analysis of the FECG during spontaneous labor in the chronically instrumented fetal lamb.</p> <p>Study outline</p> <p>The study presents two case reports of intrauterine death, due to fetal hypoxia. Somatosensory evoked EEG response (SEP), to assess the integrity of the fetal nervous system, was included in the chronically instrumented fetal lamb preparation.</p> <p>Case 1 Spontaneous labor at day 143 of gestation, 28 days postoperative.</p> <p>Case 2 Spontaneous labor at day 125 of gestation, 11 days postoperative.</p> <p>Induction of hypoxia Spontaneous stress during labor</p>	<p>Case 1 FHR was largely unaltered until the last 3 hours, and then a tachycardia occurred.</p> <p>Bradycardia and fall in blood pressure occurred during the last 5 min. Significant ST waveform changes occurred during the last 12 hours of labor. The T/QRS ratio increased progressively in parallel with increase in uterine activity and degree of hypoxia.</p> <p>The fetal brain maintained its functionality until the last 30 min. Brain death occurred 6 min before the last heartbeat.</p> <p>Case 2 In this less mature fetus, the T/QRS ratio increased from 0.30 to 0.80 between 14 and 9.5 hours prior to fetal death. Cortical activity as indicated by SEP was unaffected until the last 45 min.</p>

25

Table 10. "Long term ST waveform changes in the ovine fetal electrocardiogram: the relationship to spontaneous labor and intrauterine death."

Reference: Greene KR, Rosén KG.⁹

Date	Animals	Number of animals	Method of evaluation	Results
1977 - 1982	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterized and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	12	<p>Objectives To study long-term changes in the FECG and the relationship between FECG changes and spontaneous labor and intrauterine death.</p> <p>Study outline An observational study where 12 catheterized animals were monitored. Three of them were monitored during spontaneous labor, six developed long-term ST waveform changes and three fetuses died during the postoperative period.</p> <p>Induction of hypoxia Spontaneous stress during labor</p>	<p>Uterine contraction was shown to, by themselves, induce increases in T/QRS ratio. If the ST elevation was normalized between contractions, the fetus seemed to compensate for the moderate hypoxia. When oxygenation was further reduced, the T wave remained elevated between contractions. During the final stage of labor, a progressive T/QRS increase was noticed. The lactate concentrations increased in parallel with the T/QRS increase.</p> <p>Long-term ST changes with T/QRS ratios >0.30 related to low haemoglobin levels and/or fetal hypotension. Subsequently, all these fetuses died during labor as compared to a 40% survival rate in fetuses showing a normal ST waveform. These fetuses displayed negative T waves as a sign of failing myocardial response to hypoxia. Death in uterus whatever the cause (bleeding, infection or spontaneous hypoxia) was always preceded by marked ST waveform changes.</p>

Table 11. "Electrocardiographic waveform changes and catecholamine responses during acute hypoxia in the immature and mature fetal lamb."

Reference: Widmark C, Hökegård KH, Lagercrantz H, Lilja H, Rosén KG.¹⁰

Date	Animals	Number of animals	Method of evaluation	Results
1985 -1987	<p>Lamb fetuses</p> <p>During general anaesthesia the mother and the fetus were catheterized and electrodes for FECG analysis were implanted subcutaneous in the fetus.</p> <p>The ewe was then housed in the company with another ewe and was feed hay and concentrate, with free access to water and a mineral stone.</p>	16	<p>Objectives To investigate the changes in FECG and the release of catecholamines in fetal lambs of different maturity grades, during nonacidemic fetal hypoxia.</p> <p>Study outline The study contained two groups of chronically instrumented lamb fetuses, an immature group (119 to 126 days, n=10) and a mature group (129 to 141 days, n=6).</p> <p>Hypoxia was induced and PO₂, pH, PCO₂, catecholamines and FECG were followed during hypoxic experiments.</p> <p>Induction of hypoxia Obstruction of maternal placental blood flow through complete obstruction of the maternal aorta for 60 seconds.</p>	<p>Both groups of fetuses had a marked fall in oxygen tension (immature 2.43 ± 0.12 to 1.46 ± 0.12 and mature 2.22 ± 0.15 to 1.11 ± 0.17 kPa).</p> <p>Oxygen saturation dropped from $48\% \pm 3\%$ to $17\% \pm 2$ in the immature group and from $49\% \pm 3$ to 15 ± 3 in the mature group.</p> <p>Only modest changes occurred in pH and PCO₂. Basal catecholamine concentration did not differ between the groups, but it increased more significantly in the mature group during hypoxia.</p> <p>An increase in T wave amplitude occurred in both groups during the latter part of occlusion.</p> <p>In the mature group a linear correlation was found between plasma epinephrine concentration and T/QRS ratio.</p> <p>Fetuses of both groups showed a marked bradycardia of similar magnitude during occlusion, but differed during recovery. The mature group had a slower acceleration of the heart rate. During bradycardia, the mature fetuses responded with a significant rise in mean arterial blood pressure.</p>

27

Table 12. "ECG waveform, short-term heart rate variability and plasma catecholamine concentrations in response to hypoxia in intrauterine growth retarded guinea pig fetuses."

