Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

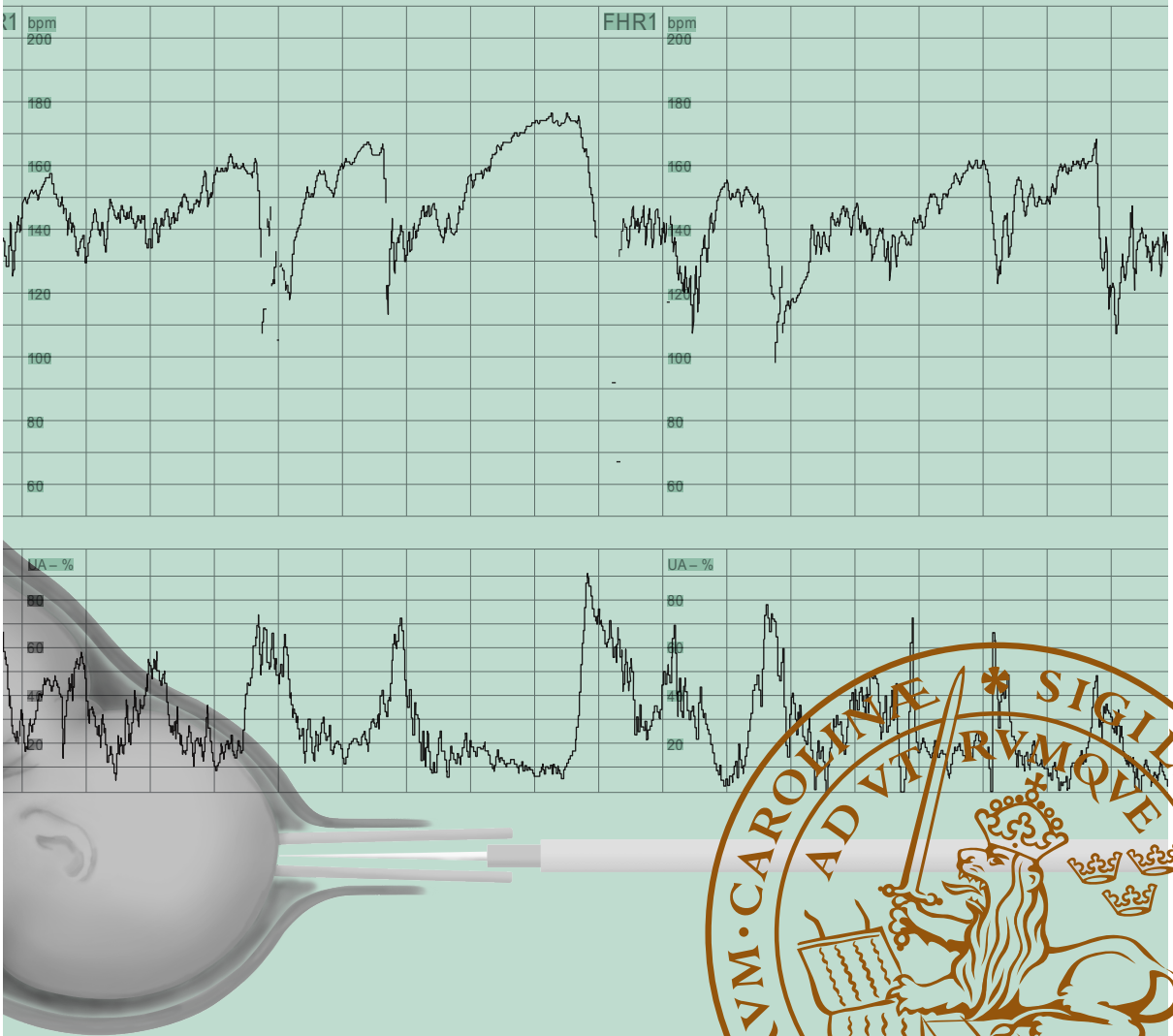
Iorizzo, Linda

2021

Document Version:
Publisher's PDF, also known as Version of record

Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

LINDA IORIZZO | FACULTY OF MEDICINE | LUND UNIVERSITY



Printed by Media-Tryck, Lund 2021 NORDIC SWAN ECOLABEL 3041 0903

LINDA IORIZZO is a consultant Obstetrician at the Department of Obstetrics and Gynaecology, Helsingborg Hospital. Her research interest is to improve fetal monitoring during labor for safer deliveries for both the mother and the fetus. This thesis highlights the importance of device specific cut-offs for intervention, for different point of care lactate meters. Two different lactate meters for fetal scalp blood sampling as secondary tools to Cardiotocography, were studied for possible introduction in labor care. Another secondary test, fetal scalp stimulation test, was evaluated for its predictive value for elevated fetal scalp lactate levels.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2021:60
ISBN 978-91-8021-066-9
ISSN 1652-8220

Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

Linda Iorizzo

LUND
UNIVERSITY

DOCTORAL DISSERTATION

By due permission of the Faculty of Medicine,
Department of Clinical Sciences, Lund University, Sweden.
To be defended in Belfrage salen, BMC building D15, Klinikgatan 32
Thursday June 10, 2021, 1:00 pm.

