NEW APPROACHES ON FETAL AND MATERNAL INTRAPARTUM MONITORING

Stina Wretler

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Department of Women's and Children's health

New approaches on fetal and maternal intrapartum monitoring

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Division of Obstetrics and Gynaecology
“In an age when man has been able to measure most things from an atom to a galaxy, it is thus paradoxical that to measure his own size during the most critical and precarious period of his life, he still has to depend upon the extreme fallibility of the palpating hand.”

Dobbs and Gairdner 1966
“All of these lines across my face
Tell you the story of who I am
So many stories of where I've been
And how I got to where I am
But these stories don't mean anything
When you've got no one to tell them to
It's true I was made for you”

“The story” by Phil Hanseroth
Performed by Brandi Carlile

To my FAMILY just as it is
ABSTRACT

Background: Intrapartum fetal monitoring aims to prevent adverse outcomes due to intrapartum asphyxia. Cardiotoacography (CTG) is an established method for intrapartum monitoring. The method has high sensitivity, but low specificity and is also user-dependent and linked to both inter- and intraobserver variability. CTG might increase the risk for unnecessary interventions. One suggested method to improve CTG interpretation is computerized monitoring. Other possible ways are improved knowledge about risk factors and proper use of adjunctive technologies. One common adjunctive technology is fetal scalp blood sampling (FBS). Fetal distress is one reason for intrapartum caesarean section, but the main reason is dystocia. Today there is no way to predict dystocia. Studies have suggested that increased levels of lactate in the uterus correlates with dystocia.

Materials and Methods: Study 1 is a prospective observational study of 120 women, investigating methodological aspects of short-term-variation (STV) as a part of computerized fetal monitoring. Paper 2 and 3 study 1070 term pregnancies that underwent FBS. Study 2 is an analysis of lactacidemia in FBS compared to different CTG patterns. Study 3 is an analysis of risk factors for lactacidemia in FBS. Study 4 is a clinical observational study, of 77 women in labor, evaluating if lactate concentration in cervical fluid could be a predictor for dystocia.

Results: STV values differ between internal and external derived values. The two commercial available CTG machines for antenatal STV monitoring perform equal. Late or severe variable decelerations in combination with tachycardia are the CTG patterns with highest frequency of lactacidemia. Isolated reduced variability in an otherwise normal CTG trace is not linked to lactacidemia. Risk factors correlated to lactacidemia are minor language barriers and active bearing down. Increased concentration of lactate in cervical fluid seems to predict operative delivery.

Conclusions: These results suggest several implications on intrapartum monitoring. Intrapartum STV values should preferably be derived from internal monitoring. The same cut-off values could be used for the two commercial available machines for STV monitoring. Late and severe variable decelerations correlate to lactacidemia to the same extent. Isolated reduced variability is not a sign of hypoxia. Use of interpreters can be a possible way to avoid adverse neonatal outcome. Cervical lactate might be a possible tool in predicting dystocia.

Key words: Cardiotoacography (CTG), Caesarean section, Computerized cardiotoacography, Dystocia, Fetal blood sampling, Fetal distress, Fetal heart rate, Fetal monitoring, Lactate, Language barriers, Metabolic acidosis, Risk factors, Short term variation
I. **Fetal heart rate monitoring of short term variation (STV): a methodological observational study**
   Stina Wretler, Malin Holzmann, Sophie Graner, Pelle Lindqvist, Susanne Falck and Lennart Nordström
   *BMC Pregnancy and Childbirth* Published online: 2016 March 16

II. **Cardiotocography patterns and risk of intrapartum fetal acidemia**
    Malin Holzmann, Stina Wretler, Sven Cnattingius and Lennart Nordström

III. **Risk factors for intrapartum acidemia – a cohort study**
    Stina Wretler, Lennart Nordström, Sophie Graner and Malin Holzmann
    *Submitted*

IV. **Intrapartum cervical lactate as a predictor of operative delivery: An observational clinical study**
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<th>Full Form</th>
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<td>ACOG</td>
<td>American College of Obstetricians and Gynecologists</td>
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<td>AF-lac</td>
<td>Amniotic fluid lactate</td>
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<tr>
<td>BD</td>
<td>Base deficit</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
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<tr>
<td>Cx-lac</td>
<td>Cervical fluid lactate</td>
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<tr>
<td>CP</td>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>CTG</td>
<td>Cardiotocography</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
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<tr>
<td>FBS</td>
<td>Fetal scalp blood sampling</td>
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<tr>
<td>HIE</td>
<td>Hypoxic ischemic encephalopathy</td>
</tr>
<tr>
<td>HTA</td>
<td>The Stockholm County Health Technology Assessment</td>
</tr>
<tr>
<td>IVF</td>
<td>In vitro fertilization</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NE</td>
<td>Neonatal encephalopathy</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>SBU</td>
<td>Swedish agency for health technology assessment and assessment of social services</td>
</tr>
<tr>
<td>SFOG</td>
<td>Swedish Society of Obstetrics and Gynecology</td>
</tr>
<tr>
<td>STAN</td>
<td>ST-analysis of the fetal ECG</td>
</tr>
<tr>
<td>STV</td>
<td>Short-term-variation</td>
</tr>
<tr>
<td>WHO</td>
<td>The World Health Organization</td>
</tr>
</tbody>
</table>
1 BACKGROUND

Introduction

Obstetric care is unique because we usually treat and care for two healthy individuals. Pregnancy and to give birth is something healthy. Some pregnant women can suffer from a disease and develop complications during pregnancy and delivery. This could be a slow process, but also an abrupt unexpected life-threatening event for both mother and fetus.

To give birth is for most women a life event with great expectations. The role of the obstetric care is to make this life event as safe and as natural as possible. The goal is a healthy mother and healthy new born child. Being a health care professional in this situation is a balance between avoiding unnecessary medical surveillance/intervention and to maintain a safe delivery process. We do not want to take unnecessary risks but we want to intervene as little as possible.

To maintain this sophisticated balance intrapartum monitoring is essential. The aim with intrapartum monitoring is to deliver healthy fetuses, with minimal risks and complications for the woman in labor, our surveillance should help us to prevent and not to predict.

Fetal outcomes to avoid

For a fetus the delivery is a challenge, after nine months in the warm, well-nourished environment in the uterus the fetus becomes exposed to contractions. All oxygen and energy reaches the fetus through the placenta and the umbilical cord. During the delivery process this circulation is affected by the contractions and from time-to-time decreased circulation could be a too big challenge for the vulnerable fetus.\(^1\) A healthy fetus has the capacity to tolerate the stress of being born. The fetus uses defence mechanisms regulated by the autonomic nervous system, one is the ability to redistribute blood to central organs (heart, brain and adrenals).\(^2\)

A low pH in fetal blood has two main reasons. The first is accumulation of carbon dioxide (CO\(_2\)) due to reduced elimination of CO\(_2\) via the umbilical cord. This is called respiratory acidosis. This is seldom a problem, since the fetus has the capacity to get rid of the CO\(_2\) immediately after delivery.\(^2\) The other reason for pH to decrease is elevated levels of acids, mainly lactate produced due to anaerobic metabolism. Anaerobic metabolism occurs due to lack of oxygen, the process generates a little bit more than 5% of the energy that had been
produced if oxygen had been present. In an anaerobic metabolism the cell uses glucose to produce pyruvate (glycolysis). Pyruvate will be converted to lactate with hydrogen ions as a consequence. This is called metabolic acidosis. This will increase the lactate levels in the tissue, but also decrease the pH value.\(^3\)

If the process of hypoxia continues, chemoreceptors can be affected and thereby the fetal heart rate. The elevated concentrations of stress hormones cause a vasoconstriction and an elevated blood pressure. In elongation both hypoxia and ischemia occur in the tissues. Brain damage is a very late stage in this process and the brain damage is not a primary injury but a consequence of a process initiated by the acidosis. This process and the condition with low blood flow and oxygenation is called asphyxia.\(^1, 2\)

Figure 1. A needle for every child born at Karolinska University hospital in Solna 2011. Photo by Stina Wretler, New year’s eve 2011

Asphyxia can occur during pregnancy, intrapartum or during the first hours of life. Asphyxia which occur post-partum is often caused by fetal diseases. Asphyxia during pregnancy is often referred to as chronic hypoxia. It is caused by maternal diseases and conditions as preeclampsia, diabetes and immunization. These fetuses could get permanent brain damage and the pregnancy could also end with stillbirth.\(^2\)
Intrapartum asphyxia can occur due to an obstetric catastrophe such as rupture of the uterus, placenta abruption, umbilical cord prolapse or severe maternal hypotension. Even so the main reason for intrapartum asphyxia is the delivery process, with its uterine contractions.²

Most fetuses suffering from intrapartum asphyxia recover in a few days. Still intrapartum asphyxia can cause neonatal encephalopathy (NE).⁴,⁵ Encephalopathy develops during the first 24 hours after birth and is not possible to predict. Asphyxia also affects other organs than the brain, but these effects are mostly reversible. It is the grade of how affected the brain is, which determine the long term prognosis.² Sarnat and Sarnat defined criteria for NE (table 1).⁶ NE is not always associated with asphyxia or intrapartum events. The causes are heterogeneous and multifactorial, many pathways start in the antepartum period.⁴,⁵,⁷-⁹ The correlation between NE and intrapartum events can partly be explained by the fact that fetuses with damages which will lead to NE present their first symptoms during delivery.¹⁰ Many cases of NE are associated with events beyond the control of the clinicians. Suboptimal care could be a partial factor in some cases. Many of these cases occur in low risk pregnancies why great efforts are needed to prevent them.¹¹

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Duration &lt;24h, hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects and a normal electroencephalogram (EEG).</td>
</tr>
<tr>
<td>Stage II</td>
<td>Obtundation, hypotonia, strong distal flexion and multifocal seizures. EEG with periodic pattern sometimes preceded by continuous delta activity.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Stuporous, flaccid and brain stem and autonomic functions suppressed. EEG isopotential or with infrequent periodic discharges.</td>
</tr>
</tbody>
</table>

When encephalopathy is correlated to an asphyxia it is called hypoxic-ischemic-encephalopathy (HIE).² Most infants with HIE stage one becomes healthy. Infants with moderate to severe HIE have an increased risk for neurological and cognitive sequelae. 25% of infants with moderate HIE develop some kind of neurological sequel. Among infants with severe HIE only 50 % will survive the first years of life and among survivors 75-100% has
severe neurological sequela. Magnetic resonance imaging (MRI) is a good method to evaluate neurological damage after intrapartum asphyxia.\textsuperscript{2}

In this context the most feared long term complication is cerebral palsy. Cerebral palsy (CP) is uncommon with an incidence of approximately 200 children/year in Sweden\textsuperscript{12} and most cases of CP are caused by other reasons than intrapartum complications.\textsuperscript{8, 13, 14} Intrapartum event as cause of asphyxia related to neonatal morbidity and mortality is rare, but it is preventable and therefore important to investigate.\textsuperscript{15}

It is complicated to find a causal relationship between intrapartum events and later diagnosed CP, since some fetuses with asphyxia have other causes which could be linked to the CP or could have made the fetus more fragile and more likely to become distressed. CP has often a multifactorial pathway. The proportion of CP which could be directly associated to intrapartum hypoxia is estimated to less than 10 %.\textsuperscript{8, 13, 14, 16} Since CP is not solely linked to asphyxia it could be problematic to use as a measure of perinatal care.

Umbilical cord artery pH and base deficit (BD) are important diagnostic tools regarding intrapartum asphyxia, but the stage of HIE is a better predictor for prognosis.\textsuperscript{2} An umbilical cord artery BD $>12$ mmol/L or pH $<7.00$ confirms that a fetus has been exposed to hypoxia.\textsuperscript{7, 8, 17, 18} In 1999 the international cerebral palsy task force published an international consensus statement about intrapartum events and CP. They had defined special criteria to define an acute intrapartum hypoxic event which could support causal relationship to the future handicap.\textsuperscript{8} Umbilical cord pH is used clinically to access information about how the fetus has handled the delivery process. Umbilical cord artery pH is widely accepted as a predictive neonatal outcome.\textsuperscript{19} A low Apgar score at 5 minutes is associated to birth asphyxia and an increased risk for CP, epilepsy, seizures and mental retardation.\textsuperscript{20, 21}
Criteria for an acute intrapartum hypoxic event

Essential criteria

1. Evidence of metabolic acidosis at birth; umbilical arterial cord or very early neonatal blood samples (pH<7 and base deficit >12 mmol/L)
2. Early onset of severe or moderate neonatal encephalopathy in infants of ≥34 weeks gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type

Criteria that together suggest an intrapartum timing but by themselves are non-specific

4. A sentinel (signal) hypoxic event occurring immediately before or during labor
5. A sudden, rapid, and sustained deterioration of the fetal heart rate pattern usually after the hypoxic sentinel event where the pattern was previously normal
6. Apgar score of 0-6 for longer than 5 minutes
7. Early evidence of multisystem involvement
8. Early imaging evidence of acute cerebral abnormality

In conclusion important outcomes in this area of research are Apgar score, umbilical cord blood gas and lactate analyses, NE, HIE and CP. Since seizures are one of the more severe symptoms and a well-defined symptom it is often used as a substitute outcome in this area.

Maternal outcomes to avoid

One concern with intrapartum monitoring is that we want to avoid unnecessary interventions. By interventions we usually mean instrumental vaginal deliveries and caesarean sections. In developed countries these are generally safe procedures, but they are connected to more risk than spontaneous vaginal deliveries in the whole population. Still these interventions are necessary procedures for some women and/or fetuses. WHO recommends a caesarean section rate between 10 and 15% to maintain the balance with most benefits for women and infants.22

Worldwide there is a problem with an increasing amount of caesarean sections. 32 % of all births in the US were caesarean deliveries 2007.23 The caesarean section rate is also high in Asia (27.3%).24 In Sweden we have an increased rate since the 1970ies (5%), but over the last years the rate has been relatively stable around 17% (2015).25

Caesarean sections are linked to several complications for both woman and fetus. For the woman caesarean section increases the risk for severe post-partum hemorrhage,26 placenta previa and placenta abruption in the following pregnancies,27 unexplained intrapartum
stillbirth in future pregnancy\textsuperscript{28} and uterine rupture in future vaginal deliveries.\textsuperscript{29} In addition to this the woman has the risk for the usual complications to abdominal surgery. There are also risks for the fetus one of the most common complications is initial respiratory problems.\textsuperscript{30}

In the discussion about fetal monitoring the fear is that monitoring might increase intervention rate, still the most common reason for intrapartum caesarean section is dystocia.\textsuperscript{31,32} Aside the increased risk for caesarean section, a long time in labor is also linked to a negative experience of childbirth for the woman.\textsuperscript{33}

**Risk factors**

When we interpret cardiotocography (CTG) we do not just look at the trace but we also assess the woman in labor and evaluate her fetus - a CTG trace should always be interpreted in its context.\textsuperscript{34} In this area we need to find out which risk factors that correlates to the different outcomes. The risk factors should be a part in our decision about what the fetus can handle. By this follows that the most important risk factors are the ones known during pregnancy and labor.

The thought of dividing pregnancies into high and low risk pregnancies to optimize intrapartum care is not new. In the end of the 1960ies a research group tried to identify a risk score as help in clinical practice.\textsuperscript{35} To study risk factors is important because some are adjustable and a negative outcome could be prevented. To gain knowledge about risk factors scientifically proofed is to make obstetric care less person bound and also a way to optimize clinical resources.

Previous studies have linked different risk factors to different steps in the process of asphyxia (table 2).\textsuperscript{4,5,9,20,36-41} However, these adverse outcomes are not exclusively caused by birth asphyxia, but some are potentially preventable with improved intrapartum management.\textsuperscript{4,5,7,8,11,14,15,37,42,43} Most outcomes have multifactorial etiologies.\textsuperscript{4,5,36} Since neither CP nor NE are most often not solely caused by asphyxia we cannot take for granted that their risk factors are directly associated with asphyxia. Studies have been performed using low Apgar score or low pH in umbilical artery as outcome measures for asphyxia.\textsuperscript{20,38-41}
Table 2. Significant risk factors for neonatal outcomes in different studies.

<table>
<thead>
<tr>
<th>Title</th>
<th>Country</th>
<th>Year</th>
<th>Study population</th>
<th>Outcome</th>
<th>Significant risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors for acidaemia at Birth⁸</td>
<td>Sweden</td>
<td>1997</td>
<td>Cohort 23 016; 249 cases and 249 controls</td>
<td>pH in umbilical cord artery &lt;7.05</td>
<td>Oxytocin augmentation</td>
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<td>Meperidine administration</td>
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<td>Breech delivery</td>
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<td>Cord entanglement</td>
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<td>Male infant gender</td>
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<tr>
<td>Antepartum risk factors for newborn encephalopathy: the Western</td>
<td>Australia</td>
<td>1998</td>
<td>All cases from the birth cohort from June</td>
<td>Moderate or severe newborn encephalopathy</td>
<td>Maternal age</td>
</tr>
<tr>
<td>Australian case-control study³</td>
<td></td>
<td></td>
<td>1993 to September 1995, unclear total</td>
<td></td>
<td>Parity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cohort but 164 cases and 400 controls.</td>
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<td>Maternal employment</td>
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<td>No private health insurance</td>
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<td>Not having drunk alcohol</td>
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<td></td>
<td></td>
<td>Family history of seizures</td>
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<td>Neurological disease in family</td>
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<td>Infertility treatment</td>
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<td>Thyroid disease</td>
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<td>Severe pre-eclampsia</td>
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<td>Moderate or severe bleeding</td>
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<td>Clinically diagnosed viral illness</td>
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<td>Gestational age</td>
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<td>Abnormal placenta at delivery</td>
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<td>Birth weight of the baby</td>
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<td>Intrapartum risk factors for newborn encephalopathy: the Western</td>
<td>Australia</td>
<td>1998</td>
<td>All cases from the birth cohort from June</td>
<td>Moderate or severe newborn encephalopathy</td>
<td>Maternal pyrexia</td>
</tr>
<tr>
<td>Australian case-control study⁴</td>
<td></td>
<td></td>
<td>1993 to September 1995, unclear total</td>
<td></td>
<td>Occipitoposterior position</td>
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<tr>
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<td>cohort but 164 cases and 400 controls.</td>
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<td>An acute intrapartum event</td>
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<td>General anaesthesia</td>
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<td>Operative vaginal delivery</td>
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<td>Intrapartum caesarean section</td>
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<td>Elective caesarean – protective</td>
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<td>Low 5-minute Apgar score: A population-based register study of 1</td>
<td>Sweden</td>
<td>2001</td>
<td>Cohort 1 028 705; 7787 cases</td>
<td>Apgar score &lt;5 at 5 min</td>
<td>Maternal age</td>
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<td>Million term Births²⁹</td>
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<td>Male infant gender</td>
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<td>Birth weight</td>
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<td>Study Title</td>
<td>Country</td>
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<td>Cohort Size</td>
<td>Outcome</td>
<td>Risk Factors</td>
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| Influence of maternal, obstetric and fetal risk factors on the prevalence of birth asphyxia at term in a Swedish urban population | Sweden  | 2002 | Cohort 42 203 births; 225 cases and 225 controls | Apgar score <7 at 5 min | Single civil status  
Oxytocin augmentation  
Cardiotocography pattern  
Intrauterine meconium release  
Cord complication  
External compression to assist delivery  
Breech delivery  
Operative delivery  
Neonatal leanness  
Birth weight |
| Perinatal factors associated with cerebral palsy in children born in Sweden | Sweden  | 2006 | 2 303 case with CP from the Swedish Medical Birth Registry 1984-1198 (1.6 million infants) | Cerebral palsy | Maternal age  
Parity  
Smoking  
Diabetes typ 1  
Preeclampsia  
Being a twin  
Abruptio placentae  
Breech presentation  
Vaginal birth  
Instrumental delivery  
Emergency caesarean delivery  
Preterm delivery  
Low apgar score  
Male infant gender  
Birth weight |
| Acidemia at birth, related to obstetric characteristics and to oxytocin use, during the last two hours of labor | Sweden  | 2008 | Cohort 28 486 deliveries, 305 cases and 610 controls | pH in umbilical cord artery <7.05 | Oxytocin augmentation  
≥6 contractions per 10 minutes  
Cord entanglement |
| Risk factors for asphyxia associated with substandard care during labor | Sweden  | 2010 | 177 cases, 1 141 772 controls from the Swedish Medical Birth Register | Encephalopathy caused by asphyxia with suspected substandard care during labor | Maternal age  
Short maternal stature  
Previous caesarean delivery  
Diabetes  
Twin  
Gestational age  
Induced delivery  
Epidural analgesia  
Opioid analgesia  
Dystocia  
Night-time delivery  
Breech  
Male infant gender  
Birth weight |
<table>
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<tr>
<th>Study Description</th>
<th>Country/Region</th>
<th>Year</th>
<th>Cohort Size</th>
<th>Outcomes</th>
<th>Risk Factors</th>
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<tr>
<td>Antepartum and intrapartum risk factors for neonatal encephalopathy at term³</td>
<td>Italy</td>
<td>2010</td>
<td>Cohort 30 580 infants; 27 cases and 100 controls</td>
<td>Neonatal encephalopathy</td>
<td>Obesity, Previous caesarean section, Nonreactive FHR before labor, Abruptio placentae</td>
</tr>
<tr>
<td>Risk factors for severe neonatal acidosis⁴</td>
<td>France and Canada</td>
<td>2011</td>
<td>Cohort of 37 235; 226 cases and 226 controls</td>
<td>pH in umbilical cord artery &lt;7.00</td>
<td>Maternal age, Prior neonatal death, Prior caesarean delivery, Abnormal fetal heart rate, Thick meconium, General anesthesia, Uterine rupture</td>
</tr>
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a) Year of publication
Fetal monitoring

Cardiotocography (CTG)

Cardiotocography (CTG) as a method was suggested and firstly developed by Edward Hon in the late 1950ies.\textsuperscript{44, 45} The method was fast widely accepted even if the knowledge about interpreting was deficient. At the same time the method was evaluated in clinical randomized studies. In Sweden we started to use CTG in the 1970ies.\textsuperscript{46}

To proof the value of an already introduced method is a challenge. The challenge becomes even greater because of other concurrent advancement.\textsuperscript{47} Many studies in this area were performed in departments were CTG already were in clinical use. One problem to deal with was what to compare with; is it relevant to compare with intermittent auscultation with Pinard’s stethoscope? Should fetal scalp blood sampling be used in the studies? This makes it a complex area for research.

There have been a lot of studies in this area, many of them with 500 or less included women.\textsuperscript{48, 49} Since the outcomes (NE, CP and perinatal mortality) are rare, the size of these studies is a great concern. Presently there are good reviews performed in the area, but some studies still need to be mentioned separately, because of their great impact on further studies and reviews.

The largest study is the Dublin randomized controlled trial (RCT) including 12 964 women comparing continuous CTG with intermittent auscultation. The study had wide exclusion criteria and fetal scalp blood sampling (FBS) was used as adjunctive technology. The study found no significant difference in the rate of caesarean delivery (2.4% in the CTG group and 2.2% in the auscultation group), but a significantly higher amount of forceps deliveries in the CTG group (8.2% compared to 6.3%; \( p<0.0001 \)). The main difference in neonatal outcome was that neonatal seizures and persistent abnormal neurological signs followed by survival were twice as frequent in the intermittent auscultation group.\textsuperscript{48}

Another important study is the Athens trial; a RCT comparing continuous intrapartum CTG versus intermittent auscultation. This study was performed in a context (Greece) where perinatal mortality was more common, than in other comparable study settings. The study was performed in non-expert clinics. They did not use adjunctive technologies or switched to CTG when they found abnormalities in auscultation. The study was closed prematurely (after recruitment of 1428 patients) because an interim analysis showed a higher mortality rate in the auscultation group compared to the CTG group. Perinatal death from fetal hypoxia was
0% in CTG group and 0.9% in auscultation group (p=0.03). In this study CTG increased the rate of surgical intervention for suspected fetal distress (11.2% vs. 4.8% p=0.0001). \(^{49}\)

One of the authors from the Athens trial, is a co-author in a meta-analysis of CTG studies. \(^{50}\) The meta-analysis includes studies with CTG versus intermittent auscultation. It shows that use of CTG leads to decreased perinatal mortality due to fetal distress, but an increased risk for caesarean and assisted vaginal delivery. The same analysis is performed excluding the Dublin trial and the result is the same. Worth mentioning is the fact that even if this meta-analysis showed an increased caesarean risk, the caesarean risk in the total electronic fetal monitoring group was 5.2%.

One study performed in California tackles the problem with a rare complication in a different and maybe the only correct way. \(^{51}\) This study is a case-control study where they identified all children with CP among 155,636 children in four Californian counties and compared with randomly selected controls. Retrospectively all information about the CTG patterns during delivery was collected. 78 children were included in the study (95 cases with CP but only 78 underwent CTG monitoring). The study showed an association between CP and late decelerations, decreased beat-to-beat variation or both in CTG. They also stress that these CTG patterns often are false positive. They calculated that 4 out of 100,000 infants had preventable CP, but 2324 unnecessary interventions per infant need to be performed to prevent one case of CP.

Finally we have a Cochrane review from 2017 with purpose to investigate the value of continuous CTG monitoring. \(^{52}\) In this review, comparing continuous CTG versus intermittent CTG and intermittent auscultation, over 37,000 women were included. The review concluded that CTG decreased the risk for neonatal seizures, but could not found any decreased risk for other neonatal outcomes. Continuous CTG increased the risk for caesarean section and for instrumental delivery.

The conclusion is that CTG might protect against neurological damage due to asphyxia, but that the price is an increased rate of operative deliveries.
The usage of CTG

Despite the doubtful scientific evidence for the use of CTG, CTG is one of the most widely used techniques for intrapartum fetal monitoring.\(^{52,53}\)

In 2015 International Federation of Gynecology and Obstetrics (FIGO) published updated consensus guidelines about intrapartum fetal monitoring. These documents are a unique overview of intrapartum monitoring, the physiology beyond it and adjunctive technologies.\(^{53-57}\) FIGO admit that intermittent auscultation is reliable in low-risk pregnancies even if half of the panel members considered continuous monitoring optional in second stage of labor.\(^{55}\)

Despite scientific proof most experts believed that continuous CTG should be used in monitoring in risk pregnancies/deliveries and as a complement when intermittent auscultation detects anomalies. The documents conclude that regular CTG training is necessary and that the risk with CTG is unnecessary interventions.\(^{53}\) FIGO stresses the need for adjunctive technologies due to high sensitivity and low specificity in CTG monitoring and that the existing data in summary support that FBS reduces interventions. Other suggested adjunctive technologies is fetal scalp stimulation, STAN and computer analysis of CTG.\(^{54}\)

In Sweden the use of CTG is “gold standard” in intrapartum fetal surveillance. According to a survey from 2010 all Swedish departments use admission test (a first CTG trace when a woman arrive to a labor ward). Most departments use either continuous or intermittent CTG during first stage of labor.\(^{58}\) The Swedish national board of Health and Welfare (in Swedish Socialstyrelsen) recommends admission test and intermittent CTG during first stage of labor in low-risk pregnancies, otherwise continuous CTG.\(^{59}\) There is one Swedish prospective randomized trial performed, published in 1994, studying intermittent versus continuous CTG in low risk labors.\(^{60}\) This study concluded that intermittent CTG is a safe as continuous monitoring in low-risk labors.

2015 Swedish agency for Health Technology Assessment and Assessment of Social Services (SBU) published a commentary on previous editions of the two Cochrane reviews about admission test and continuous CTG monitoring during labor.\(^{46,52,61}\) SBU criticize that the included studies are published 20 to 40 years ago and it is doubtful if the results could be used in a Swedish context nowadays. This conclusion mirrors the reasons for why CTG is so widely used despite the weak scientific proofs. It is totally clear that the fetuses do not get harmed by CTG, probably the opposite. Potentially CTG increases the rates of operative deliveries. But still the increase is small compared to the overall risk. The caesarean section
rate in the whole study population in the Cochrane review was 4.5% compared to 17% in Sweden 2011.\textsuperscript{25}

In 2002 85% of all births in the US were monitored with CTG.\textsuperscript{62} A population study from the US shows decreased perinatal mortality most likely due to CTG.\textsuperscript{63} The American Congress of Obstetrics and Gynecologists (ACOG) accepts intermittent auscultation in low risk pregnancies. They recommend continuous CTG monitoring in high risk conditions.\textsuperscript{34}

**CTG interpretation**

CTG monitors the fetal heart rate with either a Doppler probe on the mother’s abdomen or through a scalp electrode applied to the fetal head. The external device uses the Doppler function to detect movements in the fetal heart. The internal device detects the R-wave of the fetal electrocardiogram (ECG). The contractions are monitored by another probe on the mother’s abdomen.\textsuperscript{53}

How we should interpret CTG is an ongoing debate.\textsuperscript{64-66} Which parameters to take into consideration seem accepted.\textsuperscript{34, 53, 66-70} A CTG description should include five different variables: baseline fetal heart rate, variability, occurrence of accelerations, occurrence of decelerations and frequency of contractions. There exist many different guidelines about how to interpret CTG.\textsuperscript{34, 53, 66-70} Most guidelines are consensus documents and define variables similarly. The Swedish Society of Obstetrics and Gynecology (SFOG) has published CTG guidelines, updated 2016 (figure 2).\textsuperscript{70}

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**Figure 2.** The Swedish CTG interpretation guidelines from SFOG.
A normal baseline fetal heart rate is defined as a heart rate between 110 and 160 beats per minute (bpm). Normal variability is defined as variability between 5 and 25 bpm. Acceleration is defined as an increase in fetal heart rate with at least 15 bpm for at least 15 seconds. Decelerations are defined as a decrease in fetal heart rate and could be described as early or late decelerations and variable decelerations.\textsuperscript{66-68} Contractions is described as frequency during 10 minutes and 5 or less is considered normal.\textsuperscript{67}

However, there are different opinions about what is a normal baseline? How to describe decelerations? How important are accelerations? Most clinical guidelines divide CTG traces into three groups: Normal, suspicious/aberrant and pathological.\textsuperscript{34, 53, 66-68, 70} Dealing with normal and pathological traces is relatively standardized in most settings. A normal CTG trace can almost rule out hypoxia.\textsuperscript{64} The current debate concentrates on the suspicious traces. This group is also the most inconclusive in different CTG classifications.\textsuperscript{54, 65}

**Inter- and intraobserver variability**

Despite many well established guidelines CTG interpretation is difficult. Several studies show large variation between and within different interpreters.\textsuperscript{71-77} Guidelines do not seem to decrease this issue.\textsuperscript{76} The problem is most explicit for baseline variability and decelerations.\textsuperscript{76} However, updated guidelines and excessive education in interpretation seem to increase the unanimity.\textsuperscript{62, 78, 79}
Adjunctive technologies

Because of the high sensitivity and the low specificity in CTG interpretation there is a need for adjunctive technologies, especially in the low risk group where fetal distress is rare. The poor inter- and intraobserver reproducibility in the interpretation of a CTG trace make this even more important.

The most common used adjunctive methods in Sweden are fetal scalp blood sampling (FBS) and ST-analysis of the fetal ECG (STAN). Computerized fetal intrapartum monitoring is another suggested method.

STAN

ST-analysis of the fetal ECG (STAN) is a complement to ordinary CTG. The theory is that a fetus exposed to hypoxia develops ECG changes similar to what is seen in myocardial infarcts.

The fetal ECG is monitored through a scalp electrode and a reference electrode at the mother’s leg. A machine reports changes as ST-event in a trace combined with ordinary CTG. When there is a normal CTG the ST-event is not relevant and should be ignored and if the CTG trace is ominous and defined “preterminal” according to the STAN-guidelines, the doctor should react without looking at the ST-events.

The largest study comparing CTG with or without STAN is a RCT from the US, including 11 108 women. In conclusion the results from this study are that there were no differences in neither intervention rates or neonatal outcome between labors monitored with CTG with or without STAN.

A Cochrane review was performed 2015 and includes seven RCT (27 403 women), where one is the RCT from the US mentioned above. The review concluded that less FBS were performed if STAN were used (RR 0.61; 95% CI 0.41-0.91), but only 9671 babies were included in this part of the study. There were also fewer operative vaginal deliveries if STAN was used (RR 0.92; 95% CI 0.86-0.99). The conclusion is that the weak possible benefits from the use of STAN need to be considered against the disadvantages with the method.
Computerized CTG interpretation

Computerized interpretation could be a way to eliminate the risk of human errors, and make the surveillance less user-dependent.

Antenatal computerized CTG monitoring is an established method. It has been more complicated to create a computerized system for intrapartum monitoring, despite several attempts.

Computerized antenatal monitoring

A system for computerized antenatal monitoring was developed by Dawes and Redman during the 80ies and early 90ies. This group, the Oxford group has developed this system gradually and the system in use today is Sonicaid FetalCare™. This system is a computerized monitoring system which combines ordinary CTG parameters with short-term-variation (STV) analysis in relation to specific criteria. The analysis is summarized with a conclusion: if Dawes Redman criteria are fulfilled or not.⁹⁰⁻⁹³ Fulfilled Dawes Redman Criteria is linked to vigorous fetuses and corresponds to a normal CTG trace.⁹¹, ⁹³, ⁹⁴

This system is built of a complex algorithm with an even more complex flow-chart for the conclusion. Data analysis is performed after 10 minutes and then every two minutes. When the criteria are fulfilled or after 60 minutes the printer prints a summary (figure 4).⁹⁰, ⁹³ For the Dawes-Redman criteria to be fulfilled in summary these criteria’s need to be approved¹:

- At least one period with “increased variability”
- STV > 3.0 msec.
- Long-term-variation within 3 SD of the normalvalues or STV > 5 msec.
- At least one fetal movement or 3 accelerations
- Baseline between 116-160 beats per minute
- No deep decelerations
- No sinusoidal pattern
- Signal loss < 30 %

STV is an essential part of this criteria. The real STV (beat-to-beat variation in the fetal heart rate) is not possible to get from signal derived by an ultrasound transducer. STV can neither be estimated visually. The Oxford system therefore uses a computerized derived STV value. Firstly the system excludes part of the CTG trace with decelerations and signal loss. Then it
uses the epoch-to-epoch (3.75 second) variation as a measure of STV, calculating the difference between the average pulse-interval values for adjacent epochs. These values are then averaged over minutes and then over longer time periods. The reason for this is that periods with great signal loss mostly are periods with high activity and this calculation assure that these periods are equally weighted in the analysis.\textsuperscript{90-93}

A STV value of less than 3.0 msec correlates to stillbirth and severe birth acidemia.\textsuperscript{93, 95-99} STV normally increases with gestational age and it is recommended, when possible, to use every single fetus as it owns control.\textsuperscript{91, 95} STV is an earlier sign of an affected fetus than decelerations, since it is computerized it is not either user dependent.\textsuperscript{91, 93} Computerized CTG monitoring is assumed to reduce perinatal mortality antepartum.\textsuperscript{100}

Figure 4. A report from the Sonicaid system.
**Computerized intrapartum monitoring**

Intrapartum computerized monitoring is suggested to improve the inter- and intraobserver variability in CTG interpretation. There are great expectations. Many attempts have been performed, with different approaches, some including information about maternal and fetal characteristics. Some groups have succeeded to develop system as good as experienced clinicians.

To develop a computerized intrapartum system is much more complicated than to develop an antenatal system. The CTG trace is more complex since the interpreter has to take contractions into consideration. The fetal heart rate is more dynamic, an effect of the autonomic nervous system due to the stressful situation. There are implications that intrapartum STV is higher than antenatal STV due to this stress. STV also increases towards the end of pregnancy. STV for intrapartum use is so far not fully evaluated.

When discussing the use of STV it is important to differ between STV as a stand-alone method and as a part of a system. Evaluation of STV as a stand-alone method has so far not shown any association to adverse outcome intrapartum, but the study size and that the included cases are mostly healthy might be an explanation. In a review from 2016 the conclusion is that STV appears to be a moderate predictor for fetal acidemia antenatally, but if it should be used alone or as part of a system is not clear.

In this area it is important to differ between central fetal monitoring systems as MILOU™ and Guardian™, and computerized CTG monitoring system as Omniview –SisPorto™, INFANT™ and OxSys™. In a very short time these three computerized CTG monitoring system have been presented and evaluated.

A group in Portugal has developed Omniview-SisPorto™ 3.5 which is a monitoring system with visual and sounds alerts based on CTG and STAN. The system is constructed by commonly known CTG interpretation guidelines (FIGO guidelines). This system is developed for both antepartum and intrapartum monitoring. The aim with this system and performed studies was to prove if this system could reduce the rate of umbilical cord artery metabolic acidosis compared to continuous CTG monitoring. Recently the results were published. It is a RCT performed in five clinics in United Kingdom. STAN and FBS were allowed in both study arms. 7730 women were randomized to the study. No differences were found either in primary or secondary outcomes. The authors highlights that there was a low rate of affected newborns in both study arms.
The INFANT™ Collaborative group has performed a multicenter RCT (UK and Ireland) comparing continuous CTG with or without addition of a decision-support software (INFANT™). INFANT™ is a supplement to the monitoring system Guardian™. INFANT™ analyse the quality of fetal heart rate signals and displays baseline, variability, accelerations, type and timing of decelerations and contraction pattern. The system makes a conclusion from this material which ends up with a colour code where the colour code indicates the severity of the CTG changes. Their outcome was neonatal mortality or morbidity. They also performed a follow-up development assessment of a sample of children at 2 years age. 47 062 women were recruited to the study. No significant differences were seen in any outcome, neither in mode of delivery. They conclude that computerized interpretation of CTG does not improve clinical outcome.¹⁰⁶

The Oxford group has developed a system called OxSys™ for intrapartum use.¹¹⁵ This is a CTG based system including STV.⁸⁵ It uses the CTG interpretation guidelines from ACOG, but a bit modified due to computer reasons and combines this with STV in an algorithm. STV is calculated in the same way as in Sonicaid FetalCare™.⁸⁵ The results from this study are just published. They used a cohort of 22 790 laboring women to both develop and evaluate this system. Their conclusion is that the system is in concordance with clinical management. The system seems to be as good as clinicians.¹⁰⁴

Three experienced research groups have developed computerized systems for intrapartum monitoring. These systems seem to be as good as clinicians, if this is bad or good is a delicate question.

**Fetal scalp blood sampling (FBS)**

FBS was introduced parallel to CTG in the 1960ies. Saling introduced the method and early studies were performed by Beard. The method comprises of a small blood-sample from the fetal scalp, collected through an amnioscope at a vaginal exam of the woman in labor. The fetal blood is used for analysis to recognize if the fetus is suffering from acidosis as a sign of hypoxia. This method was introduced before CTG was widely available and fully evaluated.¹¹⁶-¹¹⁹

Nearly 40 years after publication there is one single trial who still is remarkable in this area of research. The trial was performed in Denver, Colorado including 690 high risk pregnancies. It was a three armed trial comparing; auscultation, CTG and CTG with the option to take FBS.
The trial showed no differences in neonatal outcome. The rates of caesarean section were significant higher in the CTG group compared to the auscultation group. The authors drew the conclusion that CTG did not improve neonatal outcome but increased the risk for caesarean. When looking at this trial more in detail, the auscultation group had only one caesarean due to fetal distress, meanwhile the CTG group had 16 caesareans due to fetal distress (7%), which was a significant difference. There was also a difference in caesarean rate than comparing CTG with or without FBS. In the group with FBS the caesareans due to fetal distress was 8 (3%). However, this difference was not significant. In their conclusion they wrote that if we should use CTG FBS may be required. In this study there was one-to-one care which makes auscultation possible.

Initially, pH was analyzed in FBS sampling. The method requires 30-50 microliters blood and the analysis takes on average 47 seconds, but the total time for the method is often much longer. The fetus may have a low pH value because of either respiratory or metabolic acidosis. Early studies suggested a full blood gas analysis to differ between respiratory and metabolic acidosis. Lactate was first suggested in the 1980ies. The method was further developed in the middle of the 1990ies. This method only requires 5 microliters of blood and the analysis can be performed at the bedside in only 60 seconds. It is proven that the lactate concentration in the fetus is mainly of fetal origin.

Kruger et al performed a retrospective study of FBS and found that lactate is a more sensitive method than pH for predicting low Apgar score (<4 at 5 min) or moderate to severe hypoxic-ischemic encephalopathy (HIE). They suggest cut-off values for lactate to 4.8 mmol/L (Lactate Pro™) and urged that it will result in the same amount of interventions as cut-off for pH 7.20. In the interpretation of lactate values the reference values between commercially available devices differ.

Lactate concentration in FBS increase during second stage of labor. Due to this different cut-off values have been suggested for first and second stage of labor.

In Sweden two RCT’s have been performed comparing pH and lactate in FBS. Westgren et al (1998) showed no differences in perinatal outcome or delivery mode between FBS with pH or lactate analyses, but they found more frequent unsuccessful sampling in the pH group. Wiberg-Itzel et al performed a multicenter RCT comparing pH and lactate analyses at FBS (pH cut-off <7.21 and lactate >4.8 mmol/L) and found no differences in acidemia at birth. One conclusion from this study is that lactate has no false-negative tests. Wiberg-Itzel et al had protocol violations in 10.4 % in the pH group and 1.2% in the lactate group, due to failed
sampling or analysis. Lactate was analysed in high proportion of failed pH sampling, which was not allowed due to the protocol. This could have influenced the result in favour of pH, as without protocol violation the clinician could either deliver the fetus – with the effect of increasing the intervention rate – or let labor progress with risk of developing acidemia. It is likely to believe that pH sampling would have result in more operative deliveries if lactate is not available as an option.

A Cochrane review was published in 2015 including the two Swedish RCT’s mentioned above (N=3348).\(^1\)\(^{34}\) The review concluded no difference in fetal outcome but a much better success rate in sampling with lactate.

Holzmann et al performed a secondary analysis of the material from Wiberg-Itzel et al and looked at perinatal outcome in a subgroup of the 5% most acidemic fetuses defined as scalp pH below 7.17 or lactate over 6.6 mmol/l.\(^{133, 135}\) The authors found that neonatal morbidity occurred in 10% or less in this high-risk group. The conclusion was that FBS is an early marker which can be used to prevent severe birth acidemia and that lactate might be an earlier marker than pH because in the pH group the delivery were performed faster and still there were no differences in neonatal outcome.

There are many supporters for the use of FBS even if the method so far has not been evaluated in any RCT large enough to proof a difference in CTG monitoring with and without FBS. There is also criticism towards the method.\(^{136}\) Criticism towards FBS concerns the fact that the fetal head is compressed during labor and that influence the blood flow to the fetal scalp. Opponents mean that the only reason for FBS still being in use is the lack of an alternative.\(^{137, 138}\)

Researchers seem to agree that if we should perform FBS lactate analysis has benefits compared to pH. It is easier to collect and most likely an earlier marker than pH.\(^{121, 127, 139, 140}\) FBS is generally well tolerated by the women in labor.\(^{141}\) FBS reduces the proportion of false positive tests with CTG and is likely to reduce the rate of caesarean deliveries.\(^{52, 116, 120}\)

In the UK NICE guidelines recommends use of FBS.\(^{58}\) FBS is today used in all Swedish labor wards.\(^{58}\)

Since Haverkamp performed the Denver trial 40 years ago there have been thoughts to repeat the same study but with a larger study population. 2015 a study protocol was published for the Flamigo trial. This was an Australian study which aimed to compare CTG and CTG with
FBS. The protocol caused great expectations. The planned recruitment according to the power analysis in the Australian New Zealand Clinical Trial register (March 2017) was 600 women, but recruitment was stopped after 123 women. No results have been published so far.

A Dutch study is included in the Netherlands trial register; the SCALP trial. It is a multicentre RCT. Women were planned for monitoring with CTG with or without STAN and if the CTG became abnormal they would randomly be assigned to either FBS or not. Planned closing date was April 2015. So far no results have been published.

Maternal monitoring

Labor dystocia is the most common reason for intrapartum caesarean section. To monitor the contractions and the progress in labor we use the contraction pattern from the CTG and the partogram. The contractions are monitored by a transducer on the pregnant abdomen. It is possible to use either an external or an internal transducer. The internal transducer is a form of catheter which is introduced inside the uterus through a vaginal exam. Internal monitoring seems to give better information about the quality of contractions, but have not been proven to improve outcome. 2017 the diagnosis dystocia is mainly a question of wait and see.

Uterus physiology

pH affects the effectiveness of the smooth muscles in the uterus. A low pH causes less frequent and weaker contractions. It has been shown that human myometrial cells can produce lactate both under aerobic and anaerobic metabolism. A high concentration of lactate in myometrial tissue reduces both strength and frequency of contractions. Lactate effects the contractions by the change in pH. Capillary blood samples have been collected from the uterotomy in women who underwent caesarean section. These samples had a higher lactate concentration when the caesarean was due to dystocia compared to women who had normal progress of labor.

Lactate has previously been used in sports to evaluate performance. Since the uterus is a working muscle it is a natural thought that it, like other muscles can be exhausted due to lactacidemia. The entire uterus receives blood supply from the internal iliac arteries
which supplies the body of uterus (corpus) as well as the cervix through the uterine arteries.\textsuperscript{154}

**The Partogram**

In the 1950ies the partogram was developed and evaluated for monitoring progress in labor. The partogram is yet a central part of documentation in the labor ward. The alert and action line, which we still use as helpful tools in the diagnosis of dystocia were introduced in the 70ies. The cervicograph was developed in the US and the action and alert line were derived from data from a Rhodesian hospital.\textsuperscript{155,156} The alert and action lines were developed to help midwives with limited access to obstetricians, to safely manage intrapartum care. In this early partograms an action line of four hours’ delay was used.\textsuperscript{157,158}

The partogram is at present a clinical tool with unclear clinical value.\textsuperscript{159,160} According to Cochrane there is no evidence for using the partogram, but the partogram may have an effect in areas with less access to healthcare resources.\textsuperscript{160} The partogram is nevertheless a useful tool in documentation.\textsuperscript{159}

**Amniotic fluid lactate (AF-lac)**

One suggested method to predict dystocia is to measure lactate concentration in amniotic fluid (AF-lac). Regardless of stage of labor there are higher concentrations of lactate in amniotic fluid compared to FBS.\textsuperscript{161}

Studies have suggested that elevated AF-lac is associated with dystocia and caesarean or instrumental delivery. A discussed cut-off value is 10.1 mmol/l.\textsuperscript{162-164} AF-lac has been suggested as a complement to the partogram in predicting dystocia.\textsuperscript{165} Still the method has not been fully evaluated in any intervention study.

The Stockholm County Health Technology Assessment (HTA) gave a statement of opinion in 2016. They concluded that it today is no indication to analyze AF-lac in laboring women to predict dystocia.\textsuperscript{166}
2 AIMS

The general aim of this thesis was to investigate and improve established and new methods for intrapartum monitoring.

The specific aims of each study were:

- To methodologically study if short-term-variation (STV) is a possible complementary parameter to CTG in intrapartum fetal monitoring. (Study 1)

- To investigate the association between different CTG patterns and lactacidemia in FBS. (Study 2)

- To study the association between different potential intrapartum known risk factors and lactacidemia in FBS. (Study 3)

- To study if cervical lactate could be a possible marker for labor dystocia and if maternal uterine and fetal scalp lactate correlates. (Study 4)
3 MATERIALS AND METHODS

Study 1

Population and study design

This is a prospective observational study. The study includes women at Karolinska University Hospital, Stockholm, Sweden between September 2011 and April 2015. Totally 120 women were included in the study. The study is built of three subgroups (figure 5).

Figure 5. Subgroups in study 1

<table>
<thead>
<tr>
<th>Subgroup A</th>
<th>Subgroup B</th>
<th>Subgroup C</th>
</tr>
</thead>
</table>
| - 100 women in active first stage of labor  
- Singleton pregnancies  
- ≥37 week gestation  
- Cephalic presentation  
- Fetal monitoring with scalp electrode |
| - 20 women from subgroup A |
| - 20 women prior to labor  
- Singleton pregnancies  
- ≥36 week gestation |

All women were monitored according to national and clinical guidelines for CTG surveillance. In subgroup A we collected STV values with internal monitoring. Table 3 shows population characteristics.

20 of the women in subgroup A is subgroup B. In these women we compared STV values derived from both external and internal monitoring, simultaneously. The twin function of the CTG machine made this possible.

Subgroup C was simultaneously monitored with two different brands of CTG monitors, Sonicaid™ and EDAN™. Clinical indications for monitoring were suspected but not confirmed ruptured membranes, breech presentation prior to external cephalic version, admission test before induction of labor and maternal diabetes.
Table 3. Maternal, labor and neonatal data for study 1, subgroup A.

<table>
<thead>
<tr>
<th>Population characteristics</th>
<th>numbers and medians (range) N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (days)</td>
<td>281 (261-296)</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>31 (17-43)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>62</td>
</tr>
<tr>
<td>Multiparous</td>
<td>38</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>61</td>
</tr>
<tr>
<td>Ventouse/forceps</td>
<td>21</td>
</tr>
<tr>
<td>Caesarean</td>
<td>18</td>
</tr>
<tr>
<td>Epidural</td>
<td>81</td>
</tr>
<tr>
<td>Oxytocin infusion</td>
<td>55</td>
</tr>
<tr>
<td>Apgar &lt; 7 at 5 minutes</td>
<td>2</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>8</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3493 (2520-5030)</td>
</tr>
</tbody>
</table>

STV

Sonicaid™ is an established CTG monitor for antenatal monitoring of STV with external Doppler monitoring. EDAN™ is a new CTG monitor which has equipment for both external Doppler and internal scalp electrode monitoring including a twin function. EDAN™ is recommended for intrapartum monitoring, but the STV function has not previously been evaluated and is presently not recommended for clinical use.

Sonicaid™ and EDAN™ use the same algorithm to estimate STV values. Sonicaid™ presents one STV value at the end of the CTG trace either as soon as the Dawes-Redman criteria are fulfilled or after 60 minutes if the criteria are not fulfilled. EDAN™ presents a first value after 10 minutes and then new values are added continuously up to 60 minutes.
External fetal monitoring is performed by an ultrasound device on the woman’s abdomen, the internal monitoring through a scalp electrode on the fetus’s head detecting the time intervals between heart beats by identifying R waves on the fetal ECG.53

Statistics

For statistical analyses Statistica™ version 10 (Statsoft Inc, Tulsa, OK) was used. Data are presented as numbers, medians/means and standard deviations, when appropriate, percentage and range. Mann-Whitney U-test was used for comparison between continuous variables. Correlation between two parameters was calculated with Spearman Rank Correlation. Evaluation of agreement between different monitoring modes is displayed in Bland-Altman plots.

Ethics

The study was approved by the Regional Ethics committee in Stockholm (Dnr: 2014/2006-31/4). Participants gave oral consent to participate in the study.

All CTG traces were performed according to clinical indications. The information about STV values was no ground for clinical decisions. The only disadvantage for the participating woman was that she in some cases needed to have one or two extra abdominal probes during a short time period.

Study 2 and 3

Population and study design

Study 2 is a prospective observational cohort study including women who underwent FBS due to a non-reassuring CTG trace. Study 3 is a secondary analysis of the same cohort. In study 2 the purpose was to correlate different CTG patterns to lactacidemia in FBS. Study 3 is an analysis of potential intrapartum known risk factors for lactacidemia in FBS. The cohort was collected at the labor ward Karolinska University Hospital, Stockholm, Sweden from February 2009 to February 2011 (table 4).
All laboring women who underwent FBS and had a simplex pregnancy, ≥ 34 weeks of gestation and with a fetus in cephalic presentation were included in the study (N=1070). During the study period FBS was performed in 10.5% (1070/10143) of all deliveries at Karolinska University Hospital.

**CTG**

All women were monitored with CTG according to Swedish guidelines. In conclusion this means that all women had an admission CTG, if the admission test was normal the woman was considered at low risk and intermittent CTG monitoring every two hours was recommended during first stage of labor. Women at high risk, having epidural analgesia or oxytocin augmentation had continuous CTG monitoring. During second stage of labor all women had continuous CTG monitoring. For CTG interpretation the department followed guidelines from SFOG.

**CTG classification**

All CTG traces 60 minutes prior to each FBS were retrospectively interpreted by a senior obstetrician (Lennart Nordström), blinded to the lactate concentration at sampling. For all traces baseline, variability, accelerations, type of decelerations and duration of CTG pattern were documented. FIGO definitions were used. All traces were divided into different groups according to the various CTG pattern (table 6-9). Simple variable decelerations and early decelerations were considered as normal.

**FBS**

The decision to perform FBS was made by the attending obstetrician. FBS were collected by a vaginal examination, 5 µL of fetal scalp blood was collected after wiping dry from amniotic fluid and applying silicone gel. Lactate Pro™ (KDK Corp. Kyoto, Japan) was used for all analysis. The cut-off value for acidemia was a lactate concentration above 4.8 mmol/L, which was found in 94 (8.8%) of the cases.
Table 4. Population characteristics for study 2 and 3.

<table>
<thead>
<tr>
<th>Population characteristics (N=1070)</th>
<th>Medians (range) and numbers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>31 (15-47)</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>283 (239-298)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>772 (72.1)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>298 (27.9)</td>
</tr>
<tr>
<td>Delivery mode</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>418 (39.1)</td>
</tr>
<tr>
<td>Ventouse</td>
<td>352 (32.9)</td>
</tr>
<tr>
<td>Caesarean</td>
<td>300 (28.0)</td>
</tr>
<tr>
<td>Previous caesarean</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>109 (10.2)</td>
</tr>
<tr>
<td>No</td>
<td>961 (89.8)</td>
</tr>
<tr>
<td>Maternal body mass index&lt;sup&gt;a&lt;/sup&gt; (N=1030)</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>32 (3.1)</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>620 (60.2)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>253 (24.6)</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>86 (8.3)</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>39 (3.8)</td>
</tr>
<tr>
<td>Onset of labor</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>690 (64.5)</td>
</tr>
<tr>
<td>Induced onset</td>
<td>380 (35.5)</td>
</tr>
<tr>
<td>Oxytocin at sampling</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>652 (60.9)</td>
</tr>
<tr>
<td>No</td>
<td>418 (39.1)</td>
</tr>
<tr>
<td>Epidural analgesia at sampling</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>862 (80.6)</td>
</tr>
<tr>
<td>No</td>
<td>208 (19.4)</td>
</tr>
<tr>
<td>Birth weight (N=1068) (grams)</td>
<td>3510 (1638-5340)</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (1.4)</td>
</tr>
<tr>
<td>No</td>
<td>1055 (98.6)</td>
</tr>
<tr>
<td>Hypoxic ischemic encephalopathy&lt;sup&gt;b&lt;/sup&gt; (N=1061)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (0.09)</td>
</tr>
<tr>
<td>No</td>
<td>1060 (99.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Body mass index is equal to the weight (kilograms) divided with the square of the woman’s height (meters)

<sup>b</sup> Infant who had got the diagnosis hypoxic ischemic encephalopathy at discharge from the hospital
Risk factors

Information on maternal, infant and intrapartum characteristics was collected from the medical records. Only factors known at sampling were included in the study. Nicotine use was defined as smoking or snuffing before or during pregnancy. Languages barriers were divided into none, minor or major. The woman was classified as having minor language barrier if a relative translated or 2nd language was used and as having major language barrier if professional interpreter was used. All intrapartum information was recorded as risk factors (intrapartum fever, epidural, oxytocin augmentation, active pushing) only if they have occurred prior to sampling. Birth weight was used as a proxy for intrauterine growth restriction, and fetal gender was also included in the database since it is possible to know at sampling.

Statistics

For statistical analyses Statistica™ version 11 (Statsoft Inc. Tulsa, OK) was used for all analyses in study 2 and Statistica™ version 10 and 13 (Statsoft Inc. Tulsa, OK), were used for all analyses in study 3.

In study 2 a power calculation was performed based on an interim analysis of 176 cases.

Background data are presented as medians, range and percentages. Chi-square test and Fisher’s exact test were used for comparison of frequencies. Mann-Whitney U-test was used for comparison between groups.

In study 3 logistic regression was used to calculate crude odds ratios (COR) and adjusted odds ratios (AOR) and their 95% confidence intervals (CI). Firstly a univariate analysis of potential risk factors was performed. If the p-value in the univariate analysis was <0.2 the risk factor was included in the stepwise forward multivariate logistic regression analysis.

A p-value <0.05 was considered significant in both studies.
Ethics

Study 2 and 3 were approved by the Regional ethics committee of Stockholm (2008/1618-31 and 2011/478-32). All CTG traces and all FBS were performed upon clinical indication.

Study 4

Population and study design

This is a clinical study performed at the labor ward at Karolinska University Hospital in Stockholm between May 2011 and February 2017. The population was recruited among women who underwent FBS due to non-reassuring fetal heart rate pattern. Characteristics of the study population are presented in table 5.

Table 5. Characteristics of the study population.

<table>
<thead>
<tr>
<th>Population characteristics (N=77) (medians [range] and numbers [%])</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (year)</td>
<td>32 (19-43)</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>285 (249-296)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>59 (77)</td>
</tr>
<tr>
<td>Previous caesarean</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Maternal body mass index(^a) (kilogram/meter(^2))</td>
<td>25.5 (17-40)</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>54 (70)</td>
</tr>
<tr>
<td>Oxytocin infusion during labor</td>
<td>68 (88)</td>
</tr>
<tr>
<td>Intrapartum fever(^b)</td>
<td>35 (45)</td>
</tr>
<tr>
<td>Epidural analgesia</td>
<td>72 (94)</td>
</tr>
<tr>
<td>Delivery mode</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Ventouse/forceps</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Caesarean</td>
<td>41 (53)</td>
</tr>
</tbody>
</table>

a) N=76
b) Defined as 38 C degrees or more
**Cervical lactate and amniotic fluid lactate sampling**

In addition to FBS for analysis of lactate concentration fluid samples from cervical tissue and when possible amniotic fluid were collected. To collect fluid samples from cervical tissue the same method as for FBS was used. The fluid collected from the cervix looked like a mixture of blood and extracellular fluid. If amniotic fluid was visible it was collected by putting a capillary in a suitable pouch. There were no technical problems with collecting Cx-lac, but AF-lac was not always visible.

All analyses were performed bed-side using Lactate Pro™ (KDK Corp. Kyoto, Japan). A method evaluated for FBS and AFL lactate concentration determination.\(^{126, 168}\)

The attending clinician was blinded to the Cx-lac and AF-lac value and the results were not used in clinical management. Afterwards maternal and labor information were collected and correlated to the results.

**Statistics**

For statistical analysis, we used Statistica for Windows version 10 (Statsoft Inc. Tulsa, OK, USA). Data are reported as medians, ranges and percentages. Chi-square test was performed for comparison of proportions and Mann-Whitney U-test or Kruskal-Wallis test were used for continuous variables. Correlation was calculated using Spearman Rank Correlation or linear regression. A p-value <0.05 was considered significant.

**Ethics**

The study was approved by the regional ethics committee of Stockholm (2011/1075-31/3). Since this study included invasive sampling participants got oral and written information about the study and gave consent to participate.

The sampling did not cause the woman in labor any more inconvenience than the FBS did. All samples were destroyed after analysis.
4 RESULTS

Study 1

In subgroup A the median STV for all cases (N=100) was 7.1 msec (range 1.3-25.9). In comparison between early (cervix 3-6 cm) and late first stage of labor (7-10 cm) there were no differences (median 7.1 vs 6.8 msec; p=0.80) (figure 6).

![Figure 6. Box plot of STV and Cervical dilatation.](image)

All fetuses in subgroup B had at least 10 calculations of STV with simultaneous external and internal monitoring (in total 463 values). Median delta STV (internal-external) was 0.0 msec (range -2.9 – 5.5). In the lower distribution of STV (<8 msec) the scalp electrode derived lower values compared to externally derived values. In the higher distribution of STV (>8msec) the result was the contrary. The correlation between STV from internal monitoring and delta STV (internal-external) was positive and significant (r=0.70; p<0.01) (figure 7).
Subgroup C was simultaneously monitored externally with both brands of machines. The mean difference between STV Sonicaid and STV EDAN (delta-STV) was 0.6 msec (SD ±1.17) (median 0.9 msec) within a range of -2.0 – 2.6. There was no significant correlation between STV Sonicaid and delta-STV (r=0.35; p=0.14) (figure 8).
Study 2

1070 women with 2134 FBS were included in the study. The results are presented both for first sampling (N=1070) and last sampling, since 52% of the women had more than one FBS. Women in active pushing prior to sampling are excluded in the analysis of women with late sampling.

CTG interpretation prior to the first FBS shows that 23% of the cases had a normal CTG trace. In this study the definition of normal includes normal baseline and variability without serious decelerations. Simple variable and early decelerations were allowed. Isolated absence of accelerations was also considered as normal.

Traces showed severe variable decelerations in 12% and late decelerations in 5% of the cases. The distribution of CTG patterns between the groups are presented in table 6.

Cases with normal CTG pattern and cases with isolated reduced variability had a high amount of normal lactate concentrations at first FBS (97.5% and 97.4%) (table 6). There was no significant difference in comparison between amounts of lactacidemia (lactate > 4.8 mmol/L) between the groups.

The highest frequency of elevated lactate concentrations was found in the groups with severe or late decelerations in combination with tachycardia (25% and 20% respectively) (table 6). These groups also had a higher median lactate concentration than the normal group (3.8 and 3.1 mmol/l) (table 7).
Table 6. Proportions of fetal lactacidemia at 1st FBS in groups with different CTG patterns.

<table>
<thead>
<tr>
<th>CTG-pattern</th>
<th>Total numbers (%)</th>
<th>Numbers with lactate &gt;4.8 mmol/L</th>
<th>% (95% CI)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal baseline and variability</td>
<td>242 (22.6)</td>
<td>6</td>
<td>2.5 (0.1-4.5)</td>
<td></td>
</tr>
<tr>
<td>Reduced variability</td>
<td>154 (14.4)</td>
<td>4</td>
<td>2.6 (0.1-5.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Absent variability</td>
<td>32 (3.0)</td>
<td>4</td>
<td>12.5 (0.4-24.6)</td>
<td>0.020</td>
</tr>
<tr>
<td>Increased variability</td>
<td>10 (0.9)</td>
<td>2</td>
<td>20.0 (0-50.2)</td>
<td>0.035</td>
</tr>
<tr>
<td>Bradycardic episode</td>
<td>46 (4.3)</td>
<td>10</td>
<td>21.7 (9.4-34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>124 (11.6)</td>
<td>10</td>
<td>8.1 (3.2-12.9)</td>
<td>0.027</td>
</tr>
<tr>
<td>Tachycardia + reduced variability</td>
<td>149 (13.9)</td>
<td>9</td>
<td>6.0 (2.2-9.9)</td>
<td>0.102</td>
</tr>
<tr>
<td>Severe variable decelerations</td>
<td>127 (11.9)</td>
<td>18</td>
<td>14.2 (8.0-20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations</td>
<td>58 (5.4)</td>
<td>8</td>
<td>13.8 (4.6-22.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + reduced variability</td>
<td>28 (2.6)</td>
<td>4</td>
<td>14.3 (0.5-28.1)</td>
<td>0.013</td>
</tr>
<tr>
<td>Late decelerations + reduced variability</td>
<td>25 (2.3)</td>
<td>3</td>
<td>12.0 (0-25.7)</td>
<td>0.042</td>
</tr>
<tr>
<td>Severe variable decelerations + tachycardia</td>
<td>32 (3.0)</td>
<td>8</td>
<td>25.0 (9.1-40.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + tachycardia</td>
<td>30 (2.8)</td>
<td>6</td>
<td>20.0 (4.8-35.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Missing + undefinable pattern</td>
<td>13 (1.2)</td>
<td>2</td>
<td>15.4</td>
<td>0.057</td>
</tr>
<tr>
<td>Total</td>
<td>1070</td>
<td>94</td>
<td>8.8</td>
<td></td>
</tr>
</tbody>
</table>

a) P-value calculated with two-tailed Fisher’s exact test in comparison with normal CTG
Table 7. Median of lactate concentration at first FBS in groups with different CTG patterns.

<table>
<thead>
<tr>
<th>CTG-pattern</th>
<th>Median (mmol/L)</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; – 95&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal baseline and variability (242)</td>
<td>2.2</td>
<td>1.3–4.3</td>
<td></td>
</tr>
<tr>
<td>Reduced variability (154)</td>
<td>2.15</td>
<td>1.3–4.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Absent variability (32)</td>
<td>2.35</td>
<td>1.2–7.2</td>
<td>0.833</td>
</tr>
<tr>
<td>Increased variability (10)</td>
<td>3.4</td>
<td>1.7–7.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Bradycardic episode (46)</td>
<td>3.15</td>
<td>1.4–6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachycardia (124)</td>
<td>2.4</td>
<td>1.6–5.3</td>
<td>0.013</td>
</tr>
<tr>
<td>Tachycardia + reduced variability (149)</td>
<td>2.4</td>
<td>1.4–5.0</td>
<td>0.223</td>
</tr>
<tr>
<td>Severe variable decelerations (127)</td>
<td>3.2</td>
<td>1.7–6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations (58)</td>
<td>3.2</td>
<td>1.8–6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + reduced variability (28)</td>
<td>3.1</td>
<td>1.8–6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + reduced variability (25)</td>
<td>3.2</td>
<td>1.9–4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + tachycardia (32)</td>
<td>3.8</td>
<td>1.8–7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + tachycardia (30)</td>
<td>3.1</td>
<td>1.8–6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing + undefinable pattern (13)</td>
<td>3.2</td>
<td>1.3–6.8</td>
<td>0.478</td>
</tr>
<tr>
<td>All groups (1070)</td>
<td>2.6</td>
<td>1.4–5.7</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> p-value calculated with Mann-Whitney U-test comparison with normal baseline and variability.
The results from the first FBS is in concordance with the results from the last FBS. In the group with a normal CTG trace 4.8% had an elevated concentration of lactate. CTG traces with late or severe variable decelerations were associated with high lactate concentration in 22% of the cases (table 8).

The CTG traces associated with highest amount of high lactate concentration were the one with severe or late decelerations with tachycardia (33% and 49%, respectively). In these groups the median lactate concentration was twice as high as in the group with a normal CTG trace (table 9).
Table 8. Proportions of fetal lactacidemia at last FBS\(^a\) in groups with different CTG patterns.

<table>
<thead>
<tr>
<th>CTG-pattern</th>
<th>Total numbers(^a) (%)</th>
<th>Numbers with lactate (&gt; 4.8) mmol/L</th>
<th>% (95% CI)</th>
<th>P-value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal baseline and variability</td>
<td>187 (21.1)</td>
<td>9</td>
<td>4.8 (1.7-7.9)</td>
<td></td>
</tr>
<tr>
<td>Reduced variability</td>
<td>113 (12.7)</td>
<td>5</td>
<td>4.4 (0.6-8.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Absent variability</td>
<td>32 (3.6)</td>
<td>7</td>
<td>21.9 (6.7-37.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Increased variability</td>
<td>7 (0.8)</td>
<td>2</td>
<td>28.6 (0-73.7)</td>
<td>0.053</td>
</tr>
<tr>
<td>Bradycardic episode</td>
<td>36 (4.1)</td>
<td>12</td>
<td>33.3 (17.2-49.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>106 (11.9)</td>
<td>16</td>
<td>15.1 (8.2-22.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Tachycardia + reduced variability</td>
<td>128 (14.4)</td>
<td>7</td>
<td>5.5 (1.5-9.5)</td>
<td>0.800</td>
</tr>
<tr>
<td>Severe variable decelerations</td>
<td>97 (10.9)</td>
<td>21</td>
<td>21.6 (13.3-30.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations</td>
<td>49 (5.5)</td>
<td>11</td>
<td>22.4 (10.3-34.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + reduced variability</td>
<td>28 (3.2)</td>
<td>8</td>
<td>28.6 (10.7-46.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + reduced variability</td>
<td>34 (3.8)</td>
<td>10</td>
<td>29.4 (13.3-45.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + tachycardia</td>
<td>33 (3.7)</td>
<td>16</td>
<td>48.5 (30.5-66.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + tachycardia</td>
<td>30 (3.4)</td>
<td>10</td>
<td>33.3 (15.4-51.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing + undefinable pattern</td>
<td>8 (0.9)</td>
<td>2</td>
<td>25.0</td>
<td>0.067</td>
</tr>
<tr>
<td>Total</td>
<td>888</td>
<td>136</td>
<td>15.3</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Cases with active pushing prior to sampling excluded

\(^b\) \(p\)-value calculated with two-tailed Fisher’s exact test in comparison with normal CTG
Table 9. Median of lactate concentration at last FBS in groups with different CTG patterns.

<table>
<thead>
<tr>
<th>CTG-pattern (n) (^a)</th>
<th>median (mmol/L)</th>
<th>5(^{\text{th}}) – 95(^{\text{th}}) percentile</th>
<th>P-value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal baseline and variability (187)</td>
<td>2.3</td>
<td>1.4-4.8</td>
<td></td>
</tr>
<tr>
<td>Reduced variability (113)</td>
<td>2.3</td>
<td>1.3-4.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Absent variability (32)</td>
<td>2.6</td>
<td>1.2-6.9</td>
<td>0.373</td>
</tr>
<tr>
<td>Increased variability (7)</td>
<td>3.1</td>
<td>1.8-6.8</td>
<td>0.077</td>
</tr>
<tr>
<td>Bradycardic episode (36)</td>
<td>3.3</td>
<td>1.3-8.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachycardia (106)</td>
<td>3.0</td>
<td>1.7-6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tachycardia + reduced variability (128)</td>
<td>2.5</td>
<td>1.4-5.2</td>
<td>0.204</td>
</tr>
<tr>
<td>Severe variable decelerations (97)</td>
<td>3.4</td>
<td>2.0-6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations (49)</td>
<td>3.2</td>
<td>2.4-4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + reduced variability (28)</td>
<td>3.8</td>
<td>1.8-5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + reduced variability (34)</td>
<td>4.5</td>
<td>2.7-6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe variable decelerations + tachycardia (33)</td>
<td>4.4</td>
<td>1.9-7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late decelerations + tachycardia (30)</td>
<td>4.2</td>
<td>2.1-6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing + undefinable pattern (8)</td>
<td>4.1</td>
<td>2.1-8.1</td>
<td>0.013</td>
</tr>
<tr>
<td>Total (888)</td>
<td>2.8</td>
<td>2.1-4.0</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Cases with active pushing prior to sampling excluded

\(b\) p-value calculated with Mann-Whitney U-test comparison with normal baseline and variability
Study 3

Firstly a univariate logistic regression was performed including 21 potential risk factors for lactate >4.8 mmol/L (table 10). In cases where repetitive scalp blood samples had been performed, only the first sample was included in this analysis.

The analysis showed a significant result for language barriers (minor) (OR 2.54; CI 1.26-5.11), stage of labor at sampling (active bearing down) (OR 2.46; CI 1.12-5.39) and maternal height (<155 cm) (OR 2.15; CI 1.08-4.26). Epidural analgesia at sampling turned out as a significant protecting factor (OR 0.60; CI 0.37-0.97).

An analysis of language barriers compared with maternal height showed that women with language barriers were significantly shorter than women without language barriers (13.4% of women with language barriers were <155 cm compared with 4.7% of women without language barriers; p<0.05). This information supported a theory that maternal height is an intermediate for language problems. Therefore maternal height was removed from further analysis. A multivariate logistic regression analysis was performed (table 11). Minor language barriers (OR 2.21; CI 1.05-4.67) and active pushing (OR 2.68; CI 1.20-6.00) turned out as significant risk factors.

When excluding women in active pushing only epidural remained as a significant protecting factor (OR 0.54, CI 0.32-0.91).
Table 10. Univariate logistic regression

<table>
<thead>
<tr>
<th>Risk factors (N=1070)</th>
<th>Numbers (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Language barriers</strong> (N=1068)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>831 (77.8)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Minor</td>
<td>62 (5.8)</td>
<td>2.54 (1.26-5.11)</td>
<td>0.009</td>
</tr>
<tr>
<td>Major</td>
<td>175 (16.4)</td>
<td>1.35 (0.78-2.34)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Stage of labor at sampling (N=1014)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation 3-6 cm</td>
<td>340 (33.5)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Cervical dilatation 7-10 cm</td>
<td>385 (38.0)</td>
<td>0.87 (0.51-1.48)</td>
<td>0.62</td>
</tr>
<tr>
<td>Cervix fully dilated</td>
<td>237 (23.4)</td>
<td>0.75 (0.40-1.41)</td>
<td>0.37</td>
</tr>
<tr>
<td>Active pushing</td>
<td>52 (5.1)</td>
<td>2.46 (1.12-5.39)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Maternal height</strong> (N=1043)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥155cm</td>
<td>974 (93.4)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>&lt;155cm</td>
<td>69 (6.6)</td>
<td>2.15 (1.08-4.26)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Epidural analgesia at sampling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>208 (19.4)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>862 (80.6)</td>
<td>0.60 (0.37-0.97)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;41 weeks</td>
<td>722 (67.5)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>≥41 weeks</td>
<td>348 (32.5)</td>
<td>1.53 (0.99-2.36)</td>
<td>0.053</td>
</tr>
<tr>
<td><strong>Quality of amniotic fluid (N=1064)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>555 (52.2)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Other</td>
<td>509 (47.8)</td>
<td>1.50 (0.97-2.30)</td>
<td>0.066</td>
</tr>
<tr>
<td><strong>Preeclampsia/hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>988 (92.3)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>82 (7.7)</td>
<td>0.37 (0.12-1.21)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>In vitro fertilization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1026 (95.9)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>44 (4.1)</td>
<td>0.23 (0.03-1.71)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 years</td>
<td>863 (80.7)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>&gt;35 years</td>
<td>207 (19.3)</td>
<td>1.31 (0.79-2.16)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Maternal body mass index</strong> (N=1030)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>32 (3.1)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>620 (60.2)</td>
<td>1.13 (0.33-3.84)</td>
<td>0.84</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>253 (24.6)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>86 (8.3)</td>
<td>1.04 (0.62-1.75)</td>
<td>0.88</td>
</tr>
<tr>
<td>&gt;35.0</td>
<td>39 (3.8)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>0.59 (0.14-2.52)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>772 (72.1)</td>
<td></td>
<td>Ref</td>
</tr>
<tr>
<td>Multiparous without previous caesarean</td>
<td>189 (17.7)</td>
<td>0.93 (0.54-1.61)</td>
<td>0.80</td>
</tr>
<tr>
<td>Multiparous with previous caesarean</td>
<td>109 (10.2)</td>
<td>0.65 (0.26-1.61)</td>
<td>0.36</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------</td>
<td>------------------</td>
<td>------</td>
</tr>
<tr>
<td>Nicotine use prior to or during pregnancy (N=1055)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>880 (83.4)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>175 (16.6)</td>
<td>0.80 (0.44-1.48)</td>
<td>0.48</td>
</tr>
<tr>
<td>Time from rupture of membranes to sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤18 hours</td>
<td>937 (87.6)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>&gt;18 hours</td>
<td>133 (12.4)</td>
<td>0.83 (0.42-1.63)</td>
<td>0.58</td>
</tr>
<tr>
<td>Fever prior to sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>961 (89.8)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>109 (10.2)</td>
<td>1.19 (0.61-2.30)</td>
<td>0.61</td>
</tr>
<tr>
<td>Oxytocin prior to sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>418 (39.1)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>652 (60.9)</td>
<td>0.90 (0.58-1.38)</td>
<td>0.61</td>
</tr>
<tr>
<td>Time in active labor prior to sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 hours</td>
<td>1010 (94.4)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>≥12 hours</td>
<td>60 (5.6)</td>
<td>1.16 (0.49-2.78)</td>
<td>0.73</td>
</tr>
<tr>
<td>Fetal weight&lt;sup&gt;d&lt;/sup&gt; (N=1068)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>48 (4.5)</td>
<td>1.17 (0.45-3.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>Appropriate for gestational age</td>
<td>987 (92.4)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>33 (3.1)</td>
<td>---</td>
<td>0.99</td>
</tr>
<tr>
<td>Fetal gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>518 (48.4)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Male</td>
<td>552 (51.6)</td>
<td>0.93 (0.61-1.42)</td>
<td>0.75</td>
</tr>
<tr>
<td>Diabetes&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1042 (97.4)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (2.6)</td>
<td>0.79 (0.19-3.40)</td>
<td>0.76</td>
</tr>
<tr>
<td>Night time blood sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00-19:00</td>
<td>429 (40.1)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>19:00-7:00</td>
<td>641 (59.9)</td>
<td>1.03 (0.67-1.59)</td>
<td>0.88</td>
</tr>
<tr>
<td>Induced labor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>690 (64.5)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>380 (35.5)</td>
<td>1.03 (0.66-1.60)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

a) Major language barriers=assistance of interpreter
   Minor language barriers=not fluent Swedish-speaking, use of 2nd language or relative as interpreter
b) Other=Blood or meconium in the amniotic fluid
c) Maternal weight in kilograms divided by the square of maternal height in meters
d) Small for gestational age is defined as fetal weight below two standard deviations
   Large for gestational age is defined as fetal weight below two standard deviations
e) Diabetes diagnosed in medical records at any time during the present pregnancy
Table 11. Multivariate logistic regression

<table>
<thead>
<tr>
<th>Risk factors (N=1070)</th>
<th>Numbers (%)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language barriersa (N=1068)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>831 (77.8)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>62 (5.8)</td>
<td>2.21</td>
<td>1.05-4.67</td>
</tr>
<tr>
<td>Major</td>
<td>175 (16.4)</td>
<td>1.16</td>
<td>0.63-2.12</td>
</tr>
<tr>
<td>Stage of labor at sampling (N=1014)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation 3-6 cm</td>
<td>340 (33.5)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation 7-10 cm</td>
<td>385 (38.0)</td>
<td>1.03</td>
<td>0.59-1.78</td>
</tr>
<tr>
<td>Cervix fully dilated</td>
<td>237 (23.4)</td>
<td>0.95</td>
<td>0.49-1.83</td>
</tr>
<tr>
<td>Active pushing</td>
<td>52 (5.1)</td>
<td>2.68</td>
<td>1.20-6.00</td>
</tr>
<tr>
<td>Epidural analgesia at sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>208 (19.4)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>862 (80.6)</td>
<td>0.63</td>
<td>0.38-1.07</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;41 weeks</td>
<td>722 (67.5)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>≥41 weeks</td>
<td>348 (32.5)</td>
<td>1.39</td>
<td>0.87-2.22</td>
</tr>
<tr>
<td>Quality of amniotic fluid (N=1064)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>555 (52.2)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Otherb</td>
<td>509 (47.8)</td>
<td>1.40</td>
<td>0.88-2.22</td>
</tr>
<tr>
<td>Preeclampsia/hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>988 (92.3)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>82 (7.7)</td>
<td>0.52</td>
<td>0.16-1.73</td>
</tr>
<tr>
<td>In vitro fertilization</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1026 (95.9)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (4.1)</td>
<td>0.30</td>
<td>0.04-2.22</td>
</tr>
</tbody>
</table>

a) Major language barriers = assistance of professional interpreter

b) Minor language barriers = not fluent Swedish-speaking, use of 2nd language or relative as interpreter

b) Other=Blood or meconium in the amniotic fluid
Study 4

77 women in labor were included in the study. When including the first Cx-lac from every woman the median concentration of lactate was 3.7 mmol/L (range 1.1-14.8).

Concentrations of Cx-lac differed between women with spontaneous and operative delivery (vaginal or caesarean) (median 2.9 vs 4.6 mmol/l; p<0.05) (figure 9). When dividing women into three groups according to mode of delivery (spontaneous, instrumental vaginal and caesarean) the results had the same tendency but were not significant (median 2.9 vs 5.7 vs 4.2 mmol/l; p=0.07).

![Figure 9. Box-plot of cervical lactate by mode of delivery.](image)

Cx-lac concentration was compared between women who before sampling had or had not crossed a two hour delay action line in the partogram (4.6 vs 3.1 mmol/l; p=0.079).

Correlations between cervical dilatation and Cx-lac (r=0.45; p<0.05), (figure 10), cervical dilatation and FBS-lactate (N=76; r=0.05; p=0.66) and FBS-lac and Cx-lac (N=76; r=0.35; p<0.05) were calculated.
Correlation between AF-lac and Cx-lac was also calculated (N=26; \( r=0.25; p=0.22 \)).

A univariate linear regression model between Cx-lac (independent) and FBS-lac (dependent) was performed, resulting in a \( \beta \)-value of 0.17 (\( R^2=0.16; p<0.0007 \)). Univariate linear regression with AF-lac as independent and Cx-lac as dependent variable (N=20) showed no significance (\( \beta=-0.04, R^2=0.18; p=0.58 \)).

One concern was confounding due to a correlation between cervical dilatation and delivery mode. The women were therefore divided into two groups according to cervical dilatation (3 to 6 and 7 to 10 centimeters). The proportions of operative interventions were the same in the groups with lactate sampling in early and late first stage of labor (73.3% vs 68.8%; \( p=0.66 \)).
5 DISCUSSION

Study 1

Main findings

Single values of STV from 100 women were collected with a median value of 7.1 msec (range 1.3-25.9). There was no difference in STV between early or late labor.

In the comparison between internal and external monitoring the internal device calculated lower values than the external one in the lower range of STV (<8 msec), while the opposite was found in the higher range.

STV values derived from Sonicaid Fetal Care™ and EDAN™ antenatal showed good agreement.

Strengths and limitations

It is a strength that the use of the CTG machines was performed by a limited amount of clinical staff aware of the method.

The population is small and unselected. Therefore this material cannot be used to predict cut-off values for STV in the identification of acidemic fetuses.

A limitation when comparing the different brands of machines is differences in signal loss. This limitation is in principal eliminated by the fact that both machines have a limit for signal loss, where they no longer calculate STV.

Interpretation

Evaluation of a new method must start with methodological investigation. We need to know how to use the machine before we start to evaluate the method for clinical use. STV has been evaluated antenatally as a part of algorithms, but not appropriate as a stand-alone method or for intrapartum use.85, 91, 93, 94, 108-110

The population in this study is too small and too selected to be useful in generating cut-off values for STV. Nevertheless, the material gives advices about how to continue in further
studies. All women in first stage of labor could be grouped irrespective cervical dilatation. Further intrapartum studies of STV should be performed with internal monitoring.

The differences in STV between internal and external monitoring are most likely a true difference. External monitoring detects fetal heart rate from motions in the fetal heart and use the information to calculate STV. Internal monitoring is built on the fetal electrocardiogram a much more assured method. The clinical experience supports this. It is much more difficult to evaluate fetal heart rate variability in a CTG trace acquired with external monitoring than internal monitoring.

Sonicaid™ is previously well evaluated for antenatal use. Since EDAN™ uses the same algorithm to calculate STV it was likely that the antenatal recordings would be in concordance. This finding confirms that the same cut-off values could be used antenatally.

STV is a potential complement to CTG in intrapartum monitoring. The method is now evaluated in a computerized system. If STV works as a stand-alone method in intrapartum monitoring is not fully evaluated. Previous studies are small and the outcomes are rare. The method need a proper fully evaluation.

Study 2

Main findings

A normal CTG trace or a CTG trace with isolated reduced variability is seldom associated with a high lactate concentration at FBS. Fetuses presenting CTG traces with severe variable decelerations and late decelerations had the same amount of high lactate concentration. The highest prevalence of elevated lactate concentration was among fetuses with CTG traces with late or severe variable decelerations and coexistence of tachycardia.

Strengths and limitations

The liberal use of FBS and the design with all laboring women included in the study are strengths in this study. Both in the study and in the labor department, strict CTG guidelines were used. There could be a question if it is a benefit that a single reviewer interpreted all CTG traces. A single experienced reviewer excludes all problems with interobserver
variability, so in this case it can be regarded as a strength. The CTG interpretation has after the study been validated in another study.79

The limitation with largest impact is that we did not take the duration of CTG pattern into consideration. The analysis would have been too complex to draw clinical conclusions about. Another limitation is selection bias. Since we had a high amount of FBS sampling and even a large group with normal CTG traces there is unlikely that the threshold to take FBS has been too low. There is a chance that some severe CTG patterns have resulted in immediately delivery instead of FBS and that the results in the more severe CTG groups are even higher. It is unlikely that less severe CTG patterns resulted in the same so we consider our results in these groups reliable.

**Interpretation**

The reason for correlating CTG changes to FBS is the possibility to prevent fetal distress. There are few previous studies correlating intrapartum CTG changes to FBS.169-171 These studies were performed over 30 years ago and included between 85 and 279 women. A lot of changes have taken place both in CTG interpretation and FBS sampling since then. This is also the first study which correlates CTG changes to lactate in FBS, instead of pH.

The finding that isolated reduced variability had the same amount of elevated lactate concentration as a normal CTG trace is clinically important. It means that we either should not perform FBS when a CTG trace shows isolated variability or just take a single sample to exclude acidemia. Isolated reduced variability should not be regarded as a sign of hypoxia.

Previous studies have concluded that late decelerations are a severe sign. There is an association with chronic and acute hypoxia, often caused by a dysfunctional placenta.51, 172, 173 Variable decelerations have another origin, usually from compression of the umbilical cord.174 Despite the differences in origin the results from this study shows similar proportions of lactacidemia in FBS for the two types of decelerations. This is a valuable finding since it makes differentiation between the types of decelerations less important and excludes a reason for interobserver variability.

The great benefit with CTG is its high sensitivity. In this study, there is a frequency of 2.5% with elevated lactate concentration in the group with normal CTG traces. CTG has previously been considered to have a sensitivity of 80% detecting a cord artery pH below 7.17 by
CTG\textsuperscript{175} and 97\% to detect a cord artery pH below 7.15.\textsuperscript{176} Compared to these results the sensitivity of 97.5\% in this study is beyond expectation.

## Study 3

### Main findings

This study suggests three significant risk factors for lactacidemia; language barriers, active pushing and maternal height less than 155 cm. Epidural analgesia seems to be a protecting factor in this study.

### Strengths and limitations

The high proportion of deliveries monitored with FBS makes the results of this study more generalizable. Classification bias was minimized since only two persons, who worked close to each other, collected all data.

The strongest limitation is that this study included 21 risk factors in a population of 1070 women. These increase the risk of false positive results due to chance. Another limitation is that this is a secondary analysis of a previous study.\textsuperscript{177}

A possible problem in this study is the time component. To take away most of the effect of this problem all risk factors are just coded as risk factors if they were present at sampling. Active pushing could be a problem and therefore the analysis is also performed excluding women in active pushing.

### Interpretation

That language barrier turned out as an independent risk factor among many other more general acceptable is notable. Previous studies have shown that immigration is a risk factor for different unsolicited outcomes in obstetrics.\textsuperscript{178-181} One suggested explanation is suboptimal care.\textsuperscript{182,183} Communication problems are common among immigrants and it is therefore plausible that a part of the suboptimal care is language barriers. Since minor
language barriers was a risk factor but major was not it is likely to believe that this risk factor could be affected positively by routinely use of professional interpreters.

The active part of second stage of labor is hard for the fetus, the contractions decreases placental perfusion and cause intermittent fetal hypoxemia. Previous studies support that this stage of labor is though for the fetus. Lower cord artery pH is found in vaginal deliveries compared to caesarean section during first stage of labor.\textsuperscript{184} Stable concentrations of lactate is found when performing FBS in first stage of normal labor, but during second stage of labor fetal scalp lactate increases with 1 mmol/l per 30 minutes of active bearing down.\textsuperscript{130} There are two ways to handle this information. One is to use higher cut-off values for interventions during second stage of labor.\textsuperscript{131} If so we need to proof and believe that lactate concentration has increased by physiological reasons during second stage of labor. It is unclear if it is physiological or represent that this part of the delivery is harder for the fetus. To secure the fetus we need to be careful when using FBS during second stage of labor. It is important to balance all information and to seriously consider assisted delivery if possible.

Short stature has previously been correlated to adverse neonatal outcome.\textsuperscript{37, 185} In this study we could see a connection between short stature and language barriers, why we interpreted short stature as an intermediate factor. It is possible that short maternal stature is associated with low socioeconomic status, another known risk.\textsuperscript{5} Another explanation is that shortness is a risk factor for cephalo-pelvis disproportion.\textsuperscript{186, 187}

In previous studies epidural analgesia has been presented as a risk factor for adverse neonatal outcome.\textsuperscript{20, 37} This is opposite to the results from the present study. One explanation could be a healthy user effect; healthy women with normal labors are more likely to get an epidural. An epidural could decrease the woman’s levels of stress-hormones and thereby have positive effects on the woman’s circulation and give better recovery potential for the fetus.\textsuperscript{188} Women with epidural analgesia are usually more monitored during labor and therefore they got the benefits of more present staff, a beneficial factor.\textsuperscript{189}

Surprisingly few of the previously known risk factor turned out as significant risk factors in this study. It is possible that knowledges about these risk factors might have affected clinical management.\textsuperscript{40, 190}
Study 4

Main findings

It was easy to collect fluid samples from the cervix and the women seemed to tolerate the procedure well. The equipment for FBS was suitable to use. Since the fluid does not look like blood it is more appropriate to call it cervical fluid.

There is an increase in Cx-lac with progress in labor. Lactate concentration in cervix correlates to mode of delivery and seems to be a risk factor for operative delivery. Fetal lactate is mainly of fetal origin and there is no increase in lactate concentration in fetal scalp blood with progress in labor.

Strengths and Limitations

The research group is experienced in research around FBS. The results from the analysis of Cx-lac and AF-lac were blinded for the attending obstetrician.

The small study population is a limitation. This might have restricted the statistical power especially in the analysis including amniotic fluid. This study has a long study period compared to the population size, this is due to priority of another trial during a part of the study period.

Only patients with indication for FBS were included in the study. This reduces the generalizability, but was necessary due to ethical reasons, since this method has not been evaluated before.

Interpretation

In sport medicine lactate is an established factor linked to performance.\textsuperscript{152, 153, 191} Since the uterus is a muscle it is likely to believe that lactate would affect the efficiency of uterine contractions. This is supported by previous studies of capillary blood samples from the hysterotomy at caesarean sections and a study that have linked increased concentration of lactate to decrease in the frequency and force of uterine contractions.\textsuperscript{147, 148, 150} The results from this study suggest that high concentration of Cx-lac correlates with the risk for operative delivery is in concordance with this. One more supportive finding in this direction would have been higher Cx-lac in women who had crossed a two-hour action line in the partogram compared to those who had not, the results in this study had a tendency towards this but were not significant (p=0.079).
In this study there was no significant correlation between lactate concentrations in cervical fluid and amniotic fluid \((r=0.25; p=0.22)\). Previous studies have linked lactate concentrations in amniotic fluid to labor dystocia.\(^{162,163}\) The results from the present study suggest that the lactate in amniotic fluid has other origin than the uterine muscle.

There was no correlation between lactate concentration in FBS and cervical dilatation which is in concordance with previous studies.\(^{122,123,192}\) Since the linear regression model showed a \(\beta\)-value of 0.17 we consider that the transfer of lactate from uterus to fetus is limited, despite the finding of a moderate correlation between fetal scalp and cervical lactate \((r=0.35)\), and the linear regression model is in line with previous studies.\(^{123,124}\)
6 CONCLUSIONS

- Calculation of STV differs between internal and external monitoring.
- There are no differences in STV between early and late first stage of labor.
- Established antenatal cut-off values for Sonicaid™ can be used for EDAN™.
- STV might be a potential tool in intrapartum monitoring.
- Isolated reduced variability is not associated with increased rate of fetal acidemia and therefore does not require repeated FBS.
- Severe variable decelerations and late decelerations correlate equally with fetal acidemia.
- Language barriers, active pushing and maternal short stature seem to be risk factors for intrapartum asphyxia.
- A professional interpreter seems to decrease the risk for intrapartum asphyxia why all women with language barriers should be offered a professional interpreter.
- During second stage of labor and especially during active pushing the fetus should be closely monitored and the value of FBS should be considered in relations to the effect of assisted vaginal deliveries.
- Cervical lactate increases during the delivery process.
- Cervical lactate do not contribute to the lactate levels in the fetus.
- Cervical lactate is a possible clinical tool to predict the risk for operative delivery.
7 FUTURE PERSPECTIVES

• The results from study 1 suggest several methodological findings to take into consideration in further studies of STV. Previously published articles stress the value of proper evaluation of STV both as a part in computerized intrapartum monitoring and as a stand alone method. Our research group has started a cooperation with KTH Royal Institute of Technology and has began the work to find intrapartum cut-off values for STV from a larger material derived from the intrapartum monitoring system Milou™. If we succeed in this a possibility would be a RCT to compare intrapartum CTG monitoring with or without STV.

• During the study period for study 2 and 3 we performed FBS in 10.5% of all deliveries at Karolinska University Hospital in Solna. Since this cohort was collected SFOG has published new CTG guidelines, partly influenced by the study results from study 2. There have also been improvements in CTG education at the department. Today the FBS frequency is 2.8% of all deliveries and 3.1% if elective caesareans are excluded. There is a need to exclude that this decrease has affected outcomes. We therefore plan to perform a comparison of neonatal outcomes and intervention rate between the study period for study 2 and 3 and 2016.

• All intrapartum monitoring should be performed in a context. Previously published studies have suggested CTG differences between male and female fetal gender. Since we have access to a database with detailed interpretation of 2134 CTG traces we plan to perform a study comparing CTG patterns between male and female fetuses.

• The results from study 3 suggests that language barriers is a risk factor for adverse neonatal outcome, in the Swedish context. With an increasing immigrant population language barriers will be an important issue for health care professionals to deal with. Further studies are needed about how language barriers and access to interpreters affects medical outcomes as operative deliveries, frequency of perineal tears, bleeding complications and neonatal outcomes.

• Our results from study 4 suggest that cervical lactate might be a predictor for operative deliveries. We would like to perform a bigger study with a more heterogeneous population with different progress in labor to evaluate how cervical lactate correlates with progress in labor and mode of delivery.
Bakgrund

Målet med förlossningsvård är alltid ett frisk nyfött barn till en välmående nybliven mamma, utan onödiga medicinska åtgärder eller ingrepp. Våra medicinska nødutgångar i form av sugklockeförlossningar och kejsarsnitt är säkra, men vi vet att för befolkningen som helhet är vinsterna med att hålla nere antalet ingrepp stora. För det enskilda barnet eller kvinnan kan dock ingreppet vara livsnödvändigt. För att veta hur vi skall hantera denna finstämda balans är våra övervakningsmetoder för förlossningar avgörande.

För människan är födelsen livets största utmaning. Efter en oftast optimal tillvaro i livmodern påverkas fostret plötsligt av värkar. Värkarna påverkar blodtillförseln från kvinnan till fostret och detta kan under vissa omständigheter leda till syrebrist och mjölksyreansamling hos fostret. I mildare form kan fostret hantera detta och vårdpersonalen handla i tid, men i sällsynta fall leder detta fram till permanenta hjärnskador hos fostret. Allvarliga hjärnskador som t.ex. cerebral pares (CP) kan bero på syrebrist under förlossningen, även om det oftast beror på något annat.

Inom läkarkåren och barnmorskekåren finns en stor erfarenhet. Vi baserar inte sällan våra beslut om särskild övervakning av kvinna och foster på just denna praktiska erfarenhet. Besluten blir då baserade på sådana karaktäristika och symtom som vi subjektivt uppfattar som riskfaktorer. Det finns därför ett behov av att dokumentera och systematisera våra erfarenheter så vi kan bevisa vad som verkligen är riskfaktorer för vad.


När en CTG registrering är normal vet vi att fostret i magen mår bra. Vi kan också snabbt se om fostret blir akut påverkat under förlossningen. Emellan dessa ytterligare finns dock CTG registreringar som är svåra att bedöma. För att personalen på förlossningen skall veta hur fostret mår och hur de ska handlägga förlossningen vidare behövs då kompletteringsmetoder.

Den vanligaste orsaken till kejsarsnitt under pågående förlossning är inte hotande syrebrist hos barnet utan värksvaghet hos kvinnan. För att övertaka hur förlossningen går framåt använder vi i huvudsak upprepade gynekologiska undersökningar där vi med våra fingrar uppskattar hur mycket livmodertappen har öppnat sig och hur långt barnets huvud har kommit ned. Resultaten av dessa undersökningar skriver vi in i ett partogram (en kurva över hur förlossningen framskrider), med stödlinjer för hur genomsnittsförlossningen framskrider. För att veta vilka kvinnor som drabbas av värksvaghet har vi idag inga andra verktyg, vilket innebär att tiden blir central.

Tankar har funnits på om det finns någon metod för att tidigt i förlossningsförloppet ta reda på vilka kvinnor som löper risk för värksvaghet och kejsarsnitt. I tidigare studier har man visat att kvinnor som genomgår kejsarsnitt har högre halter av laktat i livmodermuskeln än vad kvinnor som genomgår kejsarsnitt av andra orsaker har. Detta har lett fram till frågan om en livmoder kan få ”mjölksyra” precis som en löpare eller skidåkare kan få.

**Studie 1**

Eftersom det är svårt att tolka CTG registreringar och det även förekommer stor variation i tolkningen mellan olika läkare och barnmorskor har tanken väckts om datoriserad CTG-tolkning. Redan under 1980 talet utvecklades detta för CTG registrering under graviditeten, men under förlossningen blir fostrets hjärtrytm mer komplex och därför har det varit svårare att utveckla datoriserad tolkning för detta. I den datoriserade tolkning under graviditet läggs stor vikt vid korttidsvariabilitet (STV – short – term – variation), som är en teoretiskt uträknad slag till slag variation i fostrets hjärtrytm. Låga värden har visat sig korrelera med fosterdöd under graviditet.

Studie 1 i denna avhandling är en metodologiskstudie som syftar till att utvärdera STV för förlossningsbruk. Vi har dels samlat in enskilda STV-värden från 100 kvinnor för att se hur
materialet fördelar sig. Vi har också jämfört STV-värden mellan tidig och sen förlossning och funnit att det inte finns någon skillnad. Vi har övervakat samma foster med både dosa på kvinnans mage och elektrod på huvudet och funnit att STV-värden skiljer sig åt mellan dessa metoder. Eftersom metoden inte tidigare används under förlossning har vi också jämfört maskinen för övervakning under graviditeten (sedan tidigare väl utvärderad) med en helt ny maskin som inte tidigare används för STV övervakning. Denna utvärdering visade att maskinerna är likvärdiga.

Slutsatserna från denna studie är att det finns möjligheter att använda STV i förlossningsövervakning. Det är dock viktigt att skilja normalvärden mellan registrering med dosa på magen och registrering med elektrod vis fostrets huvud. De två CTG maskiner som finns på den svenska marknaden visar samstämmiga värden på STV och samma gränsvärden kan användas för båda maskinerna.

**Studie 2**

För att underlätta tolkning av CTG finns det riktlinjer för tolkning, i Sverige använder vi oss av Svensk förening för obstetrik och gynekologis (SFOG:s) riktlinjer. Enskilda CTG-mönster är i tidigare studier korrelerade till olika komplikationer hos det nyfödda barnet. I denna studie var syftet att gruppera CTG-kurvor efter olika mönster och jämföra laktatnivåer i fosterblodet (vid FBS) mellan de olika grupperna. Tanken var att genom att kunna veta vilka CTG-förändringar som speglar en påverkan på fostret under pågående förlossning kunna förhindra och inte förutse en hotande syrebrist.

I denna studie fann vi att foster med normalt CTG och CTG med endast nedsatt variabilitet hade en låg risk för höga koncentrationer av laktat i blodet (2.5%). Nedsatt variabilitet har tidigare varit ett vanligt skäl till FBS och vetskapen om att denna förändring innebär en låg risk gör att vi kan minska antalet provtagningar.

Högst risk för höga nivåer av laktat i blodet hade foster med en förhöjd grundnivå av hjärtfrekvensen kombinerat med olika typer av återkommande avancerade nedgångar i hjärtfrekvensen (20-25%). Dessa typer av nedgångar i hjärtfrekvens har helt olika fysiologiskt ursprung och vetskapen om att de är lika allvarliga förenklar arbetet med fosterövervakning.
**Studie 3**

För att veta hur vi skall övervaka kvinnan och fostret under förlossningen behöver vi veta vilka riskfaktorer som vi behöver ta hänsyn till. Detta är tidigare studerat för olika typer av hjärnskador. Att veta vilka riskfaktorer som leder till hjärnskador är viktigt, men ännu viktigare är att veta vilka riskfaktorer som är kopplade till tidiga tecken på syrebrist och som därigenom kan hjälpa oss att förebygga detta.


Aktiv krystning utgjorde också en mer än fördubblad risk för höga laktat. Detta är känt sedan tidigare och stärker viken av att övervaka mer aktivt och vara mer benägen till snabba åtgärder när en födande kvinna krystar.

**Studie 4**

I nuläget är det tiden som får utvisa om en födande kvinna har drabbats av värksvaghet. Att låta ett foster uppleva värkarbete utgör en bra förberedelse för att kunna födas, men vi vet att en långdragen förlossning ökar riskerna för komplikationer både hos fostret och kvinnan.

I studie 4 har vi försökt hitta en möjligt sätt att förutse värksvaghet. Sedan tidigare vet vi att man har uppmätt höga nivåer av laktat i livmodern vid kejsarsnitt p.g.a. värksvaghet. Vid själva kejsarsnittet är redan beslutet om hur förlossningen skall avslutas gjort. För att kunna vara en hjälp i hur vi skall handlägga förlossningen behöver vi ha informationen tidigare.

Under en förlossning är den enda del av livmodern som är tillgänglig för provtagning livmodertappen. I denna studie har vi därför via en gynekologisk undersökning tagit pröver på vätskan i livmodertappen under aktiv förlossning och analyserat laktatkoncentrationen i
dessa. Informationen om dessa laktat värden har vi studerat i relation till hur förlossningen har framskridit, förlossningssätt och laktatnivåer hos fostret.

I denna studie fann vi en skillnad i laktatkonzentrationer mellan kvinnor som födde spontant och kvinnor som blev förlösta med sugklocka eller kejsarsnitt. Vi såg också att laktatkonzentrationen steg ju mer livmodertappen öppnade sig. I jämförelsen mellan laktat i livmodertappen och laktat hos fostret kunde vi se att laktat i fostret i huvudsak produceras av fostret självt.

Denna studie visar att det är möjligt att mäta laktat i livmodertappen och att det finns en möjlighet att laktatprovtagning skulle kunna vara ett sätt att förutse värksvaghet.
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