Reference: Widmark C, Jansson T, Lindecrantz K, Rosén KG.¹¹

Date	Animals	Number of animals	Method of evaluation	Results
1988 - 1989	<p>Guinea-Pig fetuses</p> <p>At mid term the doe was anaesthetized and one uterine artery was ligated on one side. She was then allowed to recover and pregnancy would continue until 63 days of gestation. The doe was then anaesthetized a second time.</p> <p>The fetuses were acutely exteriorized and subjected to graded hypoxia by letting the doe breath a low oxygen gas mixture.</p>	24	<p>Objectives To study the ST waveform of the FECG, short-term heart rate variability and plasma catecholamines in normal and growth retarded fetuses, during hypoxia.</p> <p>Study outline The study was done on 12 growth retarded fetuses and 12 of their normal littermates. FECG and short-term heart rate variability were studied during normoxia and in response to acute hypoxia. Blood was sampled and blood gases, acid-base status and catecholamine concentrations were analyzed.</p> <p>Induction of hypoxia Hypoxia was induced by letting the doe breath a low-oxygen gas mixture.</p>	<p>The T/QRS ratio was normal and similar in both groups prior to the hypoxic periods.</p> <p>In the normal sized group, T/QRS ratio increased as a response to hypoxia. The growth retarded fetuses presented a completely different pattern. Seven out of twelve fetuses showed a biphasic ST waveform, with depression and downward sloping ST segment and negative T wave, during hypoxia.</p>

X. SUMMARY OF CLINICAL STUDIES

Overview

A number of clinical studies of the STAN system have been conducted since the mid-late 1980's. These studies can be divided into 3 types: (1) Observational Studies, (2) Randomized Interventional Studies, and (3) US Bridging Studies.

Early observational studies of monitor prototypes evaluated how well fetal ECG data corresponded to events in labor and potential diagnostic performance of the STAN System (References 12-19). Later observational studies evaluated how well retrospective review of tracings by clinicians blinded to outcome could "predict" fetal compromise (References 15, 16).

The Nordic Study is an observational, non-randomized, non-interventional study that was conducted to evaluate clinical accuracy of the device. It was the only study that was both non-interventional and contained an adequate number of metabolic acidosis cases to estimate sensitivity and specificity. The results are discussed below.

Two randomized interventional studies were conducted to evaluate the impact of the ST analysis on the rate of metabolic acidosis, the Plymouth Study (Reference 20) and the Swedish RCT (References 21, 22). The Plymouth Study was a randomized, controlled, prospective study of approximately 2400 deliveries and was designed to investigate if [FHR + ST analysis] could improve the predictive value of intrapartum surveillance compared to FHR only and thereby decrease interventions, without increased risk to the fetuses. The results were a 46% reduction ($p < 0.001$) in operative deliveries for fetal distress, without an increase in operative deliveries for other reasons. The Swedish RCT is the pivotal clinical trial that demonstrated the safety and effectiveness of the STAN S21 monitor. Five thousand women in labor were randomized to be monitored with conventional FHR or with FHR plus ST data. In addition, following the Swedish RCT, the Gothenburg Study was initiated. It was a prospective, open label, general use, interventional study that evaluated how the neonatal outcome has changed with time, with the increase use of STAN in the clinic (unpublished).

The US Bridging Studies were conducted to evaluate the transferability of the STAN technology to US obstetrical wards. The first US Study was the Education Study which examined how well US clinicians learned STAN principles. The second US Bridging Study was the Clinical Use Study, a non-randomized observational, interventional study that evaluated two types of endpoints: (1) correctness of clinical decisions not to intervene in cases with non-reassuring fetal heart tracing (evaluated based on cord artery pH); and (2) level agreement between US clinicians and STAN experts (who were reviewing tracings retrospectively) on the need to intervene.

The details of the Nordic, Swedish RCT, Gothenburg, and US Bridging studies follow:

Nordic Study on Diagnostic Performance of Fetal ST Analysis - Clinical Accuracy

Study Objective

Neoventa conducted an observational, non-randomized, non-interventional study (see reference 16) to determine the clinical accuracy of the STAN fetal Heart Monitor, examining clinical outcome when ST analysis was added to conventional intrapartum fetal monitoring. The objective of the study was to examine diagnostic power of CTG plus ST analysis to identify adverse labor outcomes such as neurological symptoms and/or metabolic acidosis.

Study Hypothesis

None

Study Endpoints

Endpoints included operative delivery and intervention rates and the accuracy measures of sensitivity, specificity, positive predictive value, and negative predictive value. To determine the accuracy measures, a case was defined as warranting intervention if the case was exposed to intrapartum hypoxia or asphyxia based on neurological symptoms and/or cord artery metabolic acidosis (CA pH < 7.05 and BDecf > 12 mmol/L).

Study Methodology

This multi-center observational study was conducted between 1998-99 at 12 labor wards (8 Norwegian, 4 Swedish) and included a total of 573 women in labor. This period overlaps the conduct of the SRCT (December 1998 to June 2000). The study used a prototype of the STAN S21 called the STAN ESST, which included an algorithm that automatically identified ST events.

The investigators were instructed to manage labor cases on the basis of CTG information alone. ST information was also available, but the investigators were instructed only to check its signal quality and operation of the recorders. Afterwards, one clinical reviewer evaluated the [FHR + ST] tracings blinded to outcome and grouped them either into an intervention category or a non-intervention category according to previously developed STAN guidelines. This determination was made by visual inspection and by using a computerized algorithm that identified ST events similar to the S31.

Study Results

Fifteen infants were diagnosed as having been exposed to intrapartum hypoxia or asphyxia based on neurological symptoms and/or metabolic acidosis. The ST algorithm identified each of these cases, leading to a sensitivity of [FHR + ST] clinical guidelines to recommend intervention in these cases was 100% (15/15). The specificity of the guidelines was 95% (530/558). The positive and negative predictive values (PPV and NPV) were 35% (15/43) and 100% (530/530). The projected rate of operative interventions for fetal distress, if intervention had been taken according to [FHR + ST] guidelines, would have been only 7.5%, compared to the actual rate of 15.3%.

Study Limitations

Although instructed to not use the ST information in clinical information, the investigators could nevertheless have been influenced by this information, especially those in the three Norwegian departments that had previous experience with the STAN 8801, a prior model.

Aside from this limitation, sensitivity, specificity, PPV, and NPV can still be difficult to estimate without bias. These quantities compare the baby outcome (metabolic acidosis or normal) with the diagnostic result (intervention triggered or not). The problem is that once intervention has taken place, the outcome for the baby had the intervention not taken place is missing. As a result, only NPV can be estimated unbiasedly as the proportion of non-interventions for which a normal outcome was obtained. For this reason, in the US Clinical Use Bridging study to be described below, NPV was the only accuracy measure of the four to be considered a primary endpoint. Because estimates from non-interventional studies of the accuracy of ST have limitations, the Swedish randomized controlled interventional study (SRCT) and the two US interventional studies conducted to bridge from the European experience to the US are reported in subsequent sections.

Swedish Randomized Controlled Trial (SRCT)

Study Objective

Primary objective: To reduce perinatal morbidity as identified by a significant cord artery metabolic acidosis ($\text{pH} < 7.05$ and $\text{BDecf} > 12.0 \text{ mmol/L}$).

Secondary objectives:

- To evaluate the use of FHR and ST waveform protocols and guidelines in clinical practice.
- To reduce operative interventions.

Study Hypothesis

Primary Hypothesis:

Intrapartum monitoring with Electronic Fetal Monitoring (EFM) combined with ST waveform analysis will result in an improved perinatal outcome as compared with EFM alone.

Statistical Hypothesis: At least a 50% reduction in the number of cases with metabolic acidosis, with a power of 80% and a test performed on the 5% level.

Other study endpoints were:

- change in neonatal morbidity as identified by Apgar scores at 5 minutes, admission to special care baby unit, and neonatal seizures or other neurological abnormalities; and
- change in frequency of operative delivery.

Study Methodology

The study was conducted at three university-based labor wards in Sweden. The STAN S21 was used in both arms of the study. In the STAN arm, clinicians used T/QRS event data and ST segment analysis adjunctively with FHR tracing to manage patients according to STAN clinical guidelines. In the control arm of the study, the only data from the scalp electrode that was available to the clinician was continuous fetal heart rate tracing.

For all subjects, both umbilical cord arterial and venous blood were to be sampled according to the following strict guidelines: The cord was to be double-clamped as soon as possible after birth of the baby (before the placenta was delivered) and using pre-heparinized syringes or capillary tubes the blood was to be obtained from both an artery and the vein. An alternative acceptable procedure was to puncture both vessels directly at delivery.

Inclusion Criteria

- >36 completed gestational weeks
- in cephalic presentation
- in active labor
- intrapartum monitoring with fetal scalp electrode

Exclusion Criteria

- recording time during first stage of labor <30 minutes
- recording only represents second stage of labor
- lag time between end of recording and delivery exceeds 20 minutes
- trans-cutaneous nerve-stimulation (TENS) for analgesia

- gross fetal abnormality diagnosed prior to labor

Management Guidelines

In the control arm of the study, subjects were managed according to standard FHR-based practice. The sponsor prepared a chart describing possible fetal heart rate patterns during the first and second stages of labor, and a recommended action for the clinician to take depending on the stage of labor and the heart rate pattern. The definitions of fetal heart rate patterns for this chart were based on terminology proposed by the International Federation of Gynecology and Obstetrics (FIGO) (Reference 23).

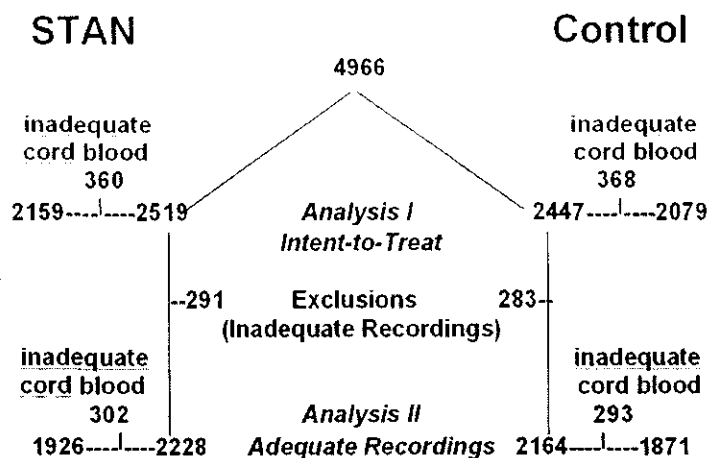
A set of clinical guidelines were developed, to be used in the [FHR + ST] arm of the study. The most significant aspect of the STAN clinical guidelines is that they recommend clinical intervention on the basis of both the ECG event data and FHR pattern.

Patient Population

The SRCT took place between December 1, 1998 and June 4, 2000. Three university-based hospital labor wards contributed approximately equally to the total number of patients in this trial: University Hospital Lund (36%); University Hospital Malmö (31%); and Sahlgrenska University Hospital, Gothenburg (33%).

Patient accounting for the SRCT is summarized in the patient tree in Figure 2. The total number of subjects treated was 4966. The FHR + ST arm enrolled 2519, and the FHR-only arm enrolled 2447. Neoventa Medical evaluated the two main clinical endpoints for this population, and referred to it as Analysis I. (The "Analysis II" will be explained below.)

Figure 2. Swedish RCT Patient Tree. Note: Because the STAN S31 monitor is a diagnostic device, "Intent to Treat" can be considered "Intent to Diagnose."



Interim Analysis

The study protocol called for an interim analysis of the data after treatment of 1600 subjects to assess the true incidence of metabolic acidosis in the study population and whether 3200 cases was sufficient 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 $\alpha = 0.05$. At interim analysis, the actual incidence turned out to be 0.65%. The results for the two arms were not blinded to Neoventa. Therefore, a second power analysis was done to calculate the number of additional cases needed. The number of additional cases was 2160. A new study deadline was set on the basis of the previous rate of recruitment.

A second result of the interim analysis was that Neoventa Medical decided to retrain clinicians in how to use the STAN system. This came about because of protocol violations that occurred during the first 1600 cases. The study results were then presented for "before retraining" ($n=2583$) and "after retraining" ($n=2383$). Because the decision to retrain came well after the planned interim analysis of the first 1600 cases, the number of subjects treated before retraining does not correspond to 1600.

Effectiveness Evaluation

For the "intent-to-treat" population (Table 13), there were 31/2079 (1.5%) cases of metabolic acidosis in the FHR-only arm and 15/2159 (0.7%) of cases in the [FHR + ST] arm ($p=0.02$). Therefore, there was a statistically significant reduction in cases of metabolic acidosis in the patients monitored with the STAN S21. The reason that the denominator numbers in these fractions are different from the actual numbers of subjects randomized in each arm is that 368 subjects in the control arm and 360 subjects in the STAN arm did not have adequate cord blood data. For example, blood

was not sampled from both an umbilical artery and the umbilical vein or there was evidence from the blood gas values that cord clamping had occurred too late for the samples to be representative of true fetal hypoxic status in utero.

A secondary endpoint was operative deliveries for fetal distress (ODFD), a category that includes instrumented vaginal deliveries including high forceps as well as cesarean section. For the intent-to-treat population, the rate was 227/2447 (9.3%) for the FHR-only arm and 193/2519 (7.7%) for the [FHR + ST] arm ($p=0.047$). This difference was statistically significant, in favor of the STAN system.

The rate for cesarean section for fetal distress (CSFD) in the intent-to-treat population was 97/2447 (4.0%) in the FHR-only arm and 87/2519 (3.5%) in the [FHR + ST] arm ($p=0.38$). This difference was not statistically significant.

Table 13. Results, Intent to Treat (Analysis I)

	FHR	FHR + ST
Cases of metabolic acidosis ($p=0.02$)	31/2079 (1.5%)	15/2159 (0.7%)
Total ODFD ($p=0.047$)	227/2447 (9.3%)	193/2519 (7.7%)
CSFD ($p=0.38$)	97/2447 (4.0%)	87/2519 (3.5%)
Apgar 1 min < 4	47/2447 (1.92%)	36/2519 (1.43%)
Apgar 5 min < 7	28/2447 (1.14%)	26/2519 (1.03%)
Admission to SCBU	181/2447 (7.40%)	169/2519 (6.71%)
Moderate or severe neonatal encephalopathy	8/2447 (0.33%)	1/2519 (0.04%)
Perinatal death	1/2519 (0.04%)	2/2519 (0.08%)

"Inadequate Recordings" (Analysis II)

Neoventa Medical performed an additional analysis of the clinical study endpoints (Analysis II) after excluding 291 cases from the [FHR + ST] arm and excluding 283 cases from the FHR-only arm. (Refer again to "patient tree" in figure 2, above.) Patients in both arms were excluded for inadequate recordings when the following criteria were met:

- less than 20 minutes of data collected with the fetal scalp electrode (37.5%)
- more than 20 minutes elapsed between removal of scalp electrode and delivery (56.1%);
- congenital malformations (1.3%); or
- "other" (5.1%)

Therefore, 93.6% of the "inadequate recordings" were related to duration of the tracing with respect to setting ECG baseline, assessing FHR and ST patterns and to time of delivery. These tracings did not meet the standards set to enable optimal

assessment of either FHR or ST information. However, they are not necessarily synonymous with "signal quality" problems.

For Analysis II, (Table 14) there was a statistically significant decrease in cases of metabolic acidosis in the [FHR + ST] arm. Also, the "p" value for the metabolic acidosis endpoint implies greater statistical significance for Analysis II than for Analysis I.

The results for Analysis II for the endpoint ODFD also reinforced the finding from Analysis I that there was a statistically significant reduction in ODFD in subjects monitored with [FHR + ST] compared with FHR-only. Again, the statistical significance of this finding improved in Analysis II.

For CSFD, in Analysis II the trend towards reduction in the [FHR + ST] arm became statistically significant ($p=0.04$).

Table 14. Results, Adequate Recordings (Analysis II)

	FHR	FHR + ST
Cases of metabolic acidosis ($p=0.01$)	27/1871 (1.44%)	11/1926 (0.57%)
Total ODFD ($p=0.009$)	173/2164 (7.99%)	132/2228 (5.92%)
CSFD ($p=0.04$)	63/2164 (2.91%)	43/2228 (1.93%)
Apgar 1 min < 4	38/2164 (1.76%)	23/2228 (1.03%)
Apgar 5 min < 7	21/2164 (0.97%)	17/2228 (0.76%)
Admission to SCBU	151/2164 (6.98%)	132/2228 (5.92%)
Moderate or severe neonatal encephalopathy	7/2164 (0.32%)	0/2228 (0.00%)
Perinatal death	0/2164 (0.00%)	0/2228 (0.00%)

Gothenburg (Centers of Excellence)

Upon completion of the Swedish Randomized Controlled Trial (SRCT) the evaluation of the STAN Fetal Heart Rate Monitoring System was continued in the city of Gothenburg, Sweden. This study was the first in a series of studies that were conducted under the auspices of the European Union Project and supported by the EU commission.

Study Objective

The objective of this prospective observational study was to evaluate the value of the STAN system for intrapartum fetal monitoring using CTG + ECG in a 24-month period of time in the total population of term deliveries in the city of Gothenburg and surrounding areas.

Study Hypothesis

None

Study Methodology

A total of 14687 term deliveries were included in the study, 4830 (32.9%) of which were monitored by STAN S21. Assessment of the condition of a newborn was based on cord artery and vein acid-base status (pH, PCO₂ and base deficit (BDecf), mmol/L) and Apgar scores. Metabolic acidosis was defined as cord artery pH < 7.05 and BDecf > 12.0 mmol/l. The analysis plan included the comparison of the first and second years of the study with regard to the use of STAN devices, metabolic acidosis rates, operative interventions for fetal distress, the rates of clinical compliance and rates of moderate/severe hypoxic neonatal encephalopathy.

Study Results

A comparison between the first and the second years revealed an increase in STAN usage from 21.8% to 37%. A significant reduction in number of cases of metabolic acidosis from 1.12 to 0.56% was observed comparing the first and second years of STAN use; OR=0.49; (95% CI 0.25 – 0.98). In cases monitored with STAN the reduction of metabolic acidosis decreased from 0.77% to 0.44% with an odds ratio (OR) of 0.58 (95 % CI 0.37-0.93). The rates of moderate/severe hypoxic neonatal encephalopathy were 0.49 and 0.36 per 1000 deliveries with STAN, respectively. A measure of clinical compliance was identification of the number of cases with prolonged response time measured by the time from the STAN indication to the time to intervene and reduction from 0.75% to 0.28%, OR=0.37 (95 % CI 0.15 -0.92) was observed. At the same time, total operative deliveries for fetal distress decreased from 6.6% to 6.1%.

The conclusion of this study was that the increased use the STAN system provides improvement in fetal outcome.

United States "Bridging Studies"

Following the April 2002 Panel meeting (ref. Section XII), the company conducted additional studies in the United States to address concerns about the applicability of the device use in the United States. The following Bridging studies are the results of their efforts.

Education Study

Study Objective

The objective of the study was to evaluate the ability of US obstetrical staff, who are experienced in the application and interpretation of standard intrapartum electronic

fetal heart rate (FHR) monitoring, to understand and apply the STAN concept of fetal ECG analysis.

Study Methodology

Thirteen US clinicians acted as raters to evaluate a library of 51 tracings from European patients whose labors were monitored with the STAN S21. This library of cases was selected on the basis of the cord artery pH values in order to challenge clinicians with a range of pathology. All of these cases had previously been evaluated in a similar fashion by Swedish clinicians considered experts in the use of the STAN monitor. The distribution of cases stratified by pH was as follows:

- pH <7.05 (9 cases)
- pH 7.05-7.14 (10 cases)
- pH \geq 7.15 (32 cases)

The tracings were presented for evaluation 3 times. Each time, the cases were presented in a random order. The 1st exam was before training on STAN and consisted of FHR-only. The 2nd was after completion of training on STAN which includes training in fetal heart rate tracings, but raters used FHR-only again. The 3rd exam immediately followed the 2nd exam for that case but allowed raters to use FHR+ST. For each case, the US investigator was to indicate whether or not an intervention was needed, and if so, the time at which the tracing indicated an intervention.

A panel of seven Swedish clinicians, considered by the sponsor to be experts in FHR+ST analysis, had previously examined the same group of 51 tracings blinded to the pH data. Agreement of the US raters with the Swedish experts is an aspect of some secondary hypotheses of the study.

Study Hypotheses

Primary Hypothesis

The mean % agreement with true intervention status among the US raters would be statistically significantly greater for Exam 3 (FHR+ST) than Exam 2 (training completed, FHR-only allowed). That is, on average, US raters are more likely to make the correct decision using FHR+ST than using FHR-only. For the purpose of defining true intervention status, intervention was considered to be warranted for a case if the cord artery pH level was < 7.15.

Secondary Hypothesis

The secondary hypothesis was that the mean absolute difference between the Swedish experts and the US raters in the median time of intervention will be less than 20 minutes.

Training for US Education Study

The STAN simplified clinical guidelines were modified prior to this study to reflect US terminology, according to the National Institute of Child Health and Human Development (NICHD) guidelines (Reference 24). Additionally, the strip chart print speed was modified for the US raters to be consistent with US standards. Otherwise, the US participants received the same training and took the same certification test as described in Section VI on STAN Training.

Primary Hypothesis Effectiveness Evaluation

Three of the 13 raters were not certified (i.e. did not pass the certification exam on the first attempt by the score of 16/18 required to pass) but still rated the tracings during exams 2 and 3. Analyses were made excluding as well as including these three raters.

For the US investigators, the mean percent agreement with true intervention status (average consensus) was 47% for Exam 1 (FHR-only, before training), 53% for Exam 2 (FHR-only, after training), and 69% for Exam 3 (FHR+ST, after training) (Table 15). From a repeated measures analysis, the difference in mean % agreement between Exams 3 and 2 was statistically significant ($p = 0.0001$).

As a benchmark for comparison, the Swedish experts as a group improved from 59% mean % agreement when reading with FHR-only to 85% when reading with FHR+ST (Table 15).

Table 15. % Agreement with True Intervention Status, as Defined by Cord Artery pH level (< 7.15 threshold), N=51 cases.

	FHR-only, before training		FHR-only, after training		FHR+ST, after training	
	Average	Range	Average	Range	Average	Range
US Raters (13)	47	37-64	53	41-67	69	43-88
EU Experts (7)	NA	NA	59	51-63	85	75-90

Secondary Hypotheses Effectiveness Evaluation

When the timing of the US investigators' decision to intervene was compared to that of the Swedish experts, the hypothesis was that the mean absolute difference between the Swedish experts and the US raters in the median time of intervention is less than 20 minutes. Neoventa Medical analyzed the proportion of cases in which the median times of intervention for the two groups differed by less than 20 minutes. The proportion of cases was 89% (8/9) for cases with pH level < 7.05 (the Swedish experts did not intervene on one of these cases), and 60% (6/10) for cases with pH 7.05-7.14,

for a total of 74% (14/19) for cases with pH <7.15. The number of cases is too small to draw statistical inference.

Clinical Use Study (CUS)

Study Objective

The objective of the CUS was to demonstrate that US obstetrical staff can appropriately use the STAN system, correctly interpret FHR+ST data and apply the STAN clinical use guidelines on a par with STAN experts. Another objective of the study was to demonstrate that the STAN system data can be properly used according to clinical guidelines yielding similar results to the results seen in the Swedish Randomized Controlled Trial.

Study Hypotheses

Primary Hypotheses

This study has the following co-primary hypotheses:

- Among cases with non-reassuring fetal heart rate (NHFHR) tracings, non-intervention by US clinicians will result in a normal outcome 75% or more of the time.
- US clinicians and a majority of the Swedish experts will agree to intervene 75% or more of the time and will agree not to intervene 75% or more of the time.

Primary Effectiveness Endpoint

- Negative Predictive Value (NPV). This value represents the probability that non-intervention results in a normal outcome in the cohort of infants with non-reassuring FHR (NRFHR) tracings, where normal outcome is defined as cord artery pH>7.12. NPV was defined as:

$$\frac{\# \text{ cases w/NRFHR, STAN allows continued labor, pH}>7.12}{\# \text{ cases w/NRFHR, STAN allows continued labor}}$$

- Positive Percent Agreement (PPA). This is the proportion of cases warranting intervention according to the STAN experts for which the US clinician decided to intervene at about the same time. Timing of the decision to intervene must be within ± 20 minutes of the majority of STAN experts in the second stage of labor, and within ± 30 minutes within the first stage of labor; and
- Negative Percent Agreement (NPA). This is the proportion of cases not warranting intervention according to the STAN experts for which the US clinician decided not to intervene.

The protocol pre-specified that since the US clinicians have clinical information available to them that is not available to the STAN experts, who only have the tracing, some failures to meet the above definition of agreement may be "overruled." Disagreements will each be reviewed, and if the disagreement is due to lack of relevant information by the STAN experts, those cases may be considered agreement.

Study Methodology

The US Clinical Use Study (CUS) was a prospective, non-randomized, non-controlled multi-center trial using the STAN S21. Thirty-nine clinicians participated at 6 sites, 3 of which were community hospitals and 3 of which were teaching hospitals. The study occurred in 3 phases: Education, Pilot, and Pivotal. Clinicians were trained during the Education Phase as described in the Education study above. They were required to pass the certification test before they could proceed to the Pilot Phase. In the Pilot Phase, they were required to complete 5 cases where fetal ECG data was collected but not used. These cases were then reviewed and discussed with either a Neoventa representative or a local expert appointed by Neoventa. This process was referred to as credentialing. Local experts were experienced physicians that have been through the credentialing process. Clinicians could not proceed to the Pivotal Phase until they had met certain goals including the demonstration of adequate understanding of STAN technology, concept, and methodology as determined by the Neoventa representative or Local expert. Sites could not proceed to the Pivotal Phase until at least 1 Clinician at the site had passed the credentialing process.

Inadequate Recordings and Signal Quality Problems during the CUS

In analyzing the data from the Swedish RCT, approximately 600 recordings were excluded because they were inadequate. Ninety-four percent of these inadequate recordings were attributed to failure to meet the 20 minute rule for setting the ECG baseline and/or lack of STAN data within 20 minutes of delivery.

During the Pilot Phase (Phase 2) of the CUS, 207 recordings were obtained, each of which consisted of at least 30 minutes of recording. Of these recordings 5.9% had signal quality issues.

During the Pivotal Phase (Phase 3) of the CUS, 95.4% of the spontaneous vaginal delivery cases had ST data within 20 minutes of delivery. Thirty-four percent of the investigators reported that it was necessary to adjust the STAN monitor or sensor in order to improve signal quality. However, 88.3% of the investigators responded on a case report form that they "agreed" or "strongly agreed" that the STAN recording provided adequate information throughout labor. Therefore, the problem of inadequate recordings observed during the Swedish RCT is resolved. With respect to signal quality per se, 3 cases of signal quality problems were traced to a connector failure within the legplate cable that connects the scalp electrode to STAN. The manufacturer of the cable provided modified cables which helped resolve this issue.

In summary, the problem of inadequate recordings has been greatly reduced since the Swedish RCT. Signal quality issues persist but are largely addressed by adjusting the monitor or the sensor. An equipment malfunction accounted for a few cases of poor signal quality and that has been addressed, although one complaint that appeared related to the legplate was reported after the cables were modified.

Primary Hypothesis Effectiveness Evaluation

A total of 530 subjects were monitored.

Primary endpoint – NPV

For the protocol threshold of $pH > 7.12$ for a normal outcome, NPV was 95.2% (180/189) with 95% CI (91.2, 97.8%), based on 189 cases with NRFHR tracing. Because this pH threshold is somewhat arbitrary (and was different from the pH threshold for normal pH of ≥ 7.15 in the US Education Study), FDA requested that Neoventa Medical stratify the results for this endpoint over a range of pH values from 7.10 to 7.15. For each of these cut off points, the NPV was $\geq 92.6\%$ and the lowest bound on the 95% CI was 87.9%. The target for success for this primary endpoint was met. This endpoint relates only to patients who experienced a period of non-reassuring fetal heart rate.

The per protocol definition of NPV given above included all cases for which STAN allowed continued labor, even if an intervention took place. In contrast, the traditional definition of NPV in this context would exclude all interventions. Therefore, NPV was recalculated under the following definition:

cases w/NRFHR, STAN allows continued labor, no intervention taken, $pH > 7.12$
cases w/NRFHR, STAN allows continued labor, no intervention taken

Using this definition, the NPV was 95.5% (127/133) with 95% CI (90.4%, 98.3%). From the lower bound on the 95% CI, the primary hypothesis of $NPV > 75\%$ was still met.

Primary endpoint - agreement on intervention

Two cases were excluded from PPA/NPA analysis. In one case, the STAN experts could not agree. In another case, the US clinician expressed both "failure to progress" and FHR+ST as cause for intervention and at the same time. Thus, 528 of the 530 cases were analyzed.

Table 16. Data Table for Calculation of NPA and PPA

N=528	STAN Expert Majority Decision			
US Clinician Decision	No intervention	Intervention 2° to FHR concern outside STAN guidelines	Intervention 2° to FHR concern within STAN guidelines	Intervention 2° to FHR+ST concern within STAN guidelines
No intervention or intervention for failure to progress	444			5
Intervention 2° to FHR concern outside of STAN guidelines	31			
Intervention 2° to FHR concern within STAN guidelines	6			
Intervention 2° to FHR+ST concern within STAN guidelines	10		1	31

$$\text{NPA} = 444 / (444 + 31 + 6 + 10) = 444 / 491 = 90.4\%$$

$$\text{PPA} = 31 / 37 = 83.8\%$$

The STAN experts saw a need to intervene in 37 tracings. The US investigators saw a need to intervene in 79 tracings. These figures are not directly comparable because, as stated earlier, the US clinicians were responding to clinical events in labor and delivery to which the STAN experts were not privy. These included 47 cases in which the STAN experts would not have intervened. Thirty-one of these cases were ones in which events known to the US clinician, unknown to the STAN expert, and **not** within the purview of the STAN guidelines were the basis for the intervention. Therefore, there were 16 cases in which US clinicians correctly intervened according to STAN guidelines and STAN experts did not (because of unavailable clinical information), and five cases in which STAN experts correctly intervened according to the guidelines and US investigators did not. All five cases had normal Apgar scores, cord acid base values and no need for special neonatal care. The clinical action of the US investigators was appropriate, although it did not meet the strict definition for agreement.

The PPA was 83.8% (31/37) with 95% CI (68.0%, 95.7%). The 95% CI lower bound indicates that the target value of > 75% was not met. Neoventa pointed out that the study was sized for showing PPA > 75% on the assumption that the true PPA is 90%.

The 90% PPA was based on the rate of agreement to intervene in the Education Study. This rate did not take into account timing of intervention. When the Education Study data are re-calculated for **both** decision **and** timing of intervention, the new rate is 74% (14/19).

In the calculation of PPA, some technical disagreements were considered to be agreements because, as discussed above, US clinicians had clinical information not available to the STAN experts. Specifically, 17 spontaneous vaginal deliveries (SVD) were considered to be in positive agreement with the STAN expert decision to intervene on these same cases because the SVD occurred within 20 minutes of the time of the decision to intervene. Agreement on such cases was pre-specified in the protocol, but not whether it would be considered a positive agreement (for inclusion in PPA) or a negative agreement (for inclusion in NPA).

When these cases are excluded, PPA was 70.0% (14/20) with 95% CI (45.7%, 88.1%). The 95% CI lower bounds indicates that the hypothesis $PPA > 75\%$ target value for PPA was still not met.

There were multiple analyses performed on these data, using different definitions for PPA, that also concluded that the 75% target was not met. The most important analysis of PPA was the original analysis in which the observed value for PPA was 83.8%. In considering that the lower bound on the 95% confidence interval of 68.0% was below the target value of 75%, it must be kept in mind that the study was not powered to detect a statistically significant PPA for this target value.

The NPA was 90.4% (444/491) with 95% CI (87.8%, 93.0%). The 95% CI lower bound indicates that the target value of $> 75\%$ was met. In the calculation of NPA, some technical disagreements were considered to be agreements because US clinicians had clinical information not available to the STAN experts. Specifically, 82 interventions for failure to progress (FTP) were considered to be in negative agreement with the STAN expert decision to not intervene on these same cases. The first row of the exam matrix above is labeled to include this situation.

When these 82 cases are excluded, the NPA was 88.5% (362/409) with 95% CI (85.0%, 91.4%). The 95% CI lower bound indicates that the hypothesis $NPA > 75\%$ target value for NPA was still met.

XII. PANEL RECOMMENDATION

The Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee met on April 22, 2002, in an open session to discuss the pre-market approval application (PMA P020001) from Neoventa Medical AB for the S21® Fetal Heart Monitor for the first time. The Panel voted that the PMA was not approvable. The reasons cited for a not approvable vote were: (1) the STAN had never undergone clinical testing in the United States at the time of the original PMA submission; (2) the differences in labor management between Sweden and the United States could

influence results; and (3) the adequacy of the STAN training program for US clinicians had not been demonstrated.

The Panel met again on June 23, 2005, in an open session to discuss the PMA for the newer S31[®] Fetal Heart Monitor model. At this meeting, the panel considered the two bridging studies that had been conducted in the interim to address deficiencies and which were intended to look at the use of STAN[®] S31 by clinicians in the United States.

The panel recommended approval of the PMA for the STAN S31[®] monitor, subject to the following conditions:

1. changes to labeling, especially the indications/usage statement to reflect that it should be used as an adjunct to the assessment of non-reassuring fetal heart rate tracings;
2. development of a complete set of education/training tools, including a required training/credentialing plan that can be adapted for different hospital settings (e.g., community vs academic, urban vs rural);
3. the inclusion of education/training materials with each monitor; and
4. a postmarket study or surveillance program to evaluate the impact of this technology in the market setting on the following endpoints:
 - cesarean delivery (compared to c-section rates before use of STAN[®] technology);
 - fetal acidemia, as evidenced by umbilical cord arterial pH at delivery;
 - Apgar scores;
 - neonatal encephalopathy;
 - why the clinician used the STAN[®] device;
 - usage rate (i.e., for what percent of labors did an institution use the STAN[®] monitor); and
 - compliance with/effectiveness of training program.

XIII. CDRH DECISION

After the first panel meeting in 2002, CDRH considered the panel's recommendation for a new prospective, randomized clinical study in the US to address the 3 issues identified above. However, CDRH concluded that the approximately 5000-patient Swedish RCT was sufficiently robust in design that a new RCT was not necessary. The applicant adequately addressed the issues via the United States Bridging studies. The preclinical and clinical data provide reasonable assurance that the device is safe and effective.

CDRH agreed with the June 23, 2005 Panel recommendation that the STAN S31[®] monitor, when used as indicated, is safe and effective for use as an adjunct to fetal heart rate monitoring to determine whether obstetrical intervention is warranted when there is increased risk of developing metabolic acidosis. The applicant revised the

physician and patient labeling as requested by the Panel and CDRH. CDRH worked with the company in the development of the education and training package.

CDRH considered the panel recommendation for a postapproval study. The study recommended by the panel would simply be looking for the same outcome measures in the same time frame as the pivotal Swedish RCT and the US bridging studies. Therefore, CDRH determined a postapproval study was not necessary.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

CDRH issued an approval order on November 1, 2005.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the physician labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-Approval Requirements and Restrictions: See approval order.

References

1. Rosén KG, Kjellmer I. Changes in the fetal heart rate and ECG during hypoxia. *Acta Physiol Scand* 1975;93:59-66.
2. Rosén KG, Isaksson O. Alterations in the fetal heart rate and ECG correlated to glycogen, creatine phosphate and ATP levels during graded hypoxia. *Biol Neonate* 1976;30:17-24.
3. Hökegård KH, Eriksson BO, Kjellmer I, Magno R, Rosén KG. Myocardial metabolism in relation to electrocardiographic changes and cardiac function during graded hypoxia in the fetal lamb. *Acta Physiol Scand* 1981;113:1-7.
4. Hökegård KH, Karlsson K, Kjellmer I, Rosén KG. ECG-changes in the fetal lamb during asphyxia in relation to beta-adrenoceptor stimulation and blockade. *Acta physiol scand* 1979;105:195-203.
5. Dagbjartsson A, Herbertsson G, Stefansson TS, Kjeld M, Lagercrantz H, Rosén KG. Beta-adrenoceptor agonists and hypoxia in sheep fetuses. *Acta Physiol Scand* 1989;137:291-299.
6. Greene KG, Dawes GS, Lilja H, Rosén KG. Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxemia. *Am J Obstet Gynecol* 1982;144:950-957.
7. Rosén KG, Dagbjartsson A, Henriksson BA, Lagercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. *Am J Obstet Gynecol* 1984;149:190-195.
8. Rosén KG, Lilja H, Hökegård KH, Kjellmer I. The relationship between cerebral cardiovascular and metabolic functions during labor in the lamb fetus and newborn. Academic Press, London. 1985.
9. Greene KR, Rosén KG. Long term ST waveform changes in the ovine fetal electrocardiogram: the relationship to spontaneous labor and intrauterine death. *Clin Phys Physiol Meas* 1989;10:33-40.
10. Widmark C, Hökegård KH, Lagercrantz H, Lilja H, Rosén KG. Electrocardiographic waveform changes and catecholamine responses during acute hypoxia in the immature and mature fetal lamb. *Am J Obstet Gynecol* 1989;160:1245-1250.
11. Widmark C, Jansson T, Lindecrantz K, Rosén KG. ECG waveform, short-term heart rate variability and plasma catecholamine concentrations in response to hypoxia in intrauterine growth retarded guinea pig fetuses. *J Develop Physiol* 1991;15:161-168.
12. Arulkumaran S, Lilja H, Lindecrantz K, et al. Fetal ECG waveform analysis should improve fetal surveillance in labour. *J Perinat Med* 1990;18:13-22.

13. Maclachlan NA, Spencer JAD, Harding K, Arulkumaran S. Fetal acidemia, the cardiotocograph and the T/QRS ratio of the fetal ECG during labor. *Br J Obstet Gynaecol* 1992;99:25-31.
14. Murphy KW, Russel U, Johnson P, Valente J. Clinical assessment of fetal electrocardiogram monitoring in labor. *Br J Obstet Gynaecol* 1992;99:22-37.
15. Luzietti R, Erkkola R, Hasbargen U, et al. European Community Multicenter Trial "Fetal ECG Analysis During Labor": ST plus CTG Analysis. *J Perinat Med* 1999;27:431-440.
16. Amer-Wählin I, Bordahl P, Eikeland T, et al. ST analysis of the fetal electrocardiogram during labor: Nordic observational multicenter study. *J Matern Fetal Neonatal Med* 2002;12:260-266.
17. Dervaitis KL, Poole M, Schmidt G, et al. ST segment analysis of the fetal echocardiogram plus electronic fetal heart rate monitoring in labor and its relationship to umbilical cord arterial blood gases. *Am J Obstet Gynecol* 2004;191:879-884.
18. Kwee A, van der Hoorn-van den Beld CW, Veerman J, et al. STAN S21 fetal heart monitor for surveillance during labor: an observational study in 637 patients. *J Matern Fet Neonatal Med* 2004;15:400-407.
19. Luttkus AK, Norén H, Stupin JH, Blad S, et al. Fetal scalp pH and ST analysis of the fetal ECG as an adjunct to CTG - A multicenter, observational study. *J Perinat Med* 2004;32:486-494.
20. Westgate J, Harris M, Curnow JS, Greene KR. Plymouth randomized trial of cardiotocography only versus ST waveform plus cardiotocogram for intrapartum monitoring in 2400 cases. *Am J Obstet Gynecol* 1993;169:1151-1160.
21. Amer-Wählin I, Hellsten C, Norén H et al. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomized controlled trial. *Lancet* 2001;358:534-538.
22. Norén H, Amer-Wählin I, Hagberg H et. al. Fetal electrocardiography in labor and neonatal outcome: Data from the Swedish randomized controlled trial on intrapartum monitoring. *Am J Obstet Gynecol* 2003;188:183-92.
23. FIGO Guidelines for the use of fetal monitoring. *Int. J. Gynaecol Obstet*, 1987;25:159-67
24. NICHHD Research Planning Workshop "Electronic Fetal Heart Rate Monitoring: Research Guidelines for Interpretation", *American Journal of Obstetrics and Gynaecology*, 1997;177:1385-90.