Faculty opponent

Professor
Magnus Westgren
Karolinska Institutet, Stockholm

Organization LUND UNIVERSITY	Document name **Doctoral dissertation**
	Date of issue 2021-06-10
Author(s) Linda Iorizzo	Sponsoring organization

Title and subtitle Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

Abstract

Background and aims Fetal surveillance during labour is used to detect fetuses at risk of compromise, achieve timely and appropriate interventions, and favourable perinatal outcomes. The drawback with cardiotocography (CTG) is the rate of false positives for fetal comprise and adjunctive tests are therefore often needed. Fetal scalp blood sampling (FBS) with lactate measurement and Fetal scalp stimulation test (FSS) are used such. Since the production of the device LactatePro™ (LP) had discontinued, resulted in an urgent need for a new device. FSS test has been suggested to be an equivalent alternative to FBS.The aims of the present thesis was to search for a new reliable POC to replace LP, to present cut-offs for intervention, based on neonatal outcome variables, and to study the predictive value for FSS test for elevated FBS lactate values.

Methods Paper 1 and 4, prospective observational studies on women with non-reassuring CTG during labour aimed to derive new cut-offs for two specific devices. Paper 2, a retrospective study aimed to evaluate whether the FSS test could be used as a good predictor of fetal well-being. In paper 3, a prospective quality study, the lactate meter StatStripXpress® (SSX) (Nova Biomedical, Waltham, US) was validated in fetal blood. From the ROC analysis based on neonatal outcomes, the cut-off for intervention was suggested.

Results Paper 1: From 701 fetal scalp blood samples the conversion algorithms proposed reference values for LP2 were: scalp lactate 6.3–7.1mmol/L=preacidemia, >7.1mmol/L=acidaemia. The coefficient of variation (CV) for LP2 varied between 4.2-23.4% for different lactate levels in cord blood. Paper 2: For FSS test for scalp lactate (LP) ≥4.2 mmol/L were: sensitivity 79% (95% CI:69.4–86.6%) specificity 42.7% (95%CI:36.9–48.7%), LR + 1.38 (95% CI:1.19–1.59) and LR- 0.49 (95% CI:0.33–0.74). Paper 3: SSX lactate values showed a close association to lactate measurement with ABL 800, R = 0.95 in cord blood. For lactate values >3 mmol/L the mean CV was 3.8% in cord blood and 6.8% in scalp blood. Paper 4: 3334 women were enrolled of which 799 were delivered within 25 minutes after FBS. The areas under the ROC curves (AUC) and corresponding optimal cut-off values for scalp blood lactate among those 799 women; metabolic acidosis defined as pH <7.05 plus BDecf >10mmol/L and/lactate >10 mmol/L, AUC 0.87(95% CI:0.77-0.97), cut-off 5.7mmol/L; pH <7.0 AUC 0.83(95% CI:0.68-0.97), cut-off 4.6 mmol/L and pH <7.05 plus BD_{ecf} ≥12mmol/L AUC 0.97(95% CI:0.92-1), cut-off 5.8mmol/L. Apgar score <7 at 5 minutes AUC 0.74(95% CI:0.63-0.86), cut-off 5.2mmol/L; and pH <7.10 plus composite neonatal outcome AUC 0.76(95% CI:0.67-0.85), cut-off 4.8mmol/L.

Conclusions We proposed new cut-offs for LP2, but the CV was unacceptably high. There is an association between the fetal ability to react to a scalp stimulus and the fetal metabolism. However, the efficiency of FSS test was too poor to rule in or rule out an elevated fetal scalp blood lactate level. In the second stage, absence of accelerations after provocation seemed to be a normal phenomenon. Scalp blood lactate measured by SSLX 25 minutes before delivery had an excellent ability to predict metabolic acidosis. To safely rule out the risk for fetal metabolic acidosis we suggest the scalp blood lactate cut-off for intervention to be ≥ 5.2mmol/L for StatstripLactate®/StatstripXpress® Lactate system.

Key words

Classification system and/or index terms (if any)

Supplementary bibliographical information		**Language**
ISSN and key title1652-8220		**ISBN** 978-91-8021-066-9
Recipient's notes	**Number of pages** 104	Price
	Security classification	

Signature  Date 2021-05-03

Secondary Tools to Cardiotocography for Fetal Monitoring during Labor

Linda Iorizzo

LUND
UNIVERSITY

Cover illustration by Frida Nilsson, Lund University

Lund University
Faculty of Medicine
Department of Clinical Sciences Lund

ISBN 978-91-8021-066-9
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University, Lund 2021

Media-Tryck is a Nordic Swan Ecolabel certified provider of printed material. Read more about our environmental work at www.mediatryck.lu.se

MADE IN SWEDEN

To my family

“You never arrive”, Meryl Streep

Table of Contents

List of Original Papers

I. Iorizzo L, Klausen TW, Wiberg-Itzel E, Ovin F, Wiberg N. Use of Lactate Pro^{TM}2 for measurement of fetal scalp blood lactate during labor – proposing new cut-offs for normality, preacidemia and acidemia: a cross-sectional study. J Maternal Neonatal Med. 2018 Jan 4;1–7.

II. Shakouri F, Iorizzo L, Edwards HMK, Vinter CA, Kristensen K, Isberg PE, Wiberg N. Effectiveness of fetal scalp stimulation test in assessing fetal wellbeing during labor, a retrospective cohort study. BMC Pregnancy Childbirth. 2020 Jun 5;20(1):347.

III. Iorizzo L, Persson KEM, Kristensen KH, Wiberg N. Reliability of the point-of care analyzer "StatStrip® Xpress^{TM}" for measurement of fetal blood lactate. Clin Chim Acta. 2019; 495:88–93.

VI. Iorizzo L, Carlsson Y, Johannson C, Berggren R, Herbst A, Wang M, Leiding M, Isberg P-E, Kristensen K, Wiberg-Itzel E, McGee T, Wiberg N. Proposed cut-off for fetal scalp blood lactate in intrapartum fetal surveillance based on neonatal outcomes: A large international prospective observational study. Submitted: BJOG-21-0419

Abbreviations

ACOG	American College of Obstetrics and Gynecology
A-CS	Acute caesarean section
ATP	Adenosine triphosphate
BiPAP	Bilevel pressure airway pressure
BD_{blood}	Base deficit in blood
BD_{ecf}	Base deficit in extracellular fluid tissue
BE	Base Excess
CI	Confidence Interval
CTG	Cardiotocography
CV	Coefficient of variation
CO_2	Carbon dioxide
FBS	Fetal scalp blood sampling
FIGO	The International Federation of Gynecology and Obstetrics
H+	Hydrogen Ion
Hb	Haemoglobin
HbF	Fetal haemoglobin
HCO_3^-	Bicarbonate
H_2CO_3	Carbonic acid
Hct	Haematocrit
HIE	Hypoxic Ischemic Encephalopathy
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
MA	Metabolic acidosis
mmol/L	Millimole per litre
MRI	Magnetic resonance imaging
NICU	Neonatal Intensive Care Unit
O_2	Oxygen
pH	Negative log of the hydrogen ion concentration
POC	Point of Care, Bedside measurement
RCT	Randomized Controlled Trial
R	Coefficient of corelation
R^2	Coefficient of determination
SD	Standard deviation

SFOG	Svensk Förening För Gynekologi och Obstetrik (The Swedish Society for Obstetrics and Gynaecology)
STAN	ST Analysis (of the fetal electrocardiogram)
SVD	Spontaneous Vaginal Delivery
VE	Vacuum Extraction

Summary in Swedish

Populärvetenskaplig sammanfattning

Den laktatmätare (mjölkssyramätare) som användes som komplement till att övervaka fostrets syresättning under förlossningen hade slutat att produceras. Det var därför bråttom att ta fram ett alternativ för att göra det möjligt att fortsätta använda metoden. Det gav upphov till den här avhandlingen, där vi ville utvärdera en ny säker laktatmätare under förlossning samt även undersöka en annan kompletterande metod för fosterövervakning.

Att föda barn på sjukhus i Sverige idag är mycket säkert. Det är väldigt sällsynt att ett barn drabbas av syrebristskador till följd av förlossningen eftersom man noggrant övervakar hur barnet mår i livmodern. Även om det är ovanligt med syrebristskador under förlossningen är det oerhört viktigt att förhindra att de sker, då barnet kan få mycket svåra medicinska skador såsom cerebral pares (CP), mental funktionsnedsättning, syn- och hörselskador.

Fostrets välmående under förlossningen beror huvudsakligen på tillgången till syre. För att övervaka att fostret får tillräckligt med syre under förlossningen används i hög och medelinkomst länder en metod som kallas kardiotokografi, CTG. Genom två dosor på mammans mage kan barnets hjärtfrekvens och livmoderns sammandragningar registreras. CTG infördes på 70-talet och är välstuderad.

Nackdelen med CTG är att metoden är väldigt känslig och kan larma för misstänkt syrebrist även om fostret i själva verket mår helt väl. Det leder ibland till ingrepp där man påskyndar förlossningen med akut kejsarