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LACTATE AS AN EARLY MARKER OF INTRAPARTUM FETAL HYPOXIA

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"It is evident that the problem
of categorizing FHR patterns
in a meaningful and objective way
will be a sizable task."
Edward Hon 1963

"This is adding apples and oranges to pears
and comparing them to grapefruit."
Dr Preston's criticism on the
Denver study 1979

To meet the eyes of a newborn baby
Pure magic – the world stops turning

How can eyes that have seen nothing
Be filled with oceans and stars

To share these moments
Every day at work
Is the greatest
Privilege

To my parents

ABSTRACT

Background: Cardiotocography (CTG) is the main method for intrapartum fetal surveillance in many countries. The method has a high sensitivity, but a poor specificity, which leads to an increased rate of interventions compared with auscultation. Fetal scalp blood sampling (FBS) was developed parallel to CTG, and can be used as an adjunct to diagnose or exclude fetal acidemia when the CTG tracing is non-reassuring. Lactate analysis has been shown as reliable as gold standard pH analysis, and FBS with lactate analysis has the advantages of a lower failure rate, shorter time from sampling to analysis result, and lactate concentration identifies the metabolic component of acidemia in contrast to pH. However, since guidelines for CTG interpretation cannot be regarded as fully evidence-based, neither can guidelines for the use of FBS. The aim of this thesis was to further increase the knowledge of FBS and measurements of fetal lactate concentrations as an adjunct in intrapartum fetal surveillance.

Materials and Methods: The study populations consisted of women with a simplex pregnancy, gestational age ≥34 weeks, cephalic presentation and indication for FBS during labor. The cohort in studies I and II were women who had participated in a former RCT at ten obstetric units in Sweden. Study I included all 2992 women randomized to either pH-, or lactate analysis, and Study II included the 1496 women with lactate analysis. The cohort in studies III and IV were all consecutive women with FBS during labor at Karolinska University Hospital Solna, Sweden, during two years. In the 1st cohort, the 95th percentile of all lactate values and the 5th percentile of all pH values were used as the definition of severe intrapartum acidemia and frequencies of adverse neonatal outcome were calculated. The neonates were classified according to birth weight as small/appropriate/large, and medians in lactate concentration at FBS were calculated in the total population as well as in acidemic cases. Neonatal outcome was analyzed according to birth weight groups. In the 2nd cohort, all CTG traces prior to FBSs were interpreted, and CTG patterns were correlated to acidemia at FBS. Delivery mode and neonatal outcome were analyzed in relation to number of FBSs during labor, 1-2 vs ≥ 3.

Results: The risk of serious adverse neonatal outcome was 10 % or less in the high risk groups with severe intrapartum acidemia, and time interval from FBS to delivery was shorter in the pH group. In comparison between birth weight groups, the median lactate concentration at FBS in acidemic fetuses did not differ, nor did the proportion of acidemic fetuses at FBS or neonatal outcome. A CTG tracing with isolated reduced variability did not increase the risk of acidemia at FBS, severe variable decelerations and late decelerations correlated equally to acidemia, and tachycardia with either of those decelerations had the highest prevalence of acidemia. Neonatal outcome did not differ in labors with ≥ 3 FBS compared with 1-2 FBS, but cesarean delivery rate was 42 % vs 23 %, with an adjusted odds ratio of 2.0.

Conclusions: Acidemia in scalp blood is an early marker of intrapartum fetal hypoxia, and FBS can be used to prevent severe birth acidemia. Lactate might react earlier than pH in the hypoxic process. Small for gestational age fetuses can produce equally amounts of lactate as a response to hypoxia as normally grown fetuses, and FBS with lactate analysis is a reliable surveillance method also for growth restricted fetuses in labor. A CTG tracing with isolated reduced variability does not necessitate repeated FBS during labor. The two types of serious decelerations correspond equally to fetal acidemia and distinguishing them is not crucial. Monitoring women with repeated FBS during labors with CTG changes is safe for the fetus, but the rate of cesarean delivery is doubled as compared to labors where 1-2 FBS are needed.

Key words: cardiotocography, fetal blood sampling, fetal acidemia, fetal hypoxia

LIST OF PUBLICATIONS

I. Holzmann M, Cnattingius S, Nordstrom L.
Outcome of severe intrapartum acidemia diagnosed with fetal scalp blood sampling.
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III. Holzmann M, Wretler S, Cnattingius S, Nordström L.
Cardiotocography patterns and risk of intrapartum fetal acidemia
Submitted.

IV. Holzmann M, Wretler S, Cnattingius S, Nordström L.
Neonatal outcome and delivery mode after repetitive fetal blood sampling during labor.
Submitted

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LIST OF ABBREVIATIONS AND DEFINITIONS

ACOG	American College of Obstetricians and Gynecologists
AGA	Appropriate for gestational age
ATP	Adenosine triphosphate
BD	Base deficit
BE	Base excess
CO_2	Carbon dioxide
CTG	Cardiotocography
DNA	Deoxyribonucleic acid
ECF	Extracellular fluid
EFM	Electronic fetal monitoring
FBS	Fetal scalp blood sampling
FHR	Fetal heart rate
FIGO	Fédération International Gynecologie et Obstetriciens
H^+	Hydrogen ion
HbA	Adult Hemoglobin
HbF	Fetal Hemoglobin
HCO_3^-	Bicarbonate
H_2CO_3	Carbonic acid
H_2O	Water
HIE	Hypoxic ischemic encephalopathy
IUGR	Intrauterine growth restriction
LGA	Large for gestational age
MAS	Meconium aspiration syndrome
Mmol	Millimoles
NADH	Nicotinamide adenine dinucleotide
NICE	National Institute for Health and Clinical Excellence
NICHHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
O_2	Oxygen
OR	Odds ratio
pH	Power of hydrogen
RANZCOG	The Royal Australian and New Zeeland College of Obstetricians and Gynaecologists
RCT	Randomized controlled trial
RCOG	Royal College of Obstetricians and Gynaecologists
SD	Standard deviation
SGA	Small for gestational age
SMFM	Society of Maternal and Fetal Medicine
SOGC	The Society of Obstetricians and Gynaecologists of Canada
SVD	Spontaneous vaginal delivery
UA-pH	Umbilical artery pH
VE	Vacuum extraction

Acidemia	Low pH in blood
Acidosis	Low pH in tissues
Active part of second stage	From start of active pushing until expulsion of the baby
First stage of labor	From onset of active labor until cervix is fully dilated
Intrauterine growth restriction	Intrauterine growth less than predestined due to pathophysiologic reasons e.g. malfunctioning placenta, chromosomal defects, infection etc.
Hypoxemia	Low oxygen content in blood
Hypoxia	Low oxygen content in tissues
Ischemia	Restricted blood supply to tissues
Lactemia	Increased lactate concentration in blood
Lactacidemia	Low pH and increased lactate concentration in blood
Metabolic acidemia	Low pH due to anaerobic metabolism and increased lactate production
Metabolic acidemia in umbilical artery	$pH < 7.05$ and $BD_{blood} > 12$ mmol/L
Neonatal death	Death before 28 days of life among live-born infants
Passive part of second stage	Descend of the fetal presenting part
Respiratory acidemia	Low pH due to accumulation of CO_2
Second stage of labor	From cervix fully dilated until expulsion of the baby
Small for gestational age	Weight less than 2 SD's (-22%) below the mean of estimated fetal weight, according to the Swedish sex-specific ultrasonically estimated fetal weight curve

BACKGROUND

INTRODUCTION

For the majority of fetuses, pregnancy is a period of uncomplicated growth and maturation of organs, with labor as the first challenge to the fetal reserves. Most fetuses start labor in a vigorous state, and cope well with the intermittent reduction in oxygen supply during labor contractions. Fetuses with reduced capacity to endure the stress of being born are exposed to the risk of hypoxic organ damage with lifelong sequels i.e. cerebral palsy.
Cardiotocography (CTG) was introduced with great expectations of reducing the rates of neonatal mortality and cerebral palsy, but randomized trials have failed to show an effect on those two outcomes when compared to intermittent auscultation.[1] Intrapartum hypoxia is only a minor contributor to cerebral palsy, whereas antenatal causes are more common.[2] However, also rare outcomes, when severe with long-lasting consequences, are important goals of preventive measures.

CTG is generally considered an important screening instrument, with very good negative predictive ability, but due to the high rate of false positive tests, CTG monitoring is associated with increased rates of cesarean deliveries in comparison with intermittent auscultation.[1] Fetal scalp blood sampling (FBS) was developed as a method of intrapartum fetal monitoring parallel to CTG, and can discriminate which fetuses that are acidemic and which are not in labors with a non-reassuring CTG trace. FBS is used and considered as a valuable adjunct to CTG in some countries,[3, 4] but considered of no additional benefit in other countries.[5] However, there are no studies that have been designed to address the impact of FBS on cesarean rate.

If a vigorous fetus enters labor and there is a successive development of hypoxia, fetal monitoring with CTG and FBS are preventive tools to enable timely intervention and delivery of a healthy non-acidemic child. If a fetus entering labor already has been exposed to antenatal hypoxia, the fetal monitoring can be used to prevent further damage. In cases with a sudden obstetric catastrophe as placental abruption, uterine rupture or umbilical cord prolapse, there is little room for preventive measures, and no indication for FBS.

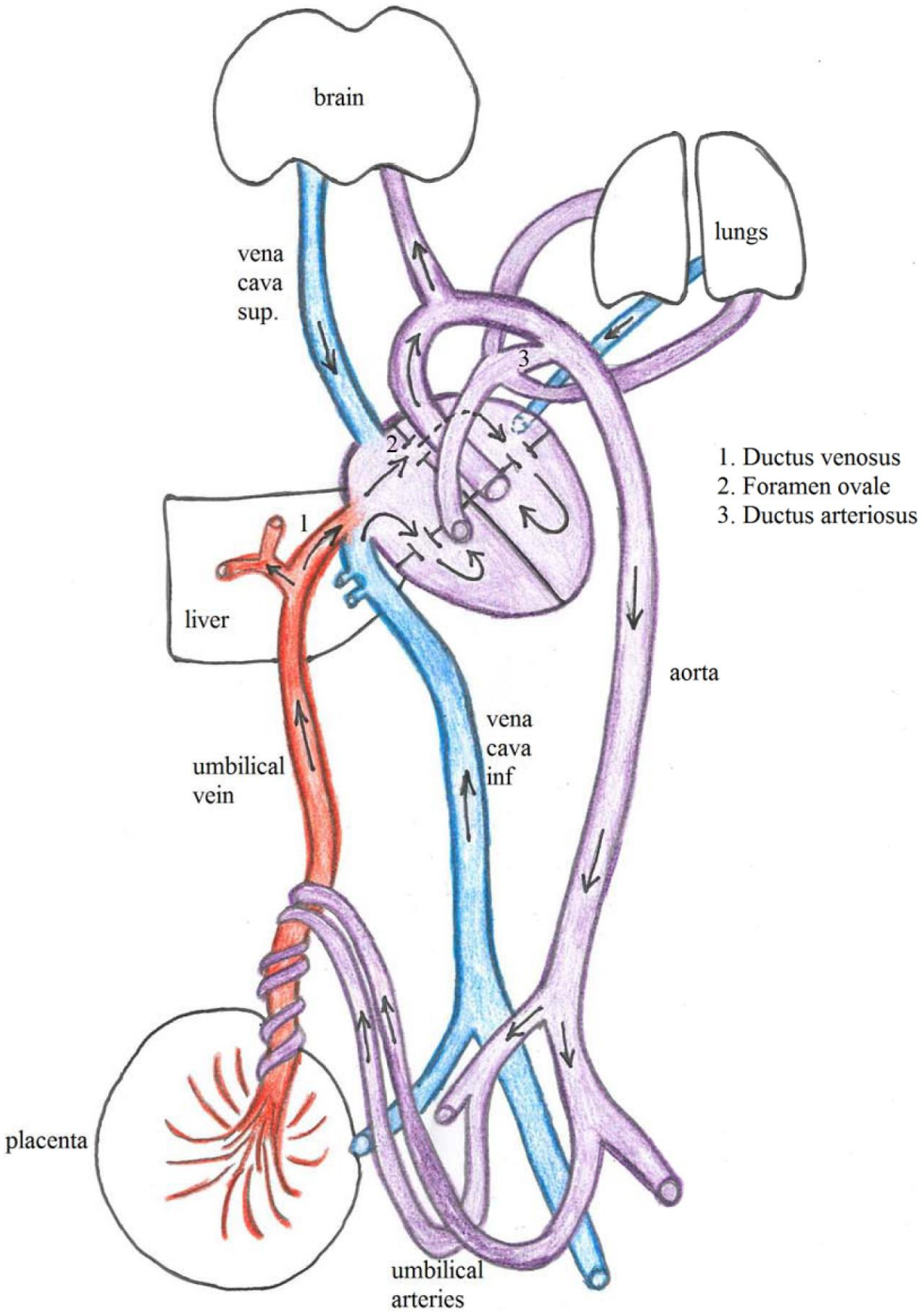
FETAL METABOLISM AND ACID-BASE BALANCE

Fetal circulation

Fetal circulation differs from adult circulation since the oxygenation of blood takes place in the placenta instead of in the lungs. There are three essential short-cuts in the fetal circulation (ductus venosus, foramen ovale and ductus arteriosus); all with the obvious purpose to prioritize well oxygenated blood to the fetal brain and heart. The short-cuts are schematically illustrated in Figure 1.
The umbilical vein transports the oxygenated blood from the placenta to the fetus, firstly passing through the fetal liver. The umbilical vein divides into the two branches supplying left and right sides of the liver, and the first short-cut – the ductus venosus, with approximately 20 % of the blood thereby bypassing the liver in term fetuses. This

fraction can increase during hypoxia, probably up to 50 %.[6] The blood mixes with deoxygenated blood when ductus venosus enters the thoracic portion of vena cava inferior, which carries blood from peripheral tissues, and where the hepatic veins also connects.

Figure 1. Schematic illustration of the short-cuts in fetal circulation.



Animal studies have shown that the stream with well oxygenated blood from the ductus venosus preferably takes the next short-cut in the fetal heart; from the right atrium through foramen ovale to the left atrium and ventricle, and goes directly to central and peripheral tissues without passing the lungs.[7, 8] The stream of deoxygenated blood

coming into the right atrium from the superior and inferior venae cavae enters the right ventricle and pulmonary trunk, and at this point the blood can take a third short-cut into the systemic circulation through ductus arteriosus. This short-cut enters the aorta after the brachiocephalic trunk has parted, and thus further mixing with deoxygenated blood takes place after the branch that supports the brain has parted. From aorta, via the internal iliac arteries, blood returns to placenta in the two umbilical arteries, which thereby carry mixed blood on the way from the fetal heart to peripheral tissues. The deoxygenated blood coming from peripheral tissues enters the inferior and superior venae cava, going back to the fetal heart, mixing with oxygenated blood in the right atrium. Therefore, most of the fetal tissues are supplied with mixed oxygenated and deoxygenated i.e. "used" blood.

There is limited access to the fetus prior to the onset of labor, and antenatal assessments include ultrasound measurements of blood flow in uterine arteries, umbilical arteries and vein, ductus venosus and arteria cerebri media. Fetal decompensation during labor can however be confirmed by blood gas and acid-base measurements of umbilical vessels immediately after delivery. As explained above, the umbilical vein blood thereby reflects the placental function, and the umbilical artery reflects the fetal status.

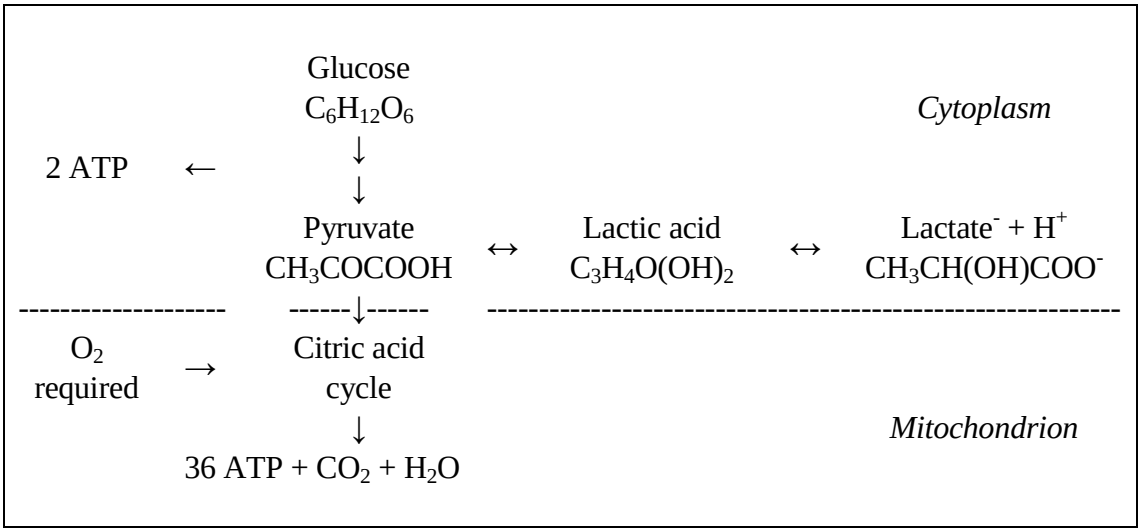
In order to guarantee sufficient oxygen supply for cellular metabolism and energy production, the fetus is dependent on many different steps in the transport of oxygen. Maternal respiration and circulation, perfusion of, and gas-exchange over the placenta, circulation in the umbilical cord, and circulation in the fetus are all important factors. A complication in either of these steps can result in hypoxic / ischemic tissue injury.

If the oxygen supply is restricted, the fetus has several compensatory mechanisms to maintain its intracellular energy production. Regarding fetal circulation, the stroke volume normally works near its functional limit, and cannot be increased as in adults, but the heart rate can be increased to increase cardiac output,[9] and the blood flow can be redirected to vital organs such as the heart, brain and adrenals.[10-12] Oxygen demand can also be lowered by decreased gross body and breathing movements,[13, 14] and even reduced brain metabolism.[15] On a cellular level, the fetus can utilize the Bohr effect i.e. reduced oxygen affinity to hemoglobin in more acidic environments. Fetal hemoglobin (HbF) otherwise has a higher oxygen affinity than adult hemoglobin (HbA), in order to optimize oxygen extraction in the placenta.

Fetal metabolism

Glucose is the main substrate for energy production. Through glycolysis, it is metabolized to pyruvate, and during this process a small amount of energy is produced in the form of two adenosine-triphosphate (ATP). Under aerobic circumstances, pyruvate enters the mitochondrion from the cytoplasm, and takes part in the citric acid cycle. Energy is produced in the form of 36 ATP, with the waste products carbon dioxide (CO_2) and water (H_2O). (Fig. 2)

Figure 2. Glycolysis and aerobic metabolism



During the transport away from the tissue, CO_2 dissolves in blood plasma and equilibrates with carbonic acid (H_2CO_3) which in turn equilibrates with its corresponding base bicarbonate (HCO_3^-) and the hydrogen ion (H^+) (Figure 3).

Figure 3. Equilibrium between carbon dioxide and hydrogen ions.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

As shown in Fig 2, lactate is not only produced under anaerobic circumstances, but there is always a steady state between pyruvate and lactate, also during aerobic metabolism. The equilibrium is normally shifted to the right with a lactate/pyruvate ratio 10:1. In situations with a decreased energy demand, lactate can via a shift in the equilibrium convert back to pyruvate, which then converts further in the gluconeogenesis, and thus, lactate can be used as fuel and after glucose, lactate is the second most important carbohydrate fuel in the fetus. Gluconeogenesis mainly takes place in the liver and heart, and in the liver, glucose can be stored as glycogen.
Maternal levels of lactate are 20-30% lower than in the fetus, but may increase in situations with intensive muscular activity, such as during labor. However, due to the slow transport of lactate over the placenta, this has limited effect on the fetal level.[16] There is also placental lactate production under aerobic conditions, and that lactate probably serves as fuel to the fetus,[17] but it also enters the maternal circulation. Thus, under aerobic circumstances, there are equilibriums between mother, placenta and the fetus regarding lactate levels.

Fetal acid-base balance

pH and buffering systems

The concentration of H^+ is measured in pH, which is defined as the negative logarithm of H^+ activity. A stable concentration of H^+ in tissues is of outmost importance for cellular function, and all organisms have buffering systems to maintain the concentration within physiologic range. The two main systems in humans are bicarbonate and proteins. The sum of buffering capacity by HCO_3^- and proteins

together is called the buffer base. HCO_3^- is the most important buffer in extracellular fluid due to its high concentration. Intracellular buffers are proteins, and the most important protein buffer for the fetus is hemoglobin since concentrations of other buffering proteins are lower than in the adult.

Base excess /base deficit

When the buffering agents are consumed due to a lowered pH, this can be calculated by use of measured pH and CO_2. Base excess (BE) is defined as the amount of acid or base required to restore pH to normal at a partial pressure of CO_2 (pCO_2) of 5.3 kPa at 37°C, at the actual oxygen saturation of the blood, expressed in mmol/L.[18] When BE is negative, i.e. there is a lack of buffer base due to metabolic acidosis, it is more convenient to use the term base deficit (BD).
As mentioned, BD is not a direct measured value, but calculated in an algorithm with measured values of pH and CO_2. BD measurement is affected by the hemoglobin concentration which is different in the fetus compared with the adult. When whole blood is used for the analysis, BD is also affected by the CO_2 concentration, although it is supposed to measure only the metabolic component. If pCO_2 increases, HCO_3^- increases and partly leaves the intravascular compartment to equilibrate with the rest of the extracellular fluid (ecf), and this shift of HCO_3^- out of the blood will increase BD.[18] Siggaard-Andersen who developed the alignment nomogram for BE, proposed that the best way to eliminate that artifact was to consider the red cells as evenly distributed over the entire extracellular fluid. As the extravascular part is about twice that of the intravascular part, the correction was achieved by dividing the actual hemoglobin concentration by 3, and thus, the BE_{ecf} was calculated at a standard hemoglobin value of 50 g/L, and called standard BE (SBE). BE_{blood} is often called actual BE (ABE).

In spite of these arguments, most clinical studies on correlations between acidemia in umbilical cord artery and neonatal outcome are performed with $BD_{blood,}$ not least the voluminous work by Low et al.[19-21] More recent work has shown a stronger correlation with neonatal outcome for BD_{blood} than for BD_{ecf} which supports continued use of this compartment for BD measurements.[22] Wiberg et al. also pointed out the importance of understanding the complexity of BD use, concerning BD not being a measured entity, but an estimate based on measured pH and pCO_2, and thus, more sensitive for introducing error. Algorithms for BD calculations may also vary between different blood gas analyzers.[22]

Respiratory acidemia

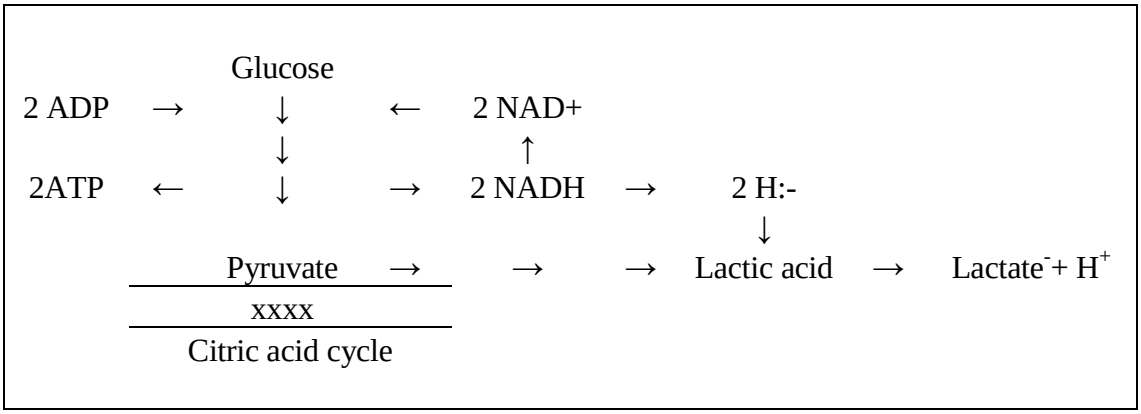
As shown by Nijland et al, the fetal pH is not linearly correlated to oxygen saturation, and the partial pressure of oxygen (pO_2) can decrease to values between 20% and 30% before anaerobic metabolism occurs, and thus metabolic acidemia.[9] However, before the oxygen supply reaches this critical level, a respiratory acidemia can occur. If placental gas exchange is impaired, the CO_2 will increase on the fetal side causing a respiratory acidemia, which is defined as reduced arterial pH due to an elevated partial pressure of CO_2. The term 'respiratory' relates to the response in the adult with hyperventilation to eliminate excess CO_2 which lowers pCO_2 and causes a rise in pH. The fetus obviously cannot eliminate CO_2 that way, but only through placental gas exchange. When this way of elimination is impaired, excess CO_2 dissolves and the

equilibration in Fig.3 shifts to the right. As HCO_3^- is the main extracellular buffer, and the system cannot buffer itself, the excess H^+ in respiratory acidemia can only be buffered by the protein system. However, when placental gas exchange is re-established, CO_2 diffuses rapidly across the placenta, and there is no evidence of tissue injury from isolated respiratory acidemia.[21]

Metabolic acidemia

Metabolic acidemia is defined as reduced pH caused by lack of buffer base, which is measured by increased BD. In a situation with restricted oxygen supply, cells switch from aerobic to anaerobic metabolism with the end products $lactate^-$ and H^+ (Figure 4). Energy production is much less, with only 2 ATP instead of 2 + 36 ATP, and the increased amounts of H^+ consumes buffering agents leading to metabolic acidemia.

Figure 4. Anaerobic metabolism



If oxygen supply is restored after an episode of hypoxia and anaerobic metabolism, pyruvate again enters the mitochondria from the cytosol, and therefore the equilibrium between lactate and pyruvate turns to the left, and lactate can be used in gluconeogenesis as explained above. The lactate/pyruvate ratio has been used as a measure of hypoxia since it increases during metabolic acidemia, however, it is not shown to perform better in predicting hypoxia than determination of lactate alone, and has never become part of clinical use.[16]

Several animal and human studies have addressed the question of lactate origin when fetal lactate concentration is increased.[23-25] Piquard et al. described several findings strongly indicating fetal origin as well in steady state labors as in labors complicated by acute stress conditions. They showed that the umbilical arteriovenous lactate differences were positive and large in all newborns and that a positive maternofetal gradient of lactate was rarely observed. In addition, there was only a very weak correlation between fetal and maternal lactate levels, indicating that the increase in lactate occurred independently in mother and fetus.[24] Thus, a fast increase in lactate concentration as a response to a relatively sudden development of hypoxia, as during labor, can be regarded as of fetal origin.

Intrauterine growth restriction and fetal acid-base status

Fetuses exposed to chronic hypoxia have also been studied with measurements of lactate concentrations. In a study by Nicolaides et al., fetuses that were small for

gestational age (SGA) were found to have hypoxemia, hypercapnia, hyperlactemia and acidosis.[26] The authors explained the hypercapnia as due to reduced gas exchange over the malfunctioning placenta, motivated by significant correlation between the degree of hypercapnia and the increased resistance in the umbilical and uterine arteries in SGA pregnancies. The authors reported it to be unlikely that lactate measured in the SGA fetuses would be of placental origin, because maternal blood lactate was not higher in the group with SGA fetuses than the group with appropriate for gestational age (AGA) fetuses, and since there was no correlation between fetal and maternal blood lactate. Diagnosis of intrauterine growth restriction (IUGR) is not possible unless serial ultrasonographic measurements are performed, and SGA is commonly used as a proxy for IUGR. The cut off used in Sweden is fetal weight less than 2 standard deviations (SD) below the mean according to the Swedish sex-specific ultrasonically estimated fetal weight curve. This corresponds approximately to the 2.5^{th} percentile. Internationally a more common definition is fetal weight less than the 10^{th} percentile.

ACIDEMIA, HYPOXIA AND CELLULAR DAMAGE

Asphyxia is generally defined as a failure of blood gas exchange, that - if persistent - leads to progressive hypoxemia and hypercapnia.[27] This may however occur transiently with no pathological bearing. Therefore, significant fetal asphyxia is defined as a failure of blood gas exchange of a duration and degree resulting in tissue oxygen debt, with an accumulation of fixed organic acids and a metabolic acidosis.[28, 29] During the 1950's, animal models of fetal monkey and fetal lamb made it possible to systematically examine the effects of hypoxia and ischemia on the fetus. Micro-electrode techniques for blood gas and acid-base analysis were concurrently developed to obtain biochemically determined measures of asphyxia in the human fetus. Animal studies and studies on acid-base status in the human fetus could confirm that the fetus can compensate for an asphyxial event up to a certain threshold and protect the brain from damage.[28] If the event exceeds that threshold, it can cause multi-organ damage including the brain, which will account for motor and cognitive deficits. When the threshold for compensation has been passed, a progressive metabolic acidemia will result in a fall in arterial blood pressure due to decreased cardiac output or reduced peripheral resistance. Thus, the explanation for neuronal damage and necrosis has several layers; the hypoxemia, the cerebral ischemia due to hypotension, and the metabolic acidemia itself. Some neurons die during the asphyxial event (primary neuronal necrosis), but many neurons die as a result of processes that take place after the event (secondary neuronal necrosis).[30] Animal studies have shown support of a primary and secondary period of neuronal death.[31]

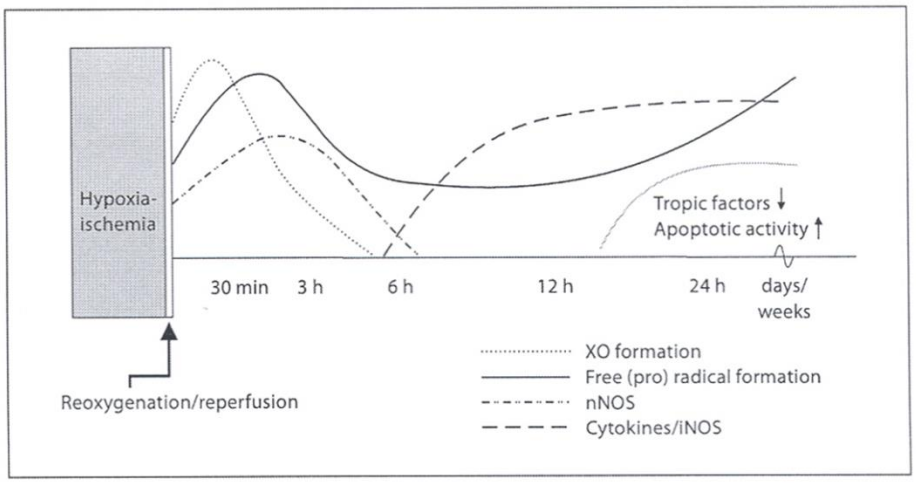
Phases of neuronal death

During the primary phase; i.e. the hypoxic event itself, there is energy failure and development of lactic acidosis resulting in two mechanisms of ion-mediated neuronal injury. There is a disturbance of intracellular chloride ions (Cl^-) with a sodium ion (Na^+) influx, which leads to intracellular edema, which in turn can lead to lysis of the neuronal cell. There is also excessive entry of calcium ions (Ca^{2+}) into the cell, which initiates a cascade of biochemical events that leads to neuronal death.

Excitotoxicity is the over-activation of neurotransmitter receptors by excitatory amino acids (e.g. glutamate and aspartate) allowing high levels of Ca^{2+} to enter the cells.[32] If the hypoxic event is resolved, a reperfusion starts, during which production of cytotoxic free radicals takes place. Following reperfusion and reoxygenation, a secondary phase of cell injury occurs, where the mitochondria are as well targets as contributors of cytotoxic agents.[33] Figure 5 schematically shows the phases of different events.

The excess intracellular Ca^{2+} activates nitric oxide synthase (NOS) with subsequent production of nitric oxide (NO•). This shifts the electron transport chain to a more reduced state, enhancing the formation of superperoxide ($•O_2^-$) by electron leakage. NO• and $•O_2^-$ reacts to form peroxynitrite (ONOO-), which is a highly reactive and toxic agent that modifies mitochondrial proteins by oxidation and/or nitrosylation which can lead to depression of mitochondrial respiration, change the membrane permeability with eventual swelling and rupture of mitochondrial membrane, and increased release of proapoptotic proteins. ONOO- also contributes to production of the hydroxyl radical (•OH), which damage proteins and DNA.[34] The production and effect of these reactive oxidative species (ROS) is called the oxidative stress.

Fig. 5. Phases of neuronal death



XO = xanthine oxidase, nNOS = neuronal nitrite oxide synthase, iNOS = inducible nitric oxide synthase

Most neurons probably survive the asphyxial insult itself, and therefore, great efforts have been done investigating effective treatment during the reperfusion phase, where hypothermia hitherto is shown to have significant positive impact. There is however a tertiary phase during which neuronal necrosis can occur, and the mechanisms of this phase are complex.

There is an inflammatory response to the acute tissue injury, with activation of microglia and astrocytes. If there is break-down of the blood-brain barrier, neutrophils and macrophages can invade, the formation of scar tissue increases the inflammation and cytokine release which leads to increased cell death.[30, 35] The actual mechanism is activation of programmed cell death, why the term apoptosis instead of necrosis often is used.

Definition of birth asphyxia

In the late 1990's, the World Federation of Neurology Group set up a task force for the prevention of cerebral palsy and related neurologic disorders. Much effort was put into defining an objective template of evidence to identify cases of cerebral palsy where neuropathology began or became established around labor and birth.[29]

In contrast to previous assumptions, several clinical epidemiological studies indicated that events leading to cerebral palsy, in most cases occur before onset of labor or in the newborn after delivery.[36, 37] It was stated that the terms "fetal distress" and "birth asphyxia" were inappropriate and should not be used clinically. "Fetal distress" should be replaced by "non-reassuring fetal status" with a description of the clinical sign or test that led to the conclusion, e.g. pathological fetal acidemia with umbilical artery pH < 7.00.

Concerning the term "birth asphyxia", the timing and onset of asphyxial changes should be described when possible, and described as fetal or antenatal if occurring before the onset of labor; as intrapartum if occurring between onset of labor and complete expulsion of the baby, and neonatal if occurring after birth. Perinatal asphyxia can be used when the timing is uncertain.[29] The task force also suggested not using the term "hypoxic ischemic encephalopathy", but instead "neonatal encephalopathy", since hypoxia and ischemia have often not been proved, and over 75% of neonatal encephalopathy have no clinical signs of intrapartum hypoxia.[38-41]

The criteria suggesting that acute intrapartum hypoxia was the cause of cerebral palsy are described below. All three of the essential criteria are necessary before an intrapartum hypoxic cause of cerebral palsy can be considered. The four latter criteria are individually only weakly associated with an acute intrapartum hypoxic event, since all of them except criterion 4 may be caused by other factors, e.g. infection. If some of criteria 4-8 are missing, the timing of onset becomes in doubt, and if they are contradictory, e.g. a normal Apgar score at five minutes, they weigh against a serious acute event.[29]

Table 1. Criteria to define an acute intrapartum hypoxic event

Essential criteria	1	Evidence of a metabolic acidosis in intrapartum fetal, umbilical arterial cord, or very early neonatal blood samples (pH < 7.00 and BD ≥ 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 FHR pattern usually after the hypoxic sentinel event where the pattern was previously normal
	6	Apgar scores of 0-6 for longer than 5 minutes
	7	Early evidence of multisystem involvement
	8	Early imaging evidence of acute cerebral abnormality

MacLennan A. BMJ. 1999 Oct.16;319(7216):1054-9. FHR = fetal heart rate

Neonatal outcome measures

In developed countries, neonatal deaths and cerebral palsy are rare with reported neonatal mortality rates of 1.2 per 1000 live births in Sweden, and frequencies of cerebral palsy approximately 2 per 1000 live births,[42, 43] and if children born at term (>36 weeks of gestation) are considered, the rates are even lower. Thus, the effects of surveillance methods and interventions on such rare endpoints are difficult to study, and many studies use surrogate outcomes such as hypoxic neonatal encephalopathy, low Apgar score and umbilical acid base measures to evaluate associations and risk factors.

The association between acidemia at delivery and neonatal complications has been demonstrated, and has shown a significant correlation between severe acidosis, i.e. umbilical artery pH (UA-pH) < 7.00 and occurrence of newborn complications.[44, 45] In a prospective population based study of newborns with acidemia defined as pH 7.05 at birth (the 1st percentile of the source population) there was an association with neonatal encephalopathy and speech problems at four years follow up.[46] Other studies have demonstrated that the majority of moderate and severe neonatal encephalopathy and other organ system complications occurred in newborns with umbilical BD above the threshold of 12 mmol/L,[21, 47] as well as a significant increase in motor and cognitive development deficits at one year of age.[48, 49]

CARDIOTOCOGRAPHY

Fetal surveillance during labor started with auscultation of the fetal heart during the 1900th century. Auscultation of the fetal heart rate and inspection of the amniotic fluid were for many years the only ways to assess fetal status during labor. The technique of electronic fetal monitoring (EFM) developed during the 1950's by the work of Hon and coworkers and Hammacher.[50, 51] The name cardiotocography (CTG) originates from the Greek words "kardia" (heart), "tocos" (childbirth) and "graphe" (writing).

Antepartum and intrapartum before rupture of membranes, only external monitoring can be used. A Doppler signal is sent toward the fetal heart, and through the Doppler effect, i.e. the changed frequency of a wave movement reflected back when meeting an object in movement, this change in the Doppler signal is recalculated to beats per minute (bpm) by the CTG machine.
Intrapartum after rupture of membranes and when the cervix is dilated at least 1 cm, internal monitoring is possible, and the fetal heart rate is then directly registered by a scalp electrode attached to the presenting fetal part. Internal monitoring is less sensitive to errors, but also invasive and infectious diseases as Hepatitis B, HIV and active genital herpes are contraindications as well as possibility of inherited coagulopathy in the fetus. Internal monitoring also restrains the woman from moving freely during labour. There should always be a clear indication for application of a scalp electrode, and as long as there is acceptable quality of external monitoring this is sufficient.
CTG was rapidly introduced into clinical practice with the hope to significantly reduce perinatal mortality and morbidity, in particular the frequency of cerebral palsy. Several uncontrolled studies had suggested that routine EFM was associated with a reduction in

intrapartum stillbirths and neonatal deaths. Parallel to the clinical use, animal and clinical studies were performed to evaluate the significance of the new information the technique gave besides the actual heart rate.

Randomized controlled trials were performed during the 1970's and 1980's, comparing CTG with intermittent auscultation. The Dublin trial with approximately 13000 participants could not show a reduction in cerebral palsy or neonatal mortality, but the rates of seizures and persistent neurologic signs in the neonatal period were halved in the EFM group compared with the group with intermittent auscultation. Follow-up at one year of age in babies with neonatal seizures revealed no difference between the groups,[52] and neither did a four-year follow-up.[53] Three children in each group that had survived neonatal seizures had been diagnosed with cerebral palsy, and the majority of children with cerebral palsy in the total study population had not shown clinical signs suggestive of intrapartum asphyxia.[53] One possible limitation of the Dublin trial was that cases with meconium-stained amniotic fluid, preterm deliveries and women with rapid course of labor and delivery within one hour from arrival in the labor ward were excluded. Through this exclusion of high-risk labors, 56 of the 82 neonatal deaths were excluded, thus minimizing the chance of showing a reduction in mortality. There was only a small difference in rates of cesarean deliveries associated with the two policies.

The Athens study was smaller with 1400 participants, but did not exclude women with risk factors as the Dublin trial. There was also a higher perinatal mortality rate in the background population in Greece, compared with the one in Ireland, and the reduction in perinatal mortality was significant and so large, that the trial was discontinued by ethical reasons.[54] A meta-analysis of the thirteen existing randomized studies comparing CTG with intermittent auscultation states that CTG is associated with a halving of neonatal seizures and a significant increase in cesarean deliveries (RR 1.63), but no differences in cerebral palsy rate or overall perinatal death rate.[1] Vintzileos et al published a meta-analysis of nine of the randomized trials, with exclusion of trials with intermittent EFM and trials comparing selective versus universal EFM. They found a significant reduction in perinatal mortality if only deaths attributed to fetal hypoxia were included.[55] They also excluded deaths that could not be attributed to the method of monitoring such as cord prolapse, congenital heart disease and hemorrhage. This way of analyzing the data has been criticized, but the authors argued that it is not reasonable to expect CTG to predict or to prevent other causes of perinatal death e.g. shoulder dystocia, placental abruption, umbilical cord prolapse or uterine rupture.

Terminology

The five parameters to assess in CTG are baseline heart frequency, variability, accelerations, decelerations and uterine contractions. During the years since the introduction of CTG, numerous different definitions and guidelines have appeared.[56-64] After almost 30 years, the guidelines of the International Federation of Gynecology and Obstetrics (FIGO) from 1987 still remains the only broad international consensus document on EFM, and many national guidelines refer to them (Table 2). However, the shortcomings are substantial with lack of objective definitions of some fetal heart rate (FHR) features, and others only vaguely defined.

Table 2. Comparison of FHR definitions in guidelines of FIGO,[56] SFOG,[64] RCOG/NICE,[57, 65] ACOG/NICHHD/SMFM,[59, 60] SOGC[61] and RANZCOG[58]

Feature	Guideline	Definition
BASELINE	FIGO / RCOG / RANZCOG	Mean level of FHR when this is stable, excluding accelerations and decelerations. Determined over a period of 5-10 min, expressed in bpm
	ACOG / SOGC	As above, and rounded to increments of 5 bpm. There must be ≥ 2 min of identifiable baseline segments, or the baseline is indeterminate.
Normal BL	FIGO / SFOG	110-150 bpm
	RCOC /ACOG / SOGC / RANZCOG	110-160 bpm
Bradycardia	FIGO	Not stated, but 110-100 bpm suspicious and < 100 pathological
	SFOG / ACOG / SOGC / RANZCOG	< 110 bpm
	RCOG	100 - 109 bpm – uncomplicated; < 100 bpm – complicated
Tachycardia	FIGO / SFOG	150-170 bpm suspicious and > 170 pathological
	RCOG / ACOG / SOGC / RANZCOG	>160 bpm (RCOG: 160 – 180 bpm uncomplicated, and > 180 bpm complicated)
VARIABILITY	FIGO	Oscillations of FHR around its mean level (long-term variability)
	RCOG / RANZOG	The minor fluctuations in baseline FHR occurring at 3-5 cycles / min. Measured by estimating difference in bpm between highest peak and lowest trough of fluctuation in a 1-minute segment of the trace
	ACOG	Fluctuations in baseline FHR, irregular in amplitude and frequency. Visually quantified as the amplitude of peak-to-through in bpm
	SOGC	Fluctuations in baseline FHR in 2-4 cycles / min, difference between highest and lowest rate during 1 min
Normal variability	FIGO/SFOG	5-25 bpm
	RCOG / RANZCOG	5 - 25 bpm between contractions
	ACOG /SOGC	Amplitude range 6 - 25 bpm (moderate variability)
Increased variability	FIGO / SFOG/ RCOG / ACOG / RANZCOG	> 25 bpm (ACOG / SOGC: marked variability)
Reduced variability	FIGO /RCOG	< 5 bpm
	SFOG	< 5 bpm but ≥ 2 bpm
	ACOG / SOGC	> undetectable and ≤ 5bpm (minimal variability)
	RANZCOG	3 – 5 bpm
Absent variability	FIGO /RCOG	Not specified
	SFOG	< 2 bpm
	ACOG/SOGC	Undetectable

	RANZCOG	< 3 bpm
ACCELERATIONS	FIGO/RCOG / RANZCOG	Transient increase in FHR ≥ 15 bpm , ≥15 seconds
	ACOG/SOGC	A visually apparent abrupt increase in FHR, peak ≥15 bpm above baseline, duration ≥ 15 seconds, but < 2 minutes from onset to return. Duration 2-10 minutes: prolonged acceleration, Duration > 10 minutes: baseline change. (If gest < 32 weeks: >10 bpm and 10 sec)
DECELERATIONS	FIGO	Transient episodes of slowing of fetal heart rate below the baseline level > 15 bpm, lasting ≥10 seconds*
	RCOG	Transient episodes of slowing of FHR below baseline level > 15 bpm, lasting ≥15 seconds
Early decelerations	RCOG	Uniform, repetitive, periodic slowing of FHR; early onset, return to baseline at end of contraction
	ACOG / SOGC	Visually apparent, usually symmetrical, gradual (≥30 sec from onset to nadir) decrease and return of FHR associated with a uterine contraction, nadir of deceleration occurring at the same time as peak of contraction.
	RANZCOG	Uniform, repetitive decrease of FHR, slow onset early in contraction, slow return by end of contraction
Late decelerations	FIGO / SFOG / RCOG	Not specified
	RCOG / RANZCOG	Uniform, repetitive periodic slowing of FHR with onset mid to end of contraction, nadir > 20 sec after peak of, and ending after contraction. If variability < 5 bpm, deceleration amplitude < 15 bpm included
	ACOG / SOGC	Visually apparent, usually symmetrical gradual (≥30 sec from inset to nadir) decrease and return of FHR, delayed in timing with nadir of deceleration occurring after peak of contraction.
Variable decelerations	FIGO	Not specified
	SFOG	Uncomplicated if duration < 60 sec, complicated if duration > 60 sec; uncomplicated further divided into duration < / > 30 sec, and amplitude < / > 60 bpm
	RCOG	Variable intermittent periodic slowing of FHR, rapid onset and recovery. Atypical if loss of primary or secondary rise in baseline rate, slow return, prolonged secondary rise, biphasic, loss of variability
	ACOG	Visually apparent abrupt (<30 sec from onset to nadir) decrease in FHR, ≥15 bpm, ≥15 sec but <2 min in duration. When associated with uterine contractions, the onset, depth and duration commonly vary with successive uterine contractions.
	SOGC	As above and uncomplicated if initial and secondary acceleration. Complicated if trough < 70bpm / duration > 60 sec / slow return to baseline / loss of variability in the trough of deceleration / prolonged secondary acceleration – overshoot >20 bpm > 20sec
Contractions	All guidelines	≤ 5 / 10 min normal

*Hypothezised to be a transcription error, since 10 sec is very difficult to discriminate with the naked eye. More logical would be 10 bpm and 15 sec, to include the flaccid but potentially alarming late decelerations.[65]

Table. 3. CTG classification systems in different guidelines

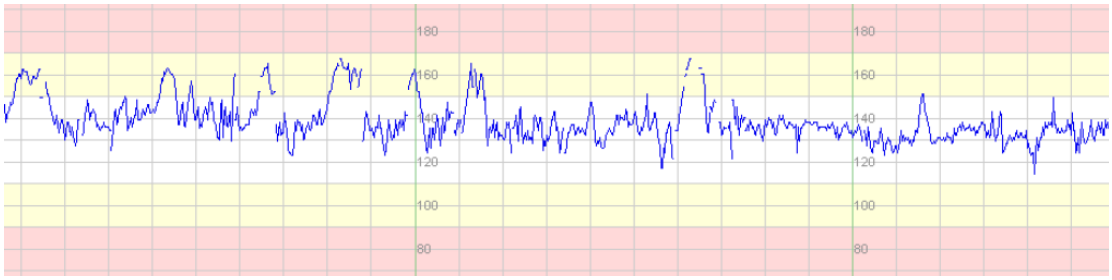
FIGO	SFOG	RCOG/NICE	ACOG	RANZCOG	SOGC
Normal	**Normal**	**Reassuring**	**Category I**	**Normal**	**Normal**
FHR 110-150 bpm Variability 5-25 bpm	FHR 110-150 bpm Variability 5-25 bpm ≥ 2 accelerations / 60 min Early decelerations Variable uncomplicated decelerations with duration < 30 sec and amplitude < 60 bpm	FHR 110-160 bpm, Variability ≥ 5 bpm, no decelerations, present accelerations	FHR 110-160 bpm, Moderate variability, Absent late or variable decelerations, Early decelerations and accelerations can be present or absent	FHR 110-160 bpm, Variability 5-25 bpm Accelerations present No decelerations	FHR 110-160 bpm, Variability 6-25 bpm, ≤ 5 bpm for < 40 min, None or occasional uncomplicated variable or early decelerations, Accelerations spontaneously or present with fetal scalp stimulation
Suspicious	**Aberrant**	**Non-reassuring**	**Category II**	**Abnormal**	**Atypical**
FHR 150-170 bpm or 100-110 bpm Variability 5-10 bpm >40 min Variability > 25 bpm Variable decelerations	FHR 100-110 bpm FHR 150-170 bpm FHR < 100 bpm ≥ 3min Variability < 5 bpm > 40 min without accelerations Increased variability < 2 accelerations/60 min Variable uncomplicated decelerations lasting 30-60 sec and / or amplitude > 60 sec (A combination of ≥ 2 aberrant parameters makes the tracing suspiciously pathological)	FHR 100-109 bpm FHR 161-180 bpm Variability < 5 bpm 40-90 minutes, Typical variable decelerations more than 50% of contractions > 90 min. Single prolonged deceleration up to 3 min (Absence of accelerations with otherwise normal trace is of uncertain significance)	All FHR tracings not categorized as I or III.	*but unlikely associated with significant fetal compromise* FHR 100-109 bpm or Absence of accelerations Early decelerations Uncomplicated variable decelerations	FHR 100-110 bpm FHR >160 bpm for 30-80 min Variability ≤ 5 bpm for 40-80 min Repetitive (≥3) uncomplicated variable decelerations Occasional late decelerations Single prolonged deceleration 2-3 min, Absence of acceleration with fetal scalp stimulation

Pathological	**Pathological**	**Abnormal**		**Abnormal**	**Abnormal**
FHR < 100bpm or > 170 bpm Variability < 5 bpm > 40 min Severe variable decelerations or severe repetitive early decelerations Prolonged decelerations Late decelerations Sinusoidal pattern	FHR > 170 bpm FHR < 100 bpm ≥ 3 min Variability < 5 bpm > 60 min without accelerations Sinusoidal pattern Variable complicated decelerations with duration > 60 sec Uniform late decelerations Combined decelerations	FHR < 100 bpm FHR >180 bpm Sinusoidal pattern ≥ 10 min, variability < 5 for ≥ 90 min. Either atypical variable decelerations over 50% of contractions or late decelerations, both for > 30 min. Single prolonged deceleration > 3 min.		*and may be associated with significant fetal compromise* Tachycardia Reduced variability Complicated variable decelerations Late decelerations Prolonged decelerations	FHR <100 bpm FHR>160 for > 80 min Erratic baseline Variability ≤ 5 bpm > 80 min or ≥ 25 > 10 min. Sinusoidal pattern ≥3 complicated variable decelerations Late decelerations > 50% of contractions Single prolonged deceleration 3-10 minutes Absent or present accelerations
	Preterminal		**Category III**	**Abnormal**	
	Absent variability without accelerations, regardless decelerations and baseline FHR		Absent variability and either: Recurrent late decelerations, recurrent variable decelerations, or bradycardia Sinusoidal pattern	*and very likely to be associated with sign fetal compromise* FHR < 100 bpm > 5min Absent variability Sinusoidal pattern Reduced variability with complicated variable or late decelerations	

Classification systems

As shown above in Figure 3, many countries have adopted some kind of classification system for CTG patterns, often quite similar to the FIGO document from 1987. Most guidelines have a three-tier classification, but with some differences in divisions and nomenclatures, as shown in Table 3. All classifications are, in similarity with the FIGO classification, consensus documents, and not evidence-based. Several concerns have been brought up in recent years, regarding the effectiveness of the classification systems.[62, 65, 66] Di Tommaso et al. compared five of the classification systems, with the finding that all classification system analyzed had a low discriminative capacity when predicting UA-pH ≤ 7.15, and that a common problem is that the vast majority of CTG traces end up in the intermediate or "suspicious group.[66]

CTG findings and correlation to fetal status



Baseline FHR

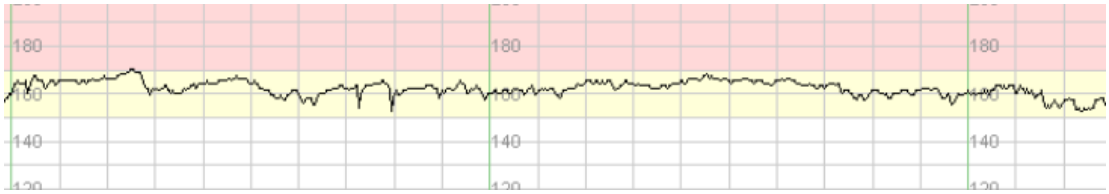
The baseline frequency had been recorded by auscultation long before the introduction of cardiotocography. Early studies by Hon revealed a mean of 140 bpm, and he stated that the majority of FHR recordings to the date of the study had been within the range 120-160.[67] As shown above, several consensus guidelines has a wider range of normality, between 110 and 160 bpm,[57-60, 68] and the FIGO consensus document as well as the current Swedish guidelines use the range of 110-150 bpm as normal interval. In a recent study, Pildner von Steinburg et al. stated after a thoroughgoing literature search that the range of normality for baseline FHR was neither international consensus nor evidence-based. They computed the baselines from nearly 79,000 consecutive CTG tracings, both antenatal and intrapartum, ranging from gestational week 24 to term, which revealed that the range of 110-150 represented the approximately 0.6th to 86th percentile in that study, and that the range 110-160 represented the 0.6th to 96th percentile.[69] The authors mean that the reason for FIGO's lowering the former range from 120-160 to 110-150 at the consensus meeting 1985, was motivated by reports of a high prevalence of abnormal fetal scalp blood analyses in cases with a baseline in the higher range.[70 71]

The baseline heart rate is dependent on a complex interaction between the autonomic nervous system, humoral and metabolic conditions in the fetal heart. Due to successive maturation of the central nervous system during pregnancy, the parasympathetic system becomes more and more dominating, and therefore there is a small but notable decrease in fetal heart rate throughout pregnancy.[56]

Tachycardia can arise from maternal fever, increased sympathetic tone in either fetus or mother, anemia in mother or fetus, thyroid overproduction and fetal arrhythmia, but most important tachycardia can be an early sign of fetal hypoxia. As previously

mentioned, the cardiac output works near its limit already under normal circumstances and cannot be increased, and thus, the only way for the fetus to compensate for decreased pO_2 in the blood is to increase the heart rate.[9]
Bradycardia can start as a vagal reflex e.g. during rapid progression of labor with compression of the fetal head and in these reflex situations, it is not a sign of, but can rapidly lead to hypoxia. In situations of maternal hypotension as in compression of vena cava, the fetal bradycardia is mediated by baroreceptors, and is quickly restored with change of maternal position. In cases with complete cessation of umbilical circulation as in cord prolapse or placental abruption, the bradycardia is due to hypoxic depression of the myocardium.[72] A rare cause of marked bradycardia without hypoxia is fetal arrhythmia, i.e. atrioventricular block.

Variability



The fetal heart rate is normally varying, both from beat to beat, and over longer periods, i.e. minutes. The former, i.e. the short term variation, is the time difference between every two beats; in most cases impossible for visual recognition, and the latter - called the long term variability, is what we assess in a usual non-computerized CTG interpretation. Animal studies have shown this variation to be dependent upon the constant balance between the sympathetic and parasympathetic nervous systems, but also upon non-neuronal components.[73] Intermittent low variability normally occurs during fetal sleep, in cycles lasting up to 45 minutes near term.[74]
A fixed FHR without variability is typically seen in anencephalic fetuses.[75] Decreased variability was associated with increased risk of cerebral palsy in a case control study by Nelson et al., and the risk persisted after adjustment for known risk factors for cerebral palsy (e.g. preterm delivery, breech presentation and maternal infection) with an OR for cerebral palsy of 2.7. However, the false-positive rate was 99.8%.[76] Williams et al. concluded that minimal or absent variability for > 1 hour was the most significant fetal heart rate parameter to predict development of umbilical artery acidemia in a cohort study of nearly 500 fetuses.[77] The proportions of reduced vs. absent variability was however not stated.

Accelerations

Accelerations are physiologic responses to fetal movements, but can also be triggered by uterine activity.[78] Other triggers are manipulations of uterus and fetus, e.g. reaction to painful events as application of scalp electrode or FBS. Accelerations are a reliable sign that the cardiovascular unit, the autonomic nervous system and the central nervous system are intact and well-functioning. Although accelerations are reassuring for a well oxygenated fetus, the opposite cannot be said. Absence of accelerations is common during labour, and gives rise to concern about the well-being of the fetus. Different stimulation tests can then be performed, and provoked accelerations through scalp stimulation by Allis clamp, FBS or digitally as well as vibroacoustic stimulation are

reported as reassuring signs of a non-acidemic fetus.[79] Clark et al. reported that none out of 169 cases with an acceleration as response to FBS had acidemia, but 19 out of 31 that did not react with an acceleration were acidemic in scalp blood. Several other studies have repeated this finding.

Decelerations

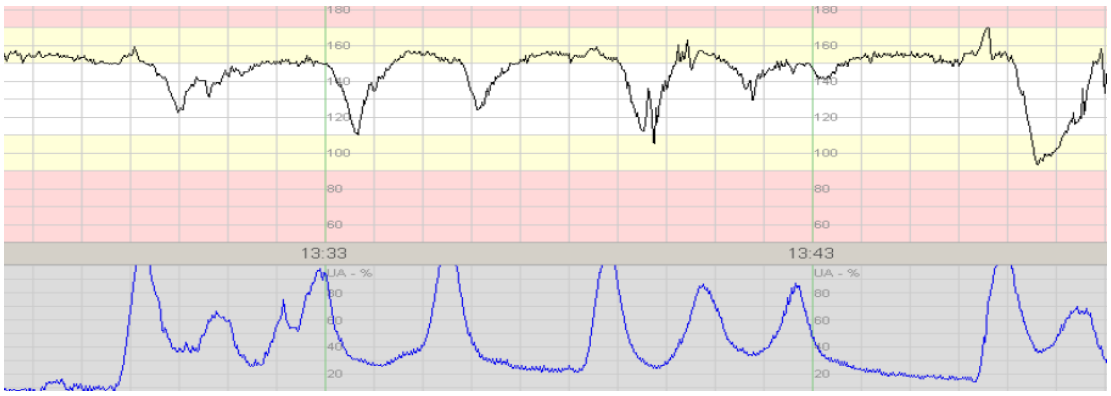
While baseline FHR, variability and accelerations can be regarded as signs of the fetal state, decelerations can be looked upon as what the fetus is exposed to e.g. contractions, pressure towards the fetal head and orbitae, a suboptimal function of the placenta or compression of the umbilical cord. Very often the eyes of doctors as well as midwives moves directly to focus on the decelerations when assessing a CTG trace, but more important than the decelerations are the baseline and variability after the end of decelerations. If baseline and variability are normal, the fetus does not have to compensate for the heartbeats "lost" during the contraction.

Decelerations are the parameter with the most varying terminology between different countries and guidelines, there have been numerous changes over the years, and there are controversies regarding definitions and subdivisions.[80, 81]

This is also the CTG parameter that varies most between different CTG interpreters i.e. has the largest inter-observer variability.[82]

With this in mind, it is however important to understand the pathophysiological mechanisms behind FHR decelerations. Several animal and human studies have in detail investigated the different origins of decelerations with a uniform and a variable shape respectively. During the first decade of CTG monitoring in clinical practice, Hon and Quilligan identified three types of decelerations; early, late and variable type, and reported that late decelerations and variable decelerations that were profound and of long duration were associated with fetal depression.[83] Kubli reported that late and severe variable decelerations were associated with fetal scalp blood acidemia.[71]

Late decelerations

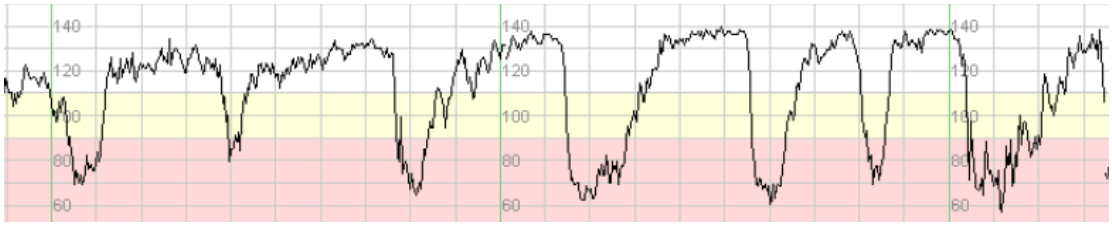


Myers demonstrated in an animal study that monkey fetuses exposed to partial hypoxia had episodes of fetal bradycardia and hypotension following uterine contractions, called Type II dips, which corresponds to the name (uniform) late decelerations used currently.[84] In the same experiment he also demonstrated the various types of cerebral damage after different degrees of hypoxia. He could report that late decelerations invariably appear when fetal arterial pH drops to levels at or below 7.10-7.15, and a concurrent pO_2 drop. He stated that the decelerations regularly follow uterine contractions by 20 to 30 seconds, and that the delay from start of contraction to the beginning of the induced deceleration reflects the time required for depletion of the O_2 stored in the intervillous space in the placenta and the transport of the O_2-deprived blood from the placenta to the fetal myocardium. Late decelerations can be discrete in both duration and amplitude even in a severely deteriorated fetal status.

In a sheep model by Parer et al., late decelerations were provoked by abrupt decrease in uterine blood flow. In sheep fetuses that were normoxic at beginning, the late decelerations were abolished by compete vagal blockade. In sheep fetuses that already had been exposed to chronic hypoxia the late decelerations could not be abolished by pretreatment with atropine.[85] They stated that late decelerations had two possible reasons. The reflex type provoked in normoxic fetuses was vagal mediated and due to chemoreceptor rather than baroreceptor activity, and the decelerations appearing in fetuses already hypoxic when exposed to impaired oxygen supply were due to direct hypoxic depression of the myocardium.

Several clinical studies have reported a significant correlation between late decelerations and neonatal morbidity.[86-88] Repetitive late decelerations gave an OR of 3.7 for cerebral palsy in a case-control study of 78 children with a cerebral palsy diagnose at 3 years of age.[76] In a case-control study of 125 preterm newborns with ultrasound-verified white matter injury, late decelerations were associated with a decreasing pH in umbilical artery, but there was no significant difference in frequency of acidemia between cases and controls.[88]

Variable decelerations



As mentioned above, decelerations have as well the most varying terminology and definition between different guidelines, as the largest inter-interpreter variation. Among the decelerations, the variable type is most unclear when it comes to terminology. Different authors and guidelines use the terms simple, mild, typical or uncomplicated for variable decelerations with duration less than 60 seconds, but some also demands pre- and post-accelerations for the definition, and some guidelines divides the uncomplicated further regarding duration more or less than 30 seconds and amplitude more or less than 60 bpm. All guidelines are fairly consistent in definition of, but not name of the more serious type of variable deceleration that can be indicative of fetal hypoxia. All guidelines demand duration of more than 60 seconds for the definition of a

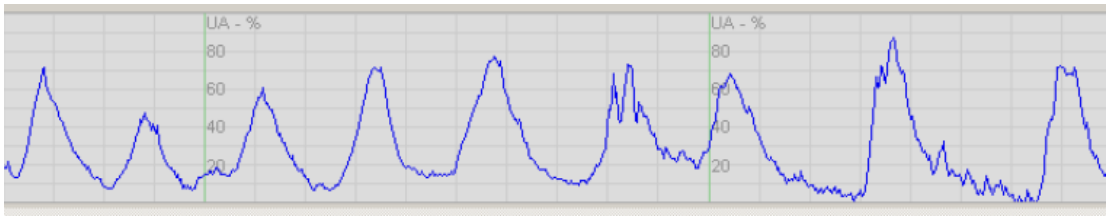
severe/atypical/complicated variable deceleration. As shown in Table 2, some guidelines also define other features of the CTG trace such as the baseline and variability, for the definition of a complicated variable deceleration.

Numerous studies on the sheep model have shown that a sudden and total occlusion of the umbilical vessels is associated with an abrupt fall in fetal heart frequency, and that the frequency returns to baseline when the umbilical circulation is restored.[89, 90] In experiments with occlusion 1:5 and 1:2.5 minutes, they could demonstrate an increased fetal mean arterial pressure during occlusions, and a reflex periodic bradycardia. Thus, these decelerations were explained by a baroreceptor response to the increased fetal blood pressure during umbilical occlusions. A review of the physiologic explanations to decelerations stresses however that the initial reflex triggering decelerations is chemoreceptor mediated.[91]
Clinical studies have reported an association to neonatal depression and birth acidemia if severe variable decelerations are present together with tachycardia or reduced / minimal variability. [92, 93]
In a large study by Hamilton et al., CTG tracings from the last 4 hours from 3 320 babies with umbilical BD_{blood} < 8 mmol/L and from 316 babies with umbilical BD_{blood} > 12 mmol/L were analyzed with computerized pattern recognition. The aim was to determine the ability of 8 subtypes of variable decelerations, defined by size and shape, to discriminate between normal umbilical blood gases and those with metabolic acidemia and neonatal encephalopathy. Of all features commonly used as grading of severity of the variable decelerations, e.g. lower baseline after deceleration, prolonged duration, loss of internal variability, biphasic shape, prolonged secondary rise, loss of pre- and post-acceleration, slow return to baseline; only 3 subtypes showed significant discrimination: those with prolonged duration, loss of internal variability or with at least two of the "sixties" criteria (depth ≥ 60 bpm, lowest value ≤ 60 bpm, duration ≥ 60 seconds). All other subtypes were no better than chance.[81] However, not even the 3 subtypes that were significantly associated with birth acidemia had an impressive predictive ability, with values ranging between 0.57 and 0.61 in the area under the receiver-operating characteristic curve.

Early decelerations

Early decelerations are one of the three types of decelerations firstly described by Hon et al. They are commonly explained as caused by compression towards the fetal head with resulting changes in cerebral blood flow.[94, 95] A vagal reflex via medullary centres reduces FHR, and a deceleration with a smooth start and end typically mirrors the contraction. They are generally in all guidelines considered benign and seldom associated with fetal hypoxia or acidemia. There are however diverging opinions regarding origin as well as interpretation.[80] In one review of decelerations, it is speculated that the discrepancy between opinions about how frequent early decelerations appear, is explained by which paper speed is used. The authors describe that the early decelerations originally described by Hon and Quilligan with a paper speed of 3 cm/min look like mild variable decelerations at 1 cm/min.[91]

Uterine contractions



External monitoring mainly gives information on the frequency of contractions. As a tocodynamometer measures the increase and decrease in myometrium tension through the abdominal wall, this is affected by placement of the probe, the tightness of the supporting elastic band, and abdominal adiposity. For information of duration of contraction, abdominal palpation can be used, but the only way to monitor the intensity and basal uterine tonus is internal monitoring. Although of theoretical importance, in a randomized trial, the use of internal monitoring of uterine contractions could not be shown to be beneficial, neither for the woman nor the fetus.[96] However, internal monitoring of contractions can be necessary if a satisfactory external recording cannot be achieved due to maternal adiposity or other reasons, especially in augmented labor.

Inter-observer variability

One of the problems with CTG is that interpretation of patterns differs between observers. Early studies during the 1980s revealed a uniform interpretation in 22-29% of cases.[97, 98] Studies during the 1990s and more recent studies used the Kappa statistics and Proportion of agreement calculations to examine intra-, and inter-observer variability in CTG interpretation. There are comparisons of as well interpretations of the different parameters, as interpretations of the classification into different tier systems. A Kappa value of > 0.75 is generally considered excellent, 0.4-0.75 fair to good, and < 0.4 poor. Kappa for classification varied in different studies between 0.48 and 0.77.[99-101] In a study by Bernardes et al., Kappa was better for baseline and accelerations (0.51 and 0.52 resp.) than for variability (0.35), and worse for decelerations (0.21-23 for early and late decelerations, and merely 0.05 for variable decelerations).[82] These unsatisfactory results have yielded discussions and debates concerning the usefulness of CTG, as well as educational programs with the aim to reach a more uniform interpretation. In a recent study from 2013 using the definitions by National Institute of Child and Health and Human Development (NICHHD), the Kappa values were remarkably higher for all parameters (K 0.97 for baseline, 0.8 for variability, 0.62 for accelerations, 0.8 for late decelerations and 0.64 for variable decelerations). They were consistent throughout the observers with varying degrees of experience.[102] The authors suggest that the uniform training and education in addition to standardized definitions and interpretation were of significant value.

FETAL SCALP BLOOD SAMPLING

Normal range of fetal pH, BD and lactate concentration

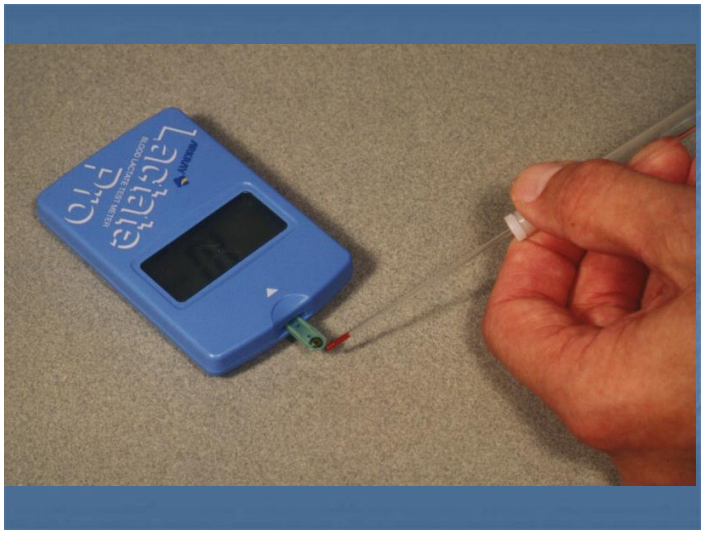
The method of FBS was developed quite shortly after the introduction of CTG. Saling et al did the first studies investigating the normal range of pH-value of fetal blood. Through FBSs during labor of 306 fetuses who were "very vigorous at birth", they set a mean value of fetal scalp pH during first stage of labor between 7.333 and 7.338. They noticed that pH values were quite stable during first stage of labor, but there was a pronounced fall late in second stage to pH values between mean value of umbilical artery (7.27) and umbilical vein (7.33). Since scalp blood is capillary blood, it is logical to have a pH value between that of oxygenated umbilical vein blood coming from the placenta, with lower pCO_2 and thereby higher pH, and deoxygenated umbilical artery blood with higher pCO_2, and lower pH having circulated through fetal tissues.
Lower limit of normal range during labor was set as the mean minus 2 SD's which was between 7.227 and 7.196. For clinical use, they suggested that fetal values between 7.20 and 7.24 should be considered as pre-pathologic, and values below 7.20 as pathologic or "acidemic".[103] Mean and normal range of fetal pH have been confirmed in other studies.[104]

Although Saling et al. in the initial studies took into account the influence of pCO_2, and calculated pH values equilibrated to normal pCO_2, with the intention to adjust for the respiratory component, this never became clinical practice. pH analysis of fetal scalp blood has been regarded as gold standard in FBS, but has several disadvantages. Since it requires a considerable amount of blood, sampling and/or analysis failure due to air contamination has been reported in 11-21% of cases.[105, 106] It does not discriminate between respiratory and metabolic acidemia, where the former is shown to be of no harm to the fetus.[21]
The main purpose of FBS is to identify fetuses with developing anaerobic metabolism and thus metabolic acidemia, when the CTG tracing is non-reassuring, with the aim to deliver the baby at "the window of opportunity" i.e. before any organ damage is established. Secondly, FBS can be used to rule out metabolic acidemia in cases with a falsely positive CTG tracing, to reduce unnecessary interventions. Since the end products of anaerobic metabolism are $lactate^-$ and H^+, lactate analysis of fetal scalp blood was an attractive alternative to pH measurements, and during the 1970's, 1980's and 1990's, lactate analysis of umbilical and fetal scalp blood was investigated.[19, 104, 107-110]

Lactate concentrations were calculated in two different low risk populations of women with means 1.2-1.7 mmol/l in whole blood.[110, 111] These values were analyzed with a prototype of the currently used meter, and correspond to 1.6-2.3 when analyzing with Lactate Pro™ (Figure 6). Lactate concentrations have been shown to be stable throughout first stage and through passive part of second stage, only increasing during the active phase of second stage of labor.[25]

There have been few studies on BD values in fetal scalp blood. Umbilical BD measures have been evaluated, and Helwig et al. reported a mean umbilical BD_{blood} of 4 mmol/L from a population of 16000 newborns.[112] The 2 SDs of 11 mmol/L corresponded well with earlier findings by Low.[113]

Fig. 6. Portable lactate meter for bedside use.



Correlations between fetal lactate, acid base status and neonatal outcome

Animal studies with experimental hypoxia have shown that lactate concentration in the heart and brain correlates to lactate concentration in umbilical arterial blood,[114] as well as with subcutaneous lactate concentration.[115, 116]
Lactate in fetal scalp blood is shown to have a good correlation with as well fetal scalp blood pH as fetal scalp blood BD,[4, 117] and also with umbilical pH, BE and lactate.[4, 117, 118]

Umbilical lactate is in several studies shown to correlate well with umbilical pH, with *r* ranging from - 0.38,[119] to -0.69.[117, 120] The study by Linet showed an even higher correlation between lactate and BD in umbilical artery blood, with $r = 0.84$, and $r^2 = 0.48$. This has been confirmed in a large Danish study of umbilical blood samples from 2554 deliveries.[121] They found similar correlations between lactate and pH ($r = - 0.73$), lactate and SBE ($r = - 0.76$) and lactate and ABE ($r = -0.83$).

There are several studies on the correlation between BD and neonatal outcome, revealing a threshold for significant metabolic acidemia at a BD between 12 and 16 mmol/L.[122] Animal studies on the lamb model showed that significant metabolic acidosis is associated with seizures, and clinical studies have described an association between severe acidemia and multi-organ dysfunction in the newborn.[45]
Early neonatal lactate correlated significantly with umbilical artery BD ($r^2 = 0.51$), when measured in radial artery blood within 30 min. Lactate concentration lower than 5 mmol/L and/or BD lower than 10 mEq/l were not followed by neurological complications. A lactate concentration greater than 9 mmol/L was associated with moderate or severe encephalopathy with a sensitivity of 84% and a specificity of 67%.[123]

Predictive and preventive lactate values

Several studies have investigated the predictive ability of lactate.[4, 118, 124, 125] In a retrospective study by Kruger et al., the fetal scalp lactate values with maximum sensitivity and specificity for moderate to severe hypoxic ischemic encephalopathy (HIE) was 6.5 mmol/L, and for Apgar score < 4 at 5 minutes 6.0. Lactate with the highest accuracy for UA-pH < 7.00 was 5.1 mmol/L.[124] In a prospective cohort study by Ramanah, a scalp lactate cutoff value of 5 mmol/L was the most predictive for neonatal acidosis.[125] Heinis et al. reported from a retrospective observational study that fetal scalp lactate < 5.4 mmol/L indicated reassuring fetal status, whereas lactate ≥6.6 mmol/L indicated metabolic acidemia in umbilical artery.
Since the aim is to prevent and not predict birth acidemia and neonatal complications, the cutoff must be set below predictive values, and in Sweden the cutoff used for recommendation of intervention is 4.8 mmol/L, which was the 75th percentile in the study by Kruger.[124] This corresponded well with the formerly used pH cutoff for fetal acidemia at 7.20, and thus, indication that intervention rates would not increase by the use of lactate analysis at FBS.

Two randomized controlled trials (RCTs) have compared lactate analysis with pH analysis of fetal scalp blood, with similar advantages of significant less failure rate (1.2-1.3 % vs 10.4-19.6 %), but no differences in neonatal outcome or intervention rate.[105, 126] Neonatal outcome measures included low Apgar score at 5 minutes, admission to neonatal intensive care unit, low UA-pH, high BD values or metabolic acidemia in umbilical artery. Comparisons were done overall as well as between those where FBS had been performed within 60 minutes prior to delivery.

The lactate concentration is stable throughout first stage of labour,[110] but increases in both mother and fetus during the active part of second stage of labour. During active pushing, lactate increases by 1 mmol/L per 30 minutes in the fetus, and by 2 mmol/L in the mother.[127] The increasing arterial-venous difference in lactate concentration in acidemic fetuses compared to non-acidemic fetuses suggests fetal origin of the lactacidemia.[24] Since there is a physiological increase in all fetuses, another cut-off value would possibly be adequate for lactate measures during active second stage. However, a limit that must be safe for all fetuses, would be difficult to set, and additionally, adding separate recommendations for different phases of labor would make the method less feasible in clinical practice.[127]

The usefulness of FBS as an adjunct to CTG monitoring

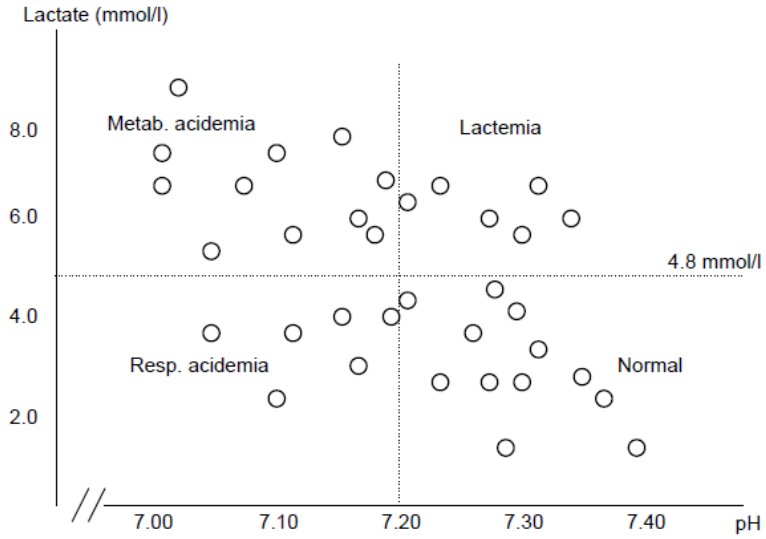
Critics of the use of FBS argue that there is no shown benefit of FBS as an adjunct to intrapartum CTG, with reference to the meta-analysis of EFM.[1] The comparison was however between RCTs with access to FBS in all arms, and RCTs without the adjunct of FBS, and the different RCTs varied largely in as well inclusion criteria, routines of intrapartum care, and levels of background risks in the study populations. The only study that randomized to CTG with or without FBS was the Denver study with 690 patients i.e. 230 in each arm. They reported a cesarean rate of 18 % in the CTG only group, and 11 % in the CTG + FBS group, and cesarean for fetal distress 7 % and 3 %, respectively. The differences were not significant; it is possible that the study was

underpowered and would have needed some 350 cases in each arm for statistical significance of the reported magnitude of differences in proportions.

When lactate analysis is used in FBS, the measured entity is the concentration of lactate ions and not pH and thus, the proper term to use would be lactemia rather than acidemia or lactacidemia. As explained above, the main reason for increased lactate production is anaerobic metabolism with lactate as the end product, and development of metabolic acidemia. Therefore, these terms will be used equally in this thesis.

Theoretically, there can be situations with increased lactate concentration and normal pH, and thus, lactemia without acidemia. Initially during incipient anaerobic metabolism, hydrogen ions produced parallel with lactate can be buffered by other buffer bases than HCO_3^- and therefore pH initially can stay unaltered for a short period. Engidawork et al. showed in an animal model, that subcutaneous lactate correlated well with intracerebral levels of lactate, pyruvate and pH. Under hypoxic conditions, the increase in subcutaneous lactate concentration preceded the pH decrease and lactate increase in the brain tissue.[115] This supports the view of lactate as an early marker in the hypoxic process.
The theoretical rationale between pH and lactate concentration is illustrated below in Figure 7. Both pH and lactate will identify a metabolic acidemia. A respiratory acidemia diagnosed with pH will have a normal result if lactate concentration is determined, and correspondingly, cases with high lactate without acidemia will not be discovered by pH. During labor, with successively increasing frequency and power of contractions and concomitant intermittent reduction in oxygen supply, it is unlikely that incipient anaerobic metabolism would regress, and in accordance with the findings of Engidawork et al., lactemia would not be an innocent situation of a false positive test, but rather an earlier stage than lactacidemia in the hypoxic process.[128]

Fig. 7. Correlation between pH and lactate and illustration of groups that will be considered abnormal dependent on analysis type.



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AIMS

The general aim of this thesis was to increase the knowledge about fetal lactate concentration and correlation to as well CTG patterns as to neonatal outcome, and to elucidate several aspects of lactate production as a fetal response to intrapartum hypoxia.

The specific aims of the individual studies were:

- To analyse short-term neonatal outcome and sampling to delivery interval in cases with severe intrapartum acidemia. (Study I)

- To compare the fetal response to hypoxia between growth-restricted fetuses and appropriately grown fetuses in terms of lactate production. (Study II)

- To study the association between different CTG patterns and intrapartum fetal lactacidemia. (Study III)

- To investigate if repeat (≥3) FBS is associated with increased risk of fetal acidemia, operative interventions and worse neonatal outcome than 1-2 FBS during labor. (Study IV)

MATERIALS AND METHODS

STUDY POPULATION

The present thesis is based on two different cohorts of women. All subjects were women who underwent fetal blood sampling during labor. They presented a CTG pattern that was assessed as non-reassuring or pathological and considered an indication for FBS by the clinician in charge.

Population in studies I and II

Subjects in study I and II were women included in a former multicenter RCT, performed in ten obstetric units in Sweden. The women had given informed consent either at antenatal clinics or at admission to the labor ward. They had a singleton pregnancy of ≥34 weeks with cephalic presentation. When intrapartum CTG tracing was non-reassuring and the attending doctor found indication for FBS, they were randomized to FBS with pH-analysis, or FBS with lactate analysis. Study I included all 2,992 women that had been randomized to either pH-analysis or lactate analysis. Due to sampling failure and several other reasons for no collection of blood, such as rapid delivery, reassuring CTG and withdrawn consent, there were 1008 women with available data in the pH group and 1354 women in the lactate group of the 1,496 randomized women to each arm. Subjects in study II were the women randomized to FBS with lactate analysis. Background data on the study population is shown in Table 4.

Table 4. Characteristics of study population in studies I and II. (medians [range], numbers [%])

		Population Study I (n=2992)	Population Study II (n=1354)
Maternal age (years)		33 (19-49)	31 (18-46)
Gestational age (weeks^{days})		40^{3} (34^{0}-44^{2})	40^{3} (34^{0}-43^{6})
Parity	Nulliparous	2334 (78.0)	1065 (78.7)
	Multiparous	658 (22.0)	289 (21.3)
Mode of delivery	VE/Forceps	786 (26.3)	342 (25.3)
	Caesarean delivery	867 (29.0)	414 (30.6)
Birth weight (g)		3565 (1590-6110)	3570 (1860-6110)

VE=vacuum extraction

Population in studies III and IV

Studies III and IV were performed in the labor ward at Karolinska University Hospital, Solna, Sweden, with approximately 4500 annual deliveries during the study period. The department is a primary obstetric service center for Stockholm County and a tertiary referral center. The study population consisted of women with a singleton pregnancy of ≥34 weeks with cephalic presentation, and indication for FBS during labor according to the clinician in charge. Characteristics of the study population are shown in Table 5. Women gave informed consent prior to sampling. After an interim analysis which revealed a probability of substantial amount of missing cases, ethic approval was

obtained for search in medical records to include all cases with FBS. During the study period there were 1070 women who underwent FBS and met the inclusion criteria.

Table 5. Characteristics of study population in studies III and IV.

	Total population N=1070
Maternal age (years)	
≤24	137 (12.8)
25-35	725 (67.8)
≥36	208 (19.4)
Nulliparous	772 (72.1)
Previous cesarean delivery	109 (10.2)
Gestational age (weeks^{days})	
34^0-36^6	36 (3.4)
37^0-40^6	724 (67.7)
≥41^0	310 (29.0)
Induction of labor	380 (35.5)
Birth weight group	
SGA	48 (4.5)
AGA	984 (92.5)
LGA	32 (3.0)
Birth weight (grams)	
<2500	30 (2.8)
2500-3999	858 (80.2)
4000-4500	149 (13.9)
>4500	29 (2.7)

SGA= small for gestational age
AGA=appropriate for gestational age
LGA= large for gestational age

STUDY DESIGN

Study I is a secondary analysis of all participants in an earlier performed RCT. Intrapartum acidemia was defined as fetal scalp blood lactate concentration above the 95th percentile in the arm with lactate analysis, and fetal scalp blood pH below the 5th percentile in the group with pH analysis. Outcome measures were UA-pH < 7.00, Apgar < 7 at 5 minutes, hypoxic ischemic encephalopathy and time interval from FBS to delivery.

Study II is a secondary analysis of the women in the lactate analysis group in the earlier performed RCT. Fetuses were divided according to birth weight group, and outcome measures were lactate concentrations at FBS during labor.

Study III is a prospective observational cohort study, where CTG tracings prior to FBSs were visually interpreted by a senior obstetrician. The CTG reviewer was blinded to the analysis result of FBS, and the CTG abnormalities were correlated to median lactate concentration and frequency of acidemia at FBS, which was the outcome measure.

Study IV is a prospective cohort study from the same study population as Study III. Women were divided into two groups according to number of FBSs during labor; women undergoing 1-2 samplings and women undergoing ≥ 3 samplings. Outcome

measures were Apgar score < 7 at 5 minutes, metabolic acidemia (pH < 7.05 and BD > 12 mmol/L) in umbilical artery and frequency of cesarean delivery.

ELECTRONIC FETAL MONITORING

Intrapartum fetal surveillance followed Swedish guidelines.[129]
All women underwent a CTG monitoring at admission to the labour ward, and if they were considered at low risk, they had intermittent CTG monitoring every 2 hours with auscultation of fetal heart rate in between. If they were considered at high risk (e.g. preeclampsia, hypertension, IUGR), if they had oxytocin augmentation or epidural analgesia they had continuous CTG monitoring. The FHR was registered using external signal unless there was suboptimal signal, or any other indication for use of scalp electrode. The EFM signal was registered at a paper speed of 1 cm / minute.

CTG pattern definitions

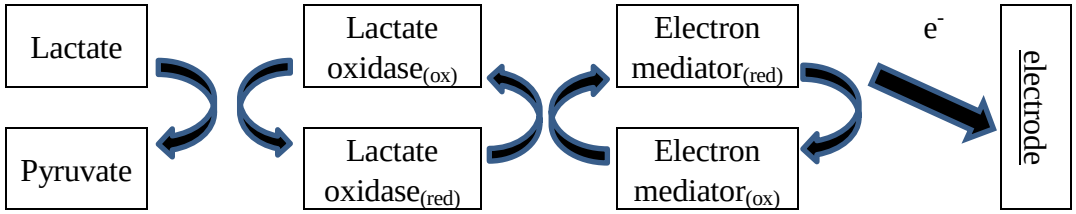
In Study III, the CTG interpretation by the blinded reviewer followed current Swedish guidelines,[64] which are based on the FIGO guidelines.[56] The CTG traces were interpreted with focus on the last 60 minutes prior to each FBS, with a structured documentation of baseline, (<110bmp=bradycardia, 110-150=normal, >150= tachycardia, variability (<2=absent, 2-4=reduced, 5-25=normal, >25=increased), accelerations (>15bpm, >15 seconds), decelerations (>15 bpm, > 15 seconds) and contractions. Severe variable decelerations were defined as having a variable shape, an abrupt fall from baseline FHR to nadir of deceleration, and duration > 60 seconds before return to baseline. Late decelerations were defined as start of deceleration after peak of contraction, a uniform shape and a gradual fall to nadir of deceleration. Early decelerations (uniform shape starting before peak of contraction) and simple variable decelerations (abrupt FHR fall and duration < 60 seconds) were referred to the normal group. We defined a bradycardic episode as baseline FHR < 110 for > 3 minutes occurring within 30 minutes before sampling, including prolonged decelerations (< 10 minutes) and bradycardia for > 10 minutes.

FETAL BLOOD SAMPLING

Fetal blood sampling was performed with the woman either in left-lateral recumbent position or supine and her legs in stirrups, as the clinician preferred. An amnioscope was introduced into the vagina and densely applied to the fetal head. The fetal scalp was wiped dry from amniotic fluid and silicone gel was applied. After minimal incision, blood was collected in a glass capillary tube; for pH-analysis at least half of the capillary tube was filled, for lactate analysis the sufficient amount was 5 µl. Lactate analysis was carried out immediately at the bedside with the lactate meter Lactate Pro™ (Arkray, Kyoto, Japan). The meters were calibrated every 50th analysis.

The meter uses an enzymatic reaction with lactate oxidase and potassium ferrocyanide as an electron mediator. The meter measures the magnitude of the anodic current of the reduced mediator by the enzymatic reaction as shown in Figure 8, and displays the lactate concentration 60 seconds after a blood sample (5 µl) is applied.

Figure 8. Enzymatic reaction in the Lactate Pro™



Cord blood sampling was performed immediately after delivery as a routine at all deliveries. Samples were taken by the assistant nurse at vaginal deliveries, and by the surgeon or assistant at caesarean deliveries. Umbilical artery and vein were punctured separately and approximately 2 ml of blood was drawn into preheparinized plastic syringes.

Blood gas and pH determinations were performed on ABL 800 Flex (Radiometer, Copenhagen) in study III and IV. In Study I and II, the ten obstetric units participating in the RCT used different blood gas analyzers, and therefore, quality checks of the acid-base measurements were performed every month during the study, by an independent company (Equalis). All departments were sent standard solutions for analysis and comparison between analyzers.

STATISTICS

Statistical analyses were performed with Statistica software, v. 10.0-12.0, StatSoft, Tulsa, USA. Values are presented as medians, ranges and percentiles due to non-normal distribution (Studies I - IV). Comparisons between two continuous variables were tested with the Mann-Whitney U-test, and between more than two groups with Kruskal-Wallis test (Studies I - IV). Correlation between two variables was estimated using Spearman rank correlation (Studies I-II). Comparisons of proportions between groups were performed with Chi-square test and Fisher's exact test where appropriate (Studies I – IV). Logistic regression was used to calculate odds ratio (OR) and to control for confounders (Study IV). A p-value <0.05 was considered statistically significant.

ETHICS

All studies were approved by the Regional Ethics Committee of the Karolinska Institutet in Stockholm, Sweden.
D-nr: 02-109 (Study I-II)
D-nr: 2008/1618-31, 2011/478-32 (Study III-IV)

RESULTS

NEONATAL OUTCOME AFTER SEVERE INTRAPARTUM ACIDEMIA – STUDY I

There were 2301 lactate analyses in 1355 women in the lactate arm. Median and 95th percentile values of the 2301 analyses were 2.9 mmol/L and 6.6 mmol/L, respectively. In the pH analysis arm, the corresponding values from 1628 pH analyses in 1008 women were 7.30 (median) and 7.17 (5th percentile).
Analyses of the last FBS in all cases of our study population with FBSs upon CTG indications similar to the study by Kruger et al,[124] revealed the 75th percentile of lactate concentration at 4.3 mmol/L and corresponding 25th percentile pH value of 7.25.

Eighty-five out of 1355 fetuses in the group with lactate analysis at FBS had lactate concentration > 6.6 mmol/L, and 68 out of 1008 fetuses in the group with pH analysis at FBS had a pH value < 7.17.
Severe neonatal morbidity occurred in 10% or less in this high risk population with scalp blood values > 95th percentile in the lactate group or < 5th percentile in the pH group. Neonatal outcome is shown in Table 6.

Of these 154 infants with severe intrapartum acidemia, defined as above, 12 (7.8%) had an UA-pH < 7.00, 16 (10.4%) had an Apgar score < 7 at 5 minutes, and 4 (2.6%) had hypoxic ischemic encephalopathy. There were no significant differences in neonatal outcomes between the two groups.

Table 6. Neonatal outcome in 154 cases with severe intrapartum acidemia.

	Scalp lactate > 6.6 mmol/l N=85 (%)	Scalp pH < 7.17 N=69 (%)	p-value
UA-pH <7.00	8 (9.4)	4 (5.8)	0.41
UA-pH <7.10	14 (16.5)	20 (29.0)	0.06
Metabolic acidemia	1 (1.2)	7 (10.1)	0.02
Apgar < 7 at 1 min	28 (32.9)	31 (44.9)	0.13
Apgar <7 at 5 min	9 (10.6)	7 (10.1)	0.93
Apgar <4 at 5 min	3 (3.5)	3 (4.3)	0.79
NICU admission	25 (29.4)	18 (26.1)	0.65
HIE	2 (2.4)	2 (2.9)	0.83
MAS	1 (1.2)	0	0.37

UA-pH=umbilical artery pH
NICU= neonatal intensive care unit
HIE=hypoxic ischemic encephalopathy
MAS=meconium aspiration syndrome

The proportion of operative vaginal deliveries was higher in the group with pH analysis, (Table 7) and the time interval from sampling to delivery was shorter than in the lactate group (median 16 vs 21 minutes, p-value 0.01). Delivery within 15 minutes after FBS occurred in 22/85 (26.8%) in the lactate analysis group and in 28/69 (40.6%) in the pH analysis group (p=0.053). Among the cesarean deliveries, the proportion of immediate cesarean delivery was higher in the pH group.

Correlation between scalp blood lactate and UA-pH at delivery was R=-0.21 ($p<0.05$) and the corresponding value for scalp blood pH was R=0.40 ($P<0.05$).

Table 7. Delivery mode in groups with lactate analysis and pH analysis at FBS, respectively

	Scalp lactate group N=85 (%)	Scalp pH group N=69 (%)	p-values
SVD	5 (5.9)	8 (11.6)	0.20
VE / forceps	21 (24.7)	26 (37.7)	0.08
Cesarean delivery	59 (69.4)	35 (50.7)	0.02
Emergency[a]	39 (45.9)	13 (18.8)	0.006[c]
Immediate[b]	20 (23.5)	22 (31.9)	

SVD=spontaneous vaginal delivery, VE=vacuum extraction

[a] regional analgesia, time taken for routine preoperative preparations

[b] general anesthesia, no preoperative preparations

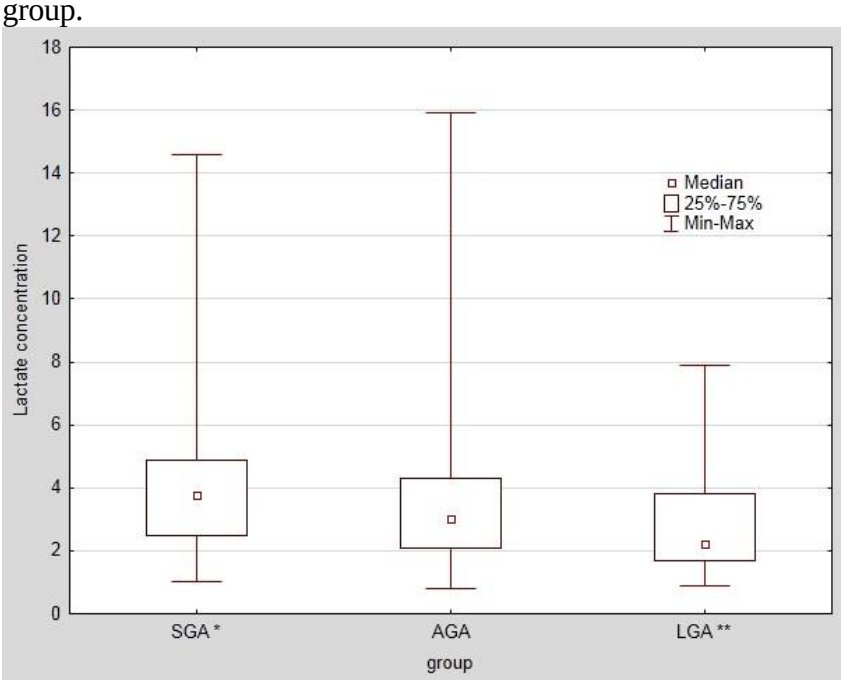
[c] immediate vs emergency

HYPOXIA AND LACTATE PRODUCTION IN THE IUGR FETUS – STUDY II

The proportions of SGA and large for gestational age (LGA) fetuses were 5.3% and 3.3% respectively. Compared with mothers of AGA and SGA infants, mothers of LGA infants were more often multiparous, had a shorter gestational age and had more often a caesarean delivery.

The median scalp lactate concentration in the SGA (n=72), AGA (n=1237) and LGA (n=45) groups were 3.8, 3.0 and 2.2 mmol/l, respectively. The median lactate concentration in the SGA group was significantly higher than in the AGA group (p=0,017), and the median lactate concentration in the LGA group was significantly lower than that in the AGA group (p=0.009). Distributions are shown in Figure 9.

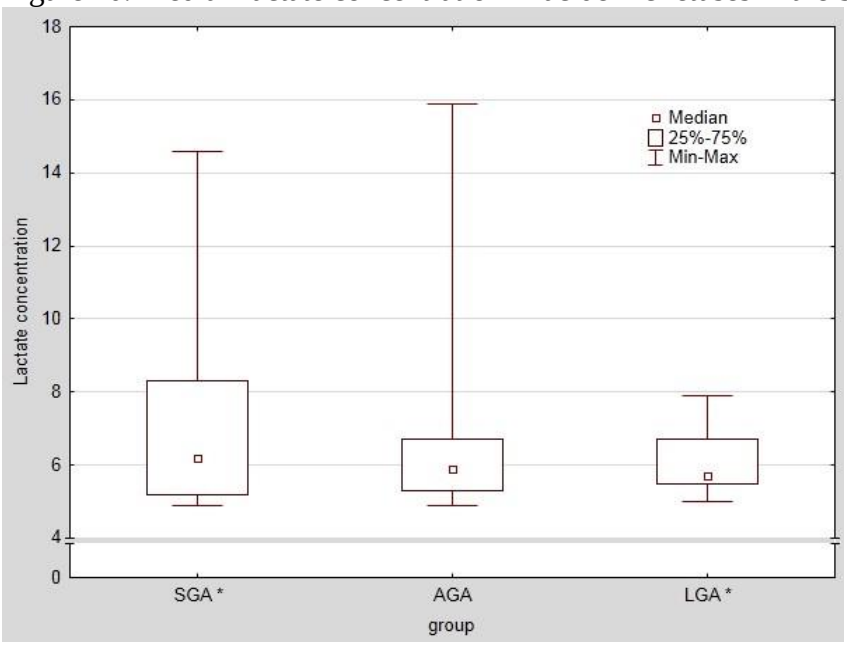
Figure 9. Median lactate concentration in the total study population by birth weight group.



SGA=small for gestational age, AGA=appropriate for gestational age, LGA=large for gestational age, * SGA versus AGA, ** LGA versus AGA

In the subgroups with scalp blood lactate concentration > 4.8 mmol/L (SGA, n=19; AGA, n=247; LGA, n=8), the median (range) values were 6.2 (4.9-14.6) for SGA, 5.9 (4.9-15.9) for AGA and 5.7 (5.0-7.9) for LGA. In these subgroups with lactemia, there were no significant differences between the SGA and AGA groups, the LGA and AGA groups or the SGA and LGA groups. (p = 0.65, p = 0.98 and p = 0.81 respectively). The distributions are shown in Figure 10.

Figure 10. Median lactate concentration in acidemic fetuses in the birth weight groups.



SGA=small for gestational age, AGA=appropriate for gestational age, LGA=large for gestational age, * SGA versus AGA, ** LGA versus AGA

The proportions of newborns with UA-pH < 7.00, metabolic acidosis or Apgar score < 7 at 5 minutes did not differ between the birth weight groups, neither when comparing all cases nor in the subanalysis of those with intrapartum acidemia (Table 8).

Table 8. Neonatal outcome in the birth weight groups

	SGA n (%)	AGA[a] n (%)	LGA n (%)	
Total number[b]	72	1237	45	p-value[c] (SGA/LGA)
UA-pH<7.10	4 (6.2)	106 (9.2)	3 (7.0)	0.40/0.62
UA-pH<7.0	0 (0.0)	20 (1.7)	0 (0.0)	0.28/0.38
Metabolic acidemia	1 (1.5)	41 (3.6)	0 (0.0)	0.38/0.21
Apgar < 7 at 5 min	1 (1.4)	40 (3.2)	1 (2.3)	0.38/0.7
N with scalp lactate > 4.8 mmol/L[d]	19	247	8	p-value[e] (SGA/LGA)
UA-pH<7.10	2 (10.6)	35 (15.2)	2 (25)	0.44/0.36
UA-pH<7.0	0 (0.0)	10 (4.3)	0 (0.0)	0.45/0.71
Metabolic acidemia	1 (5.3)	18 (7.8)	0 (0.0)	0.57/0.53
Apgar < 7 at 5 min	1 (5.3)	21 (9.1)	1 (12 .5)	0.52/0.52

SGA=small for gestational age, AGA=appropriate for gestational age, LGA=large for gestational age, UA-pH=umbilical artery pH

[a] reference group

[b] numbers with full acid-base data were 65, 1149 and 43 respectively

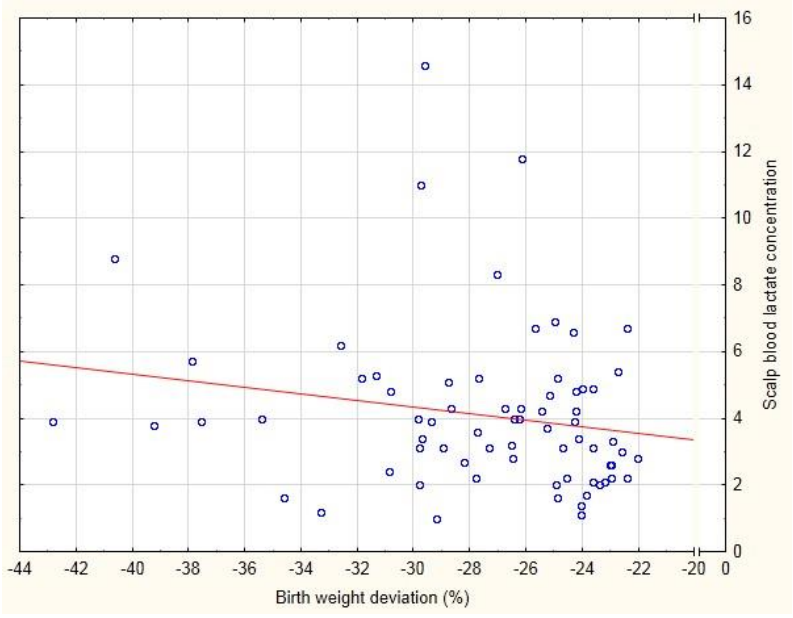
[c] X^2-test, p-value SGA: SGA vs. AGA; p-value LGA: LGA vs. AGA

[d] numbers with full acid-base data were 19, 231 and 8 respectively

[e] Fishers exact test, p-value SGA: SGA vs. AGA; p-value LGA: LGA vs. AGA

The correlation between lactate and weight deviation was analyzed in the SGA group separately. There was a weak but significant negative correlation between birth weight deviation and lactate concentration (ρ = - 0.24, p < 0.05) (Figure 11).

Figure 11. Correlation between lactate concentration and fetal weight deviation in the SGA group.



CARDIOTOCOGRAPHY PATTERNS AND RISK OF ACIDEMIA – STUDY III

During the study period, FBS was performed in approximately 11 % of all labors at the labor ward where the study was conducted. There were 2134 FBS performed on 1070 women, with a median of two samplings and range 1-8. Sixty-eight percent had their first FBS during first stage of labor and 92 % had internal CTG monitoring.

The blinded reviewer interpreted the CTG pattern prior to the first FBS as having a normal baseline and variability without serious decelerations in nearly 23 % of cases, and these will be referred to as the group with normal CTG trace. There were simple variable or early decelerations in 75 % and absence of accelerations in half of these cases. The indication for FBS according to the attending physician had been either another interpretation of decelerations or variability, or absence of accelerations in these cases.

Reduced variability, tachycardia and the combination of the two, implied FBS in 12-14%. Sever variable decelerations were twice as common as late decelerations, 12 % versus 5 %. Decelerations with tachycardia and/or reduced variability were present in approximately 3 % of cases (Table 9).

At the first FBS, cases with normal baseline and variability without serious decelerations had normal lactate concentrations in 97.5%, and isolated reduced variability was associated with a similar high proportion of normal lactate concentrations (Table 9). Within the group with reduced variability, the absence of accelerations for more than 60 minutes did not significantly increase the proportion of acidemia at FBS (4.0% [CI 95% 1.3-6.7%]).

Cases with serious (severe variable or late) decelerations had a tendency towards higher prevalence of lactacidemia compared with cases with tachycardia (14.2% and 13.8% vs 8.1% [ns]), even when the tachycardia was accompanied by a reduced variability (6.0%).
The CTG patterns with the highest frequency of pathological lactate concentration (> 4.8 mmol/L) at FBS were severe variable or late decelerations in combination with tachycardia (25% and 20% respectively).

The median lactate concentration was not higher in the group with isolated reduced variability than in the group with a normal CTG trace. Cases with tachycardia had only a slightly higher median lactate concentration than cases with a normal CTG trace (2.4 mmol/L vs 2.2 mmol/L), unless the tachycardia was accompanied by serious decelerations (Table 10).
The median lactate concentrations were in these cases 1.6 mmol/L and 0.9 mmol/L higher than in the reference group. If cases with maternal fever (>38.0°C) were excluded in cases with tachycardia the proportion of lactacidemia did not change.

Table 9. Proportions of fetal lactacidemia at first FBS in groups with different CTG patterns.

CTG-pattern	Total numbers (%)	Numbers with lactate >4.8 mmol/L	% (95% CI)	P-value[a]
Normal baseline and variability	242 (22.6)	6	2.5 (0.1-4.5)	
Reduced variability	154 (14.4)	4	2.6 (0.1-5.1)	1.0
Absent variability	32 (3.0)	4	12.5 (0.4-24.6)	0.020
Increased variability	10 (0.9)	2	20.0 (0.0-50.2)	0.035
Bradycardic episode	46 (4.3)	10	21.7 (9.4-34.1)	<0.001
Tachycardia	124 (11.6)	10	8.1 (3.2-12.9)	0.027
Tachycardia + reduced variability	149 (13.9)	9	6.0 (2.2-9.9)	0.102
Severe variable decelerations	127 (11.9)	18	14.2 (8.0-20.3)	<0.001
Late decelerations	58 (5.4)	8	13.8 (4.6-22.9)	0.001
Severe variable decelerations + reduced variability	28 (2.6)	4	14.3 (0.5-28.1)	0.013
Late decelerations + reduced variability	25 (2.3)	3	12.0 (0.0-25.7)	0.042
Severe variable decelerations + tachycardia	32 (3.0)	8	25.0 (9.1-40.9)	<0.001
Late decelerations + tachycardia	30 (2.8)	6	20.0 (4.8-35.2)	0.001
Missing + undefinable pattern	13 (1.2)	2	15.4	0.057
All groups	1070	94	8.8	

[a] p-value calculated with two-tailed Fisher's exact test in comparison with normal CTG

Table 10. Median of lactate concentration at first FBS in groups with different CTG patterns.

CTG-pattern	median (mmol/L)	$25^{th} – 75^{th}$ percentile	P-value[a]
Normal baseline and variability (242)	2.2	1.8-3.1	
Reduced variability (154)	2.15	1.7-2.6	0.0176
Absent variability (32)	2.35	1.9-3.2	0.833
Increased variability (10)	3.4	2.6-4.1	0.008
Bradycardic episode (46)	3.15	2.2-4.4	<0.001
Tachycardia (124)	2.4	2.0-3.4	0.0125
Tachycardia + reduced variability (149)	2.4	1.9-3.3	0.223
Severe variable decelerations (127)	3.2	2.3-4.2	<0.001
Late decelerations (58)	3.2	2.2-4.1	<0.001
Severe variable decelerations + reduced variability (28)	3.1	2.2-4.1	<0.001
Late decelerations + reduced variability (25)	3.2	2.7-4.1	<0.001
Severe variable decelerations + tachycardia (32)	3.8	3.1-4.8	<0.001
Late decelerations + tachycardia (30)	3.1	2.4-4.7	<0.001
Missing + undefinable pattern (13)	3.2	1.4-5.3	0.478
Total	2.6	2.0-3.4	

[a] p-value calculated with Mann-Withney test compared with normal baseline and variability.

Since approximately half of the study population underwent more than one FBS during labor, the frequency of increased lactate concentration at the last FBS also was calculated. Cases with active pushing prior to sampling were excluded in these calculations.

The rate of increased lactate concentration was 4.8 % in the group with normal baseline and variability, and 22 % if either late or severe variable decelerations occurred. If either of these decelerations occurred together with reduced variability the proportion of acidemia was 29 %, and tachycardia accompanied by decelerations was the pattern with the highest proportion of acidemia at FBS (Table 11). The median lactate concentration was still not increased in the group with isolated reduced variability, but nearly doubled in cases with tachycardia combined with serious decelerations compared with cases with a normal CTG trace (Table 12).

Table 11. Proportions of fetal lactacidemia at last FBS[a] in groups with different CTG patterns.

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

[a] cases with active pushing prior to sampling excluded
[b] p calculated with two-tailed Fisher's exact test compared with normal CTG group

Table 12. Median of lactate concentration at last FBS[a] in groups with different CTG patterns.

CTG-pattern (n)	median (mmol/L)	25th – 75th percentile	P-value[b]
Normal baseline and variability (187)	2.3	1.9-3.2	
Reduced variability (113)	2.3	1.8-2.9	0.20
Absent variability (32)	2.6	1.8-4.4	0.373
Increased variability (7)	3.1	2.1-5.7	0.077
Bradycardic episode (36)	3.3	2.7-5.2	<0.001
Tachycardia (106)	3.0	2.2-4.0	<0.001
Tachycardia + reduced variability (128)	2.5	2.0-3.3	0.204
Severe variable decelerations (96)	3.4	2.4-4.4	<0.001
Late decelerations (49)	3.2	2.4-4.6	<0.001
Severe variable decelerations + reduced variability (28)	3.8	2.5-5.0	<0.001
Late decelerations + reduced variability (34)	4.5	3.2-5.0	<0.001
Severe variable decelerations + tachycardia (33)	4.4	3.3-5.4	<0.001
Late decelerations + tachycardia (30)	4.2	3.1-5.1	<0.001
Missing + undefinable pattern (11)	4.1	3.8-6.1	0.013
Total (888)	2.8	2.1-4.0	

[a] cases with active pushing prior to sampling excluded

[b] p-value calculated with Mann-Withney test compared with normal baseline and variability

At the first FBS, there were 148 fetuses with an acceleration as a response of FBS, and two of these had lactacidemia at sampling. The proportion of acidemia among fetuses without a distinct acceleration at FBS was 76/668. At the last FBS the differences in prevalence of acidemia between cases with acceleration and those without were even more pronounced (Table 13).

Table 13. Proportions of fetal lactacidemia at first and last FBS[a] in groups with and without adequate acceleration at FBS

	First FBS n (%)	P-value[b]	Last FBS[a] n (%)	P-value[b]
Acceleration at FBS	2/148 (1.3)		2/108 (1.8)	
Acceleration with only 10 bpm at FBS	8/143 (5.6)	0.05	6/110 (5.5)	0.16
Indefinable pattern at FBS	8/111 (7.2)	0.02	18/95 (21.1)	<0.001
No acceleration at FBS	76/668 (11.4)	0.00	107/575 (18.6)	<0.001
Total	94/1070 (8.8)		133/888 (15.0)	

FBS= fetal scalp blood sampling
[a] active pushing prior to sampling excluded
[b] p-value calculated with Chi square test

NEONATAL OUTCOME AND DELIVERY MODE AFTER REPEATED FBS – STUDY IV

During the study period there were 2134 FBS performed on 1070 women in labor, which constituted approximately 11 % of all deliveries at the labor ward during the study period. The proportion of nulliparous women was higher and labor was more often induced in this cohort of women with FBS compared with the total delivering population. There were 297 women having at least one maternal complication (e.g. diabetes, preeclampsia, hypertension), and 165 had at least one fetal complication (e.g. known IUGR, oligohydramnios, immunization).

The median number of FBS was two, 48% of the population had only one FBS and the range was 1-8. Approximately two thirds of the population, 795 women, had maximum two samplings taken during their course of labor, and 275 women underwent three or more FBS.

Median time from first FBS to delivery was 88 minutes for those with 1-2 samplings and 240 minutes for those with 3 or more samplings (p=0.00). There were no differences in proportions of nulliparous women or women with a history of previous cesarean delivery between the groups. Maternal age did not differ, but there was a higher proportion of women with induced labor in the group with three or more FBS, and their gestational age at delivery was on average three days longer compared with women with 1-2 samplings.

At the last FBS, the median lactate concentration was higher in the group with multiple samplings. The proportion of cases with increased lactate concentration (>4.8 mmol/l) at the last FBS was also higher, and indication for instrumental or operative delivery was more often fetal distress in this group, compared with the group with one or two samplings. Numbers are shown in Table 14.

Table 14. Lactate concentrations at the last FBS and rates of operative delivery due to fetal distress.

	Cases with 1-2 FBS during labour	Cases with ≥ 3 FBS during labour	P-value
Lactate concentration median (range)	2.7 mmol/L (1.0-11.2)	3.9 mmol/L (1.2-9.1)	<0.001[a]
Cases with lactate >4.8 mmol/L n (%)	99/795 (12.4)	76/275 (27.6)	<0.001[b]
Cases with fetal distress as indication for delivery n (%) among cases with operative delivery[c]	228/426 (53.5)	162/221 (73.3)	<0.001[b]

[a] p-value calculated with Mann-Whitney U test
[b] p-value calculated with Chi-square test
[c] instrumental vaginal and caesarean delivery

As shown in Table 15, neonatal outcome did not differ between the groups concerning short-term neonatal outcome. There were similar proportions of neonates with metabolic acidemia or low Apgar score at 5 minutes in the groups with 1-2 and 3 or more FBS. There were neither a difference in proportions of babies needing respiratory support or admission to the neonatal intensive care unit (NICU).
Among women who underwent one or two FBS, 46 % had a spontaneous vaginal delivery (SVD) in contrast to 19 % of those having three or more FBS during labor. Of those delivered operatively, 38 % had three or more FBS, compared with 12 % of those delivered normally (Table 15).

Table 15. Neonatal outcome and delivery mode in groups with 1-2 FBS and ≥ 3 FBS. N(%).

	1-2 FBS	≥ 3 FBS	P-value[a]
Apgar score < 7 at 5 minutes[b]	9/794 (1.1)	6/272 (2.2)	0.19
UA-pH < 7.0[c]	7/618 (1.1)	2/234 (0.9)	0.72
UA-pH < 7.10[c]	34/618 (5.5)	7/234 (3.0)	0.12
Metabolic acidemia[cd]	11/616 (1.8)	3/234 (1.3)	0.61
HIE	0/795 (0.0)	1/275 (0.4)	0.09
NICU admission	42/795 (4.3)	17/275 (6.2)	0.57
Spontaneous vaginal delivery	366 (46.0)	52 (18.9)	0.000
Instrumental vaginal delivery	244 (30.7)	108 (39.3)	0.009
Caesarean delivery	185 (23.3)	115 (41.8)	0.000

UA = umbilical artery, HIE=hypoxic ischemic encephalopathy, NICU=neonatal intensive care unit
[a] p-value calculated with Chi-square test
[b] 4 cases with no Apgar score noted
[c] 218 cases with no or incomplete umbilical blood samples noted
[d] metabolic acidemia defined as pH < 7.05 and base deficit$_{blood}$ >12.

Adjustment for probable confounders revealed that women with a previous cesarean delivery, those with induced labor and nulliparous women had an increased risk of abdominal delivery as expected, but the exposure to three or more FBS was still a significant risk factor for abdominal delivery (Table 16).

FBS in early labor (cervical status 2-4 cm) was a risk factor with adjusted OR for cesarean delivery of 4.4 % (95 % CI 2.9-6.7). Adjustment for time from first FBS and cervical status at first FBS did not reduce the OR of multiple FBS.

Table 16. Crude and adjusted OR for caesarean delivery

		N	Caesarean delivery rate (%)	Crude OR	95% CI	Adj OR[a]	95% CI
Maternal age	≤24	137	23.4	0.79	0.52-1.22	0.82	0.53-1.72
	25 – 35	725	27.7	Ref		Ref	
	≥36	208	32.2	1.24	0.89-1.73	1.20	0.87-1.72
Parity and previous caesarean	Multiparous without previous cesarean	189	20.1	Ref		Ref	
	Nulliparous	772	29.0	1.62	1.10-2.39	1.61	1.07-2.42
	Multiparous with previous cesarean	109	34.9	2.13	1.25-3.62	1.97	1.14-3.41
Gestational age	<37w	36	27.8	1.13	0.53-2.39	1.12	0.52-2.41
	37-41 w	724	25.4	Ref		Ref	
	>41 w	310	34.2	1.52	1.14-2.03	1.30	0.96-1.76
Start of labour	Spontaneous	690	23.8	Ref			
	Induction	380	35.8	1.79	1.36-2.35	1.60	1.19-2.13
Oxytocin augmentation	No	301	21.3	Ref			
	Yes	769	30.7	1.64	1.20-2.25	1.27	0.91-1.77
FBSs during labour	≤2 FBS	795	23.3	Ref		Ref	
	≥3 FBS	275	41.8	2.37	1.77-3.17	2.05	1.52-2.78

[a] adjusted for all other parameters in the model

FBS in early labor (cervical status 2-4 cm) was a risk factor with adjusted OR for cesarean delivery of 4.4 (95 % CI 2.9-6.7). Adjustment for time from first FBS and cervical status at first FBS did not reduce the OR of multiple FBS.

As shown above in Table 14, of the 275 women with 3 or more FBS, 199 had normal results at the last FBS. Ninety-nine of them were in first stage of labor at the time of sampling, and 43 of these 99 women, were vaginally delivered.

DISCUSSION

The discussion will comment the studies in the order III, II, IV and I, with the purpose to follow the course of parturition.

MAIN FINDINGS

Fetuses that during labour had a CTG trace with isolated reduced variability did not have a higher median lactate concentration in scalp blood than fetuses with a normal CTG trace, not even in the absence of accelerations. Also the proportion of lactacidemia at FBS was equal to the group with a normal CTG tracing. The two types of serious decelerations i.e. severe variable and late, correlated equally to increased proportions of lactacidemia at FBS, and the median fetal scalp blood lactate at the first FBS was 1 mmol/L higher than in fetuses with normal CTG tracings. Fetuses with tachycardia in combination with either of the two types of serious decelerations had the highest proportion of lactacidemia at FBS, and at the last sampling, a doubling of the median lactate concentration compared with fetuses having normal tracings.

Fetuses that were SGA had on average slightly higher lactate concentrations than AGA fetuses. The proportion of fetuses with concentrations above the cutoff value set for acidemia was equal between SGA and AGA fetuses. Among fetuses with lactate concentrations above the cutoff for acidemia at FBS, the median lactate concentration did not differ between the SGA and the AGA fetuses, thus showing that SGA fetuses could produce lactate to the same extent as AGA fetuses in response to hypoxia in spite of smaller glycogen reserves.

Neonatal outcome was not negatively affected in cases where prolonged duration of CTG abnormalities had caused ≥ 3 FBSs compared with labors where only 1-2 FBSs had been performed. The rates of Apgar score < 7 at 5 minutes, metabolic acidemia and admission to NICU was equally low in the group with repeated FBSs as in the group with occasional FBS in spite of a longer duration of a non-reassuring CTG. However, the cesarean delivery rate was increased from 23% to 42 % in labors where CTG changes had led to more than 2 FBSs, and the OR was only marginally affected by known risk factors for cesarean delivery.

The risk of serious neonatal complications was low even in cases with severe intrapartum acidemia, i.e. lactate > 95th percentile or pH < the 5th percentile of the study population, where all underwent FBS due to a non-reassuring CTG trace. Among these high-risk cases, i.e. the 5 % of fetuses with the most pronounced acidemia at FBS, the proportion of umbilical artery pH < 7.00 was less than 10 %, and the proportion of HIE was less than 3 %. There were no differences between the groups with lactate and pH analysis. The time interval from FBS to delivery was shorter in the group with pH analysis, partly explainable by a higher proportion of vaginal deliveries, and partly by a higher proportion of immediate deliveries among the cesarean sections.

INTERPRETATION

Besides auscultation, CTG can be regarded as the main method for intrapartum fetal surveillance. CTG is considered a valuable screening method due to its high sensitivity, with a low risk of false negative cases. The specificity is however low, with many healthy fetuses having non-reassuring CTG patterns at some periods during labour, and this leads to a substantial increase in cesarean deliveries, compared with intermittent auscultation.[1]

The primary goal of intrapartum fetal surveillance is to identify those fetuses who do not cope with the stress of a vaginal delivery, i.e. the uterine contractions with concomitant decrease in oxygen supply, and to enable intervention before organ damage has occurred. At the same time, we do not want to expose laboring women to unnecessary interventions with short-, and long-term risks attached.

FBS with lactate analysis is a simple and reliable way to rule out metabolic acidemia in cases with a false positive non-reassuring CTG since false negative tests with FBS are unlikely.[126]

Fetal surveillance with CTG and FBS can however not guard against damage in fetuses that before start of labor have already been exposed to chronic hypoxia or an ischemic event. In a large retrospective study, approximately 50 % of cases with HIE were of antenatal origin.[130] There might be no ongoing acidemia, and the injury can still already have been established, but intervention can prevent further worsening. However, if a healthy fetus enters labor and there is a gradual development of hypoxia, FBS can provide preventive measures, and with timely intervention delivery of a healthy no-acidemic baby can be expected.

FBS with lactate analysis also offers a feasible way to rule in cases with a true positive non-reassuring CTG due to anaerobic metabolism and thereby metabolic acidemia with increased lactate concentration. Several studies have shown that lactate measured in fetal blood as well under normoxic as under hypoxic circumstances is of fetal and not maternal origin.[23, 24, 127] It is also shown that increased fetal glucose levels that are due to administration of 5% glucose or beta-mimetic drugs to the mother does not increase fetal lactate concentration.[131, 132] Accordingly, since the main reason for increased lactate production is hypoxia with anaerobic metabolism false positive tests are unlikely in a correctly collected blood sample.

It is important to understand that the read-off concentration is affected by analysis type; i.e. whole blood with intact erythrocytes, whole hemolysed blood, or plasma, as well as the type of analyzing machine, with the consequence that cutoff level for normal lactate concentration cannot always be fully translated between different studies and guidelines.[133]

Cardiotocographic findings as causes or signs of fetal acidemia

Common causes of concern during labor are absence of FHR accelerations, isolated reduced variability and simple variable decelerations with large amplitude, all of uncertain value regarding the risk of developing fetal acidemia.

There are animal studies elucidating pathophysiologic origins to certain CTG patterns, but many fetuses with CTG patterns that have a hypoxic explanation are born non-acidemic in a vigorous state. Human studies have correlated certain CTG patterns with

neonatal outcome, e.g. acidemia in umbilical artery,[77, 88] and cerebral palsy,[76] but umbilical acid-base status is influenced by the action taken and time interval to delivery and intrapartum asphyxia is only a minor contribution to cerebral palsy.
The most objective way to identify the CTG abnormalities that either affects the fetus to engage anaerobic metabolism, or are signs of an ongoing anaerobic metabolism, would be to measure the level of eventual metabolic acidemia at the time point of ongoing CTG pattern. Clinical studies of the relationship between different CTG patterns and acid base status in fetal scalp blood have been small with study populations between 85 and 279 women.[71, 87, 134] They were performed when the CTG technology was relatively new, and definitions of CTG parameters were different from guidelines used today. They all measured pH in fetal scalp blood, thus not being able to differentiate between respiratory acidemia which is harmless to the fetus,[21] and the potentially dangerous metabolic acidemia, which always is caused by insufficient oxygen supply and anaerobic metabolism.
The hitherto largest study is to our knowledge the study by Beard et al., that in 1969 evaluated CTG patterns and scalp blood pH in an observational cohort study of 279 high-risk patients during labor.
Our finding of a low risk of fetal acidemia in cases with tachycardia without decelerations as well as a high risk if the tachycardia was accompanied by severe variable or late decelerations correlates to their findings. They used the term beat-to-beat variation, but defined it as a variation in FHR of 5 or less bpm, thus corresponding to the currently used terms reduced and absent variability together. Our results are therefore not completely comparable; however, in their group with uncomplicated loss of beat-to-beat-variation (normal baseline and no decelerations) they reported only a slightly lower mean scalp blood pH compared with normal traces, and the mean Apgar score was not lower than in the normal group. This can partly be interpreted as in accord with our findings.
They did not specify the duration of the variable decelerations whereas we referred all variable decelerations with duration of less than 60 seconds to the normal group. With this inclusion regardless of depth of the decelerations we had a negative predictive value of 95% for lactacidemia at FBS in the normal group.

We found no association between isolated reduced variability and fetal metabolic acidemia in our study. Williams et al. stated in their study that minimal variability (i.e. reduced or absent) was the most predictive parameter for acidemia in umbilical artery.[77]
In the case-control study of 78 cases with cerebral palsy, Nelson et al. reported that reduced beat-to-beat variability was associated with a tripling of the risk for cerebral palsy.[76] The CTG traces were not available to the authors, but recorded from birth records by the attending physicians, and thereby the group probably consists of both reduced and absent variability. Thus there was no information on whether the CTG trace hade presented abnormal variability already before start of labor, and since cerebral palsy in the majority of cases have antenatal origin, these children might have already suffered damage prior to labor and not due to intrapartum hypoxia.

Considering the available scientific knowledge from both animal and human observations, it seems reasonable to separate reduced and absent variability in the assessment of fetal status. Prolonged duration of reduced variability is one of the more common deviations from what is considered a normal CTG pattern during labour (14 %

in our study population). Although reduced variability can be of significance as a possible sign of hypoxia in the light of mentioned studies, due to the extremely high false positive rate and our negative findings, it seems reliable to suggest that one FBS is enough to rule out ongoing hypoxia, and that labour can continue without repetitive FBSs if the result is normal.

Regarding accelerations, they can be considered as a reliable reassuring sign, but with a low specificity just as the entire CTG trace. Accelerations are trustworthy signs of fetal well-being, but absence of accelerations is not so informative or predictive. Several earlier studies have shown the reliability of stimulation tests in the meaning that a provoked acceleration confirms a non-acidemic fetal status.[79] However, the meta-analysis of stimulation tests does not comment the large proportion of fetuses without response to stimulation. In our study population approximately two thirds had no acceleration at FBS, thus, in the majority of cases with a non-reassuring CTG, a stimulation test by vaginal palpation would have been of little help in discriminating acidemic and non-acidemic fetuses.
In addition, 60 % of all non-acidemic cases at FBS had no CTG reaction on the stimulation by FBS, and merely 15 % of the non-acidemic fetuses reacted with an acceleration that filled the criteria (≥15 bpm, ≥15 seconds). This supports the usefulness of FBS, since in the majority of cases a stimulation test is of no help in exclusion of developing hypoxia.

Intrapartum surveillance of the IUGR fetus

IUGR is often due to a suboptimal function of the placenta, and therefore IUGR fetuses can be regarded as being closer to the threshold where the intermittent reduction of oxygen supply during labour contractions exceeds the capacity of the fetus. Unless serial measurements have been undertaken, IUGR cannot be diagnosed, and thus, SGA is often used as a proxy. Our finding of a higher median lactate concentration in the SGA group compared with the AGA group is consistent with earlier reports of fetal lactate concentrations both antepartum and at delivery,[26, 135] and are explained as caused by mild chronic tissue hypoxia and polycythemia. The lactate concentrations in both quoted studies were within normal range, and cannot be transcribed to an acute intrapartum hypoxic situation, where lactate can reach four to five times higher concentrations than in the antenatal period.[136]
When looking into the subgroups with intrapartum acidemia i.e. scalp blood lactate > 4.8 mmol/L, we found no difference in lactate concentrations between birth weight groups, and the SGA fetuses reached as high lactate concentrations as the AGA and LGA fetuses. We were concerned whether it was only the mildly growth-restricted fetuses that could respond to hypoxia with a marked increase in lactate concentration, but analysis of the SGA group revealed a weak but significant correlation in the other direction, i.e. higher lactate concentrations with larger weight deviation. The SGA fetuses were not more often depressed or acidemic at birth than AGA or LGA fetuses. We therefore found it reliable to conclude that FBS with lactate analysis is a well-functioning surveillance method also in labors where intrauterine growth restriction is suspected.

Labors requiring repeated FBS

The use of FBS as an adjunct to intrapartum CTG monitoring varies largely between countries, with reported frequencies between 3-15 % in some countries,[3, 4, 125, 137] and essentially none in other. The attitude towards the use of FBS can be considered liberal at the labor ward where this study was conducted, with a frequency of 11 % of all labors, but is comparable to other countries where FBS is a part of intrapartum fetal surveillance routines.[4]

Performance of multiple FBSs during the course of labor can be interpreted as prolonged duration of a CTG tracing that is of concern to the attending physician but not indicative of immediate delivery. There are no evidence-based guidelines how to continue labor when prolonged CTG abnormalities have already caused one or two FBSs with normal results, and the CTG continues to be non-reassuring. The National Institute of Health and Clinical Excellence (NICE) has published the recommendation that a resident should obtain an obstetric opinion from a consultant if a third FBS is considered necessary, but this recommendation is bases on consensus rather than scientific evidence.[57]

We showed that, in spite of a larger proportion of lactacidemia in fetal scalp blood at the last FBS, there were no more cases of depressed newborns or acidemia in umbilical cord in the group with multiple FBSs (≥ 3). This supports earlier findings that increased lactate in capillary blood is an early marker in the hypoxic process enabling timely intervention before tissue damage has occurred.[115] A retrospective study of 381 women with FBS found a higher proportion of admission to NICU among infants who had undergone more than one FBS during labour.[138] In our considerably larger and prospectively collected material, we could not repeat this finding. There were no differences in any of the neonatal outcome measures in our study.

Allowing labor to continue the vaginal route in the presence of a non-reassuring CTG is safe for the baby when repeated FBS is used as an adjunct to CTG. If the duration of CTG abnormalities eventually passes the threshold of fetal reserves, increase in fetal lactate concentration will give an early sign of developing hypoxia with possibility for the clinician to expedite delivery before the baby's health is jeopardized.

The consequences of repeated FBS for the woman need to be addressed. In our study population, the proportion of cesarean deliveries was doubled (from 23% to 42%) if FBS exceeded two samplings, compared with women having 1-2 samplings.

The finding of a doubled risk of cesarean delivery is in accord with the retrospective study by Heazell et al.[138] They reported an OR of 1.71 for cesarean delivery in women who required more than one FBS during labor.

The procedure of FBS can be uncomfortable for the women, and is sometimes described as difficult and time-consuming.[106, 139] This describing refers however mainly to FBS with pH analysis, where there is a considerable difference in failure rate in comparison with lactate analysis. The failure rate in pH analysis reflects as well the difficulty in collecting 30-50 µL, as the longer time it takes to success in collecting the demanded amount of blood. Women's experience of FBS is not so much studied, but Liljeström et al. recently reported that FBS was well tolerated in women who had epidural analgesia.[140]

It is not possible to draw conclusions about what impact the use of FBS might have on the cesarean delivery rate due to the study design. In the group with ≥ 3 FBS, the last sampling was normal in 72.3 % of cases, and half of those (99 cases) were in first stage of labor when the last FBS was performed. One can only speculate if continued labour would have been an alternative without the possibility to exclude fetal acidemia by FBS. Forty-three of these 99 women were vaginally delivered, and there is a considerable possibility that all 99 would have been abdominally delivered if FBS had not been an option.

Neonatal course after exposure to severe intrapartum acidemia

In labors where the FBS analysis result reveals pronounced lactacidemia, there has been uncertainty regarding the level of urgency needed, and a common question asked is whether there is linearity in the correlation between fetal scalp blood concentration and proportion of neonatal complications, and if it is possible to set a limit where immediate delivery is demanded in spite of higher risks of per-, and postoperative complications for the mother.

The study by Kruger et al. set the current used cut-off values (4.8 mmol/L for the Lactate Pro™) at the 75th percentile in a study population with FBSs indicated by CTG abnormalities.[124] The lactate value with highest accuracy according to the area under the ROC curve for moderate to severe HIE was 6.5 mmol/L, with a sensitivity and specificity of 66.7, and 93.7 respectively. Corresponding values for Apgar score < 4 at 5 minutes was 6.0 mmol/L, 50.0 and 90.4 respectively, and for umbilical artery pH < 7.00 the values were 5.1 mmol/L, 58.3 and 82.3 respectively. In our study population with FBSs upon CTG indications just like Kruger's study, the 75th percentile was lactate concentration 4.3 mmol/L and corresponding 25th percentile pH value 7.25. Thus, similar to clinical use of many other diagnostic tests, over time they tend to be used in a more "healthy" population, and on milder symptoms, which will affect the predictive values, and therefore such calculations would have been of little use, since the main goal is to avoid the outcome measure by interventions taken due to the result of the diagnostic test.

The statements possible to make from our study, is that also fetuses diagnosed with severe intrapartum acidemia by FBS, i.e. lactate concentration > 6.6 mmol/L or pH < 7.17, are still at a window of opportunity, with a relatively low risk of being severely acidemic or depressed at birth, when prompt action is taken. Most commonly, women start labor with the fetus in good condition, and a normal CTG trace at admission. When there is gradual development of acidemia, in most cases acute tocolysis with IV terbutaline enables time for preoperative preparations and the caesarean delivery to be carried out in spinal analgesia within 20-30 minutes after decision. Further statements are difficult to make, since courses of labours are influenced by so many factors. The absolute scalp blood value can only partly guide us in decision upon how rapid delivery should be expedited. Most likely the patient history, e.g. known growth restriction, presence of thick meconium, and the CTG pattern preceding the FBS result should influence this decision.

The correlations between last FBS values and UA-pH at delivery were significant, however better for FBS pH than FBS lactate. The probable explanation is firstly that in the pH group, the same entity is measured in both compartments, i.e. scalp blood and

umbilical blood, and secondly, that lactate measurements do not include the respiratory contribution to the acidemia. In addition the time from sampling to delivery was longer in the lactate group. There was a higher proportion of caesarean deliveries in the lactate arm, and it is likely that terbutaline was administered to reduce contractions and further stress in many of those cases. Since tocolysis enables reversal of the anaerobic metabolism and metabolic acidemia, this also might have contributed to the lower correlation in the lactate analysis group.

STRENGTHS AND LIMITATIONS

Data are prospectively collected in large populations in both cohorts of this thesis. The first cohort (Study I and II) consists of women in the hitherto largest randomized trial comparing pH and lactate in FBS. The second cohort (Study III and IV) consists of all consecutive cases with FBS at an obstetric unit with approximately 4500 annual deliveries during the study period. The CTG interpretation was blinded as the CTG reviewer was not aware of the FBS analysis result at the time of interpretation. The risk of failed attempts to perform FBS is small since lactate analysis was used. The reported frequency of sampling or analysis failure is 1.2-1.7 % compared with 10-20 % for FBS with pH analysis.[105, 106, 126] The risk of missing data due to unreported cases with FBS is small since the FBS results were routinely noted in the medical record.

Studies I and II are secondary analyses of a former RCT, with the objective to compare lactate and pH analyses in FBS in the prevention of birth acidemia. Thus, the study was not designed to address our hypotheses and issues.

All studies concerning CTG patterns are limited by short-comings in inter-observer agreement.[141-143] We believe our efforts in structuring the CTG interpretation have minimized this weakness. Our finding that the two types of serious decelerations correlate equally to fetal metabolic acidemia might reduce future inter-observer variation regarding decisions due to CTG changes.
We did not take the duration of different CTG patterns into account; however we believe it is unlikely that further subdivision would influence our results, but only make it more difficult to apply to clinical practice.
There is a possibility of selection bias in the proportion of groups in the study population as some CTG patterns e.g. persistent bradycardia or absent variability with or without decelerations more likely indicate immediate delivery without preceded FBS. In these groups the true proportion with lactacidemia are probably higher than in our study. Regarding the pattern of isolated reduced variability, we believe our findings can be regarded as reliable as it is unlikely that this tracing would cause a decision upon immediate delivery.

Birth weight group was used as a proxy for intrauterine growth restriction. SGA and IUGR are not entirely synonymous entities, since SGA is a statistical definition based on birth weight, gestational age and sex, and IUGR is a functional definition of a fetus that, due to placental, maternal or fetal reasons is unable to achieve its predestined weight. Thus, a SGA newborn has not necessarily been exposed to IUGR, but can be genetically small. More rarely, an AGA newborn can be growth restricted, for example

a fetus that genetically would have become LGA, might due to preeclampsia in the mother with associated growth restriction only reach AGA. We classified fetuses as SGA, AGA or LGA, according to the sex-specific ultrasonically estimated fetal weight curves, routinely used in Sweden. The Swedish definition of SGA is a birth weight > 2 SDs below the mean of estimated fetal growth, i.e. the lowest 2.5^{th} percentile, and therefore, our findings should be valid using a more common definition of SGA as less than the 10^{th} percentile.

Regarding conclusions on repetitive FBSs, the number of samplings is somehow a proxy for duration of CTG changes that are of concern to the attending physician, but not alarming enough to cause decision upon immediate delivery. The number of FBSs could be inversely related to the physician's experience of CTG interpretation, in the meaning that more junior doctors would take more samples. There is however always at least one consultant of the two doctors on call at the labor ward where the study was performed, and we find it unlikely that the experience of the attending doctor would differ between the groups.
Another limitation regarding Study IV is that sample size of the study population was calculated for other outcomes than acid base status in umbilical artery and admission to NICU. However, in comparison with a former retrospective cohort of 381 women addressing these issues,[138] we found it interesting to report that we could not repeat their finding of increased NICU admission in our considerably larger material.

CONCLUSIONS

Severe variable decelerations and late decelerations, although of different pathophysiological origins, correlate equally to fetal metabolic acidemia and distinguishing between them is not crucial in CTG interpretation. A CTG pattern with tachycardia in combination with either late or severe variable decelerations was the CTG pattern with the highest median lactate concentration and highest rate of lactacidemia at FBS. Isolated reduced variability is in most cases not associated with lactacidemia in fetal blood, and if developing fetal acidemia is ruled out with one FBS, this pattern does not require monitoring with repeat FBSs throughout labour.

The growth restricted fetus can respond to hypoxia adequately and to the same extent as appropriately grown fetuses in terms of lactate production, and FBS with lactate analysis is a safe surveillance method also in labors with a suspected intrauterine growth restriction of the fetus.

If CTG changes require monitoring with repetitive FBSs ($\geq$3), labor is still safe for the baby, but the risk of a cesarean delivery is doubled as compared to labors where CTG changes has caused 1-2 FBS. Still there is a substantial chance of vaginal delivery.

The risk of neonatal complications is low even in cases with pronounced lactacidemia in scalp blood, when proper action is taken.
Increase in fetal scalp lactate concentration is an early marker of fetal hypoxia and FBS with lactate analysis can be used to prevent birth acidemia. FBS with lactate analysis is a safe and valuable adjunct to CTG in intrapartum fetal surveillance, with no false negative tests.

FUTURE PERSPECTIVES

To cite the words of Dr Hon 50 years ago – the sizable task of categorizing CTG in a meaningful way is still ongoing.

There are several areas regarding CTG interpretation and FBS that can be further investigated.

The aspect of duration of different CTG abnormalities in relation to fetal lactate concentration can be further analyzed, with the aim to provide evidence-based and possibly more specific guidelines for FBS.

The time interval from most recent acceleration prior to FBS can be explored, to see if there is an impact on prevalence of lactacidemia.

In cases with repeated FBS, the dynamics of lactate concentration and increase can possibly be elucidated regarding different CTG patterns.

Although there are many existing studies on inter-observer variation in CTG interpretation, it would be of interest to evaluate the implication and effects of an expanded CTG education program that has been introduced at the department where Studies III and IV were performed. One aspect would be to evaluate if an education-intense approach can reduce inter observer variation, and test the reproducibility of our findings. The other aspect would be to examine if education in CTG interpretation and fetal pathophysiology has an impact of FBS frequency.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Kardiotokografi (CTG) är förutom periodvis avlyssning av fosterhjärtfrekvensen den grundläggande metoden för fosterövervakning under förlossning. Ett normalt CTG-mönster är ett betryggande tecken på ett väl syresatt foster. Dock gäller inte det motsatta, då många friska foster ofta uppvisar CTG-förändringar någon period under förlossningen. CTG har således en hög sensitivitet, men låg specificitet med många falskt positiva test. CTG kräver dessutom en visuell tolkning vilket medför en avsevärd variation mellan olika CTG-bedömare.
Parallellt med CTG-teknikens införande utvecklades metoden att via blodprovstagning från fostrets hårbotten undersöka fosterblodets surhetsgrad via pH-mätning. pH-värdet sjunker både vid förhöjd koldioxid-halt utan syrebrist, vilket är vanligt under förlossning men inte utgör någon risk för fostret, och vid ökad produktion av mjölksyra (laktat) när syretillgången är otillräcklig, och cellerna växlar till icke syrekrävande energiproduktion. För att bättre komma åt den för fostret potentiellt hotande typen av pH-sänkning undersöktes möjligheten att analysera laktatkoncentrationen i fosterblod.

Metoden är kontrollerad i randomiserade studier och jämförbar med pH analys vad gäller barnutfall och kejsarsnittsfrekvens, men har den stora fördelen av enklare provtagning och kortare tid till provsvar då metoden endast kräver 5 µl blod, och små portabla mätare finns. pH-mätning av fosterblod kräver förhållandevis mycket blod (30-50 µl) vilket medför en hög misslyckandegrad i provtagning och/eller blodanalys.
Mätning av laktathalten i fosterblod är väl utprövad och säker, och används på de flesta förlossningskliniker i Sverige och internationellt sett i flera länder. Eftersom riktlinjer för CTG-tolkning dock till stor del är expert-utlåtanden och konsensus-dokument, kan inte heller riktlinjer för skalpblodprovtagning anses vara evidens-baserade.

Detta avhandlingsarbete har syftat till att ytterligare öka kunskapen om laktatkoncentrationen i fosterblod och dess betydelse vid hotande syrebrist hos fostret under förlossningen. Ett delsyfte har varit att skapa evidensbaserade grunder för kliniska riktlinjer avseende skalpblodprovstagning som fosterövervakning under förlossning.

Neonatalt utfall efter uttalad surhetsgrad i skalpblodprov under förlossning – Studie I

Delarbete I är en subanalys av en randomiserad studie som jämförde mätning av laktat och pH-mätning i skalpblodprov under förlossning. Målsättningen för studien var att undersöka risken för komplikationer och sjuklighet i nyföddhetstiden hos de fall som vid skalpblodprovstagning haft laktatnivåer långt över gränsnivån för att aktivt förlösa barnet. Syftet var att kunna ge mer detaljerade riktlinjer för handläggande vid olika grader av förhöjd laktatkoncentration. Vid CTG-förändringar som indikerade behov av skalpblodprov hade 1496 kvinnor lottats till analys av laktat och 1496 kvinnor till pH-analys.
Vi undersökte utfallet för fostren med den mest uttalade graden av pH-sänkning respektive laktatkoncentrations-stegring i skalpblod. Beräkning av den 95:e percentilen i laktat-analysgruppen och den 5:e percentilen i pH-analys-gruppen gav gränsvärdena

laktatkoncentration 6.6 mmol/l samt pH värde 7.17, och värden över respektive under dessa nivåer definierades som allvarlig surhetsgrad i blodet under förlossning.
154 foster hade skalpblodprovsvärden utanför dessa gränser, och barnutfallet i denna högriskgrupp visade ändock låg risk för allvarlig nyföddhetskomplikation. Av de 154 nyfödda i denna högrisk-grupp hade 7.8% ett pH-värde < 7.00 i navelsträngsartär, 10,4% hade Apgar-poäng < 7 vid 5 minuters ålder och 2.6% hade syrebristrelaterad neurologisk påverkan i nyföddhetsperioden. Det förelåg ingen skillnad mellan barnen där pH analyserats och barnen som genomgått analys av laktat. Dock var tiden från provtagning till förlossning kortare i gruppen med pH-analys. Huvudorsaken till detta är sannolikt att fler blev vaginalförlösta i gruppen med pH-analys. Huruvida förlossningen avslutas med kejsarsnitt eller vaginalt med sugklocka eller tång, beror på i vilket skede av förlossningen som den för fostret hotande situationen har uppstått, och den fördelningen kan inte ha påverkats av analys-typ i en randomiserad studie, utan skillnaden i förlossningssätt mellan grupperna tolkas som orsakad av slumpen. Däremot kan det lika goda utfallet för barnen i båda grupperna trots tidsskillnaden till förlossning tolkas som att laktat är en tidigare markör än pH för begynnande syrebrist.
Studiens slutsats är att skalpblodprovstagning kan användas för att förebygga syrebristrelaterade nyföddhetskomplikationer och att risken för dessa är låga även vid uttalad surhetsgrad i blodet hos fostret vid skalpblodprovstagning.

Laktatproduktion som svar på syrebrist under förlossning hos det tillväxthämmade fostret – Studie II

Delarbete II är en subanalys av samma randomiserade studie som ovan, med de kvinnor som lottats till analys av laktat som studiepopulation. Tillväxthämmade foster är känsligare för syrebrist under förlossning än normalstora foster. De har inte depåer av reservenergi i form av lagrat socker som normalstora foster har och är därför sämre rustade att klara den påfrestning som värkarna under förlossning utgör. Eftersom laktat bara bildas vid nedbrytning av socker, var vår hypotes att laktatkoncentrationen inte stiger i samma grad hos tillväxthämmade foster som hos normalstora foster vid en utveckling av syrebrist. Laktatkoncentrationen vid skalpblodprov skulle i så fall inte spegla graden av syrebrist hos de tillväxthämmade fostren som genomgår vaginalförlossning.
Det fanns tillgängliga data på skalpblodprov hos 1354 av de 1496 randomiserade kvinnorna. Fostren delades in utifrån födelsevikt i grupperna liten/normal/stor för graviditetslängden (small for gestational age – SGA; appropriate for gestational age – AGA; large for gestational age – LGA). SGA användes som ersättningsmått för tillväxthämning. Grupperna jämfördes avseende laktatoncentration i skalpblod. Det förelåg ingen skillnad mellan viktgrupperna vad gäller andel foster med förhöjd laktatkoncentration i blodet vid skalpblodprovstagning. SGA-fostren hade något högre medelvärde än AGA-fostren, och detta kan tolkas som ett uttryck för en kronisk låggradig syrebrist. Vid analys av fostren med laktatnivåer över gränsvärdet för acidemi (surt blod), 4,8 mmol/l, sågs att SGA-fostren ökade sin laktatproduktion i samma grad som AGA-fostren. Vid analys av SGA-gruppens laktatnivåer fanns en svag men signifikant korrelation mellan fosterstorlek och laktatkoncentration, som visade att ju mindre foster desto högre laktatnivåer. Detta ger stöd för att även fostren med störst viktavvikelse kan svara adekvat på syrebrist med laktatproduktion.

Skalpblodprovstagning med laktatanalys är därför en säker övervakningsmetod även för tillväxthämmade foster som genomgår vaginalförlossning.

CTG-mönster och risk för acidemi hos fostret under förlossning – Studie III

Delarbete III är en prospektiv observationsstudie av relationen mellan olika CTG-avvikelser och förhöjd laktatnivå hos fostret. Flera CTG-mönster, såsom utdragen varaktighet av nedsatt variabilitet utan andra avvikelser, långvarig frånvaro av accelerationer (kortvariga uppgångar i hjärt-frekvensen) eller okomplicerade variabla decelerationer (kortvariga nedgångar i hjärtfrekvensen) med stor slagförlust, är av osäker patofysiologisk betydelse för fostret, men ger ofta upphov till oro för fostret hos övervakande barnmorskor och läkare. De studier som finns avseende sambandet mellan CTG-mönster och fosterpåverkan har små studiepopulationer, flera utfördes när CTG-metoden fortfarande var relativt nyintroducerad, och definitionerna av olika parametrar i CTG-tolkning i de studierna skiljer sig från våra nuvarande riktlinjer. Utfallsmåtten var i flera fall pH-värdet i skalpblodprov hos fostret, vilket inte kan särskilja den allvarliga typen av acidemi från den ofarliga varianten som beror på en ansamling av koldioxid, men ingen syrebrist. Andra studier har undersökt sambandet med navelsträngsblodets syra-bas-balans, vilken påverkas av vilken åtgärd som företagits, samt tidsintervallet till födelsen. Ytterligare andra studier har undersökt sambandet med risk för cerebral pares, men syrebrist under förlossning utgör bara en mindre del av många orsaker till cerebral pares.
Vi såg det därför intressant att undersöka sambandet mellan olika CTG-avvikelser och förhöjd mjölksyrehalt i fosterblod under förlossning.
Under studietiden utfördes skalpblodprovstagning i 1070 förlossningar, vilka utgjorde cirka 11 % av samtliga förlossningar på den aktuella förlossningskliniken. Ett CTG-mönster med nedsatt variabilitet som enda avvikelse var inte associerat med högre laktatkoncentration eller ökad förekomst av laktatkoncentration över den satta normalgränsen jämfört med ett normalt CTG-mönster. De två typerna av allvarliga decelerationer orsakade, trots olika ursprung, lika stora andelar av laktatkoncentration över normalgränsen. Foster med förhöjd hjärtfrekvens i kombination med komplicerade variabla eller uniforma sena decelerationer hade det högsta medelvärdet på laktatkoncentrationen, och den högsta andelen av värden ovanför normalintervallet.

Studieresultaten ger stöd för att flera vanliga anledningar till osäkerhet om fostrets välmående under förlossningen kan elimineras. Foster med isolerad nedsatt variabilitet under förlossning, behöver inte övervakas med upprepade skalpblodprover under förlossningen om ett enstaka prov har uteslutit pågående syrebristutveckling. Fyndet att de olika typerna av allvarliga decelerationer korrelerade lika till förhöjd mjölksyrekoncentration minskar också konsekvenserna av tolkningsvariationen mellan olika bedömare vad gäller beslut om åtgärder.

Neonatalt utfall och förlossningssätt vid upprepad skalpblodprovstagning – Studie IV

Delarbete IV är en prospektiv observationsstudie av relationen mellan antal skalpblod-provstagningar och nyföddhetskomplikationer samt risk för kejsarsnitts-förlossning.
Ibland uppstår måttliga CTG-förändringar tidigt i förlossningsförloppet, och i vissa fall föreligger ett utdraget förlossningsförlopp med måttliga CTG-förändringar som inte är så allvarliga att de leder till beslut om omedelbar förlossning. Det finns inga klara

riktlinjer för upprepad skalpblodprovstagning vid dessa situationer och huruvida det finns en övre gräns för vad som är säkert ur fostrets och lämpligt ur den födande kvinnans synpunkt. Vi undersökte därför om det fanns någon skillnad i utfall för barnen och i förlossningssätt mellan de förlossningar där enstaka (1-2) skalpblodprov tagits och de med upprepade provtagningar (3 eller fler). I gruppen med upprepade prover var medelvärdet av laktatkoncentrationen vid skalpblodprovstagning högre än i gruppen med enstaka prov, och andelen med förhöjda laktatnivåer var också högre. Dock var det ingen skillnad mellan grupperna vad gäller andel barn med låga Apgar-poäng, pH < 7.00 i navelsträngsartär, inläggning på neonatalvårdsavdelning eller neurologisk påverkan i nyföddhetsperioden. Studieresultaten visade att det är säkert för fostret att fortsätta en vaginal förlossning vid CTG-förändringar när foster-övervakningen kompletteras med upprepade skalpblodprover, då det möjliggör åtgärder och beslut om instrumentell eller kejsarsnittsförlossning i god tid innan risk för allvarlig påverkan i nyföddhetstiden uppstår.
Vad gäller den födande kvinnan var kejsarsnittsfrekvensen nästan fördubblad (42 % jämfört med 23 %) bland de förlossningar där CTG-förändringar orsakat tre eller fler skalpblodprovstagningar jämfört med förlossningar där bara enstaka prov tagits. Riskökningen kontrollerades för kända förväxlingsfaktorer som kan ge ökad risk för kejsarsnittsförlossning såsom ålder > 35 år hos kvinnan, tidigare kejsarsnitt och överburenhet, men oddskvoten påverkades endast marginellt. Ändock ska poängteras att även i gruppen med upprepade skalpblodprovstagningar födde majoriteten (60 %) vaginalt, och 1/3 av dessa spontant. Studieresultaten är användbara i handläggandet av förlossningar där CTG-förändringar givit upphov till upprepade skalpblodprovs-tagningar, när det gäller ställningstagande till fortsatt förlossning.

Slutsats

Vi har visat att skalpblodprovstagning med analys av laktatkoncentrationen är ett värdefullt komplement till CTG i fosterövervakning under förlossning. Analys av laktatnivåer i fosterblod är ett tillförlitligt sätt att utesluta utveckling av syrebrist när CTG-mönstret är avvikande.
Vi har i ett stort material visat att flera CTG-avvikelser som ofta inger oro inte har samband med syrebristutveckling. Vi har också visat att två olika typer av nedgångar i hjärtfrekvensen som har olika orsaker, och ofta tolkas olika mellan olika bedömare, ändå har samma konsekvenser i fråga om laktatproduktion hos fostret. Detta kan minska variationen mellan olika CTG-tolkare i fråga om beslut om att ta skalpblodprov eller att avsluta förlossningen aktivt.
Vi har visat att skalpblodsprovtagning med laktatanalys är en tillförlitlig övervakningsmetod även vid förlossningar av misstänkt tillväxthämmade foster.
Att fortsätta en vaginal förlossning där måttliga CTG-förändringar föranleder upprepad skalpblodprovstagning är säkert för fostret, och orsakar inte ökad andel av syrebristrelaterade komplikationer i nyföddhetstiden. Däremot ökar risken för att förlossningen avslutas med kejsarsnitt. Dock föder majoriteten av kvinnorna vaginalt även när CTG-förändringar orsakat upprepad skalpblodprovstagning.
Vi har visat att förhöjd laktatkoncentration i foster är en tidig markör i utveckling av syrebrist som gör det möjligt att förlösa barnet innan syrebristrelaterad skada sker. Även hos foster med de allra högsta nivåerna av laktat i blodet är risken för syrebristrelaterad nyföddhetskomplikation låg när adekvata åtgärder vidtas.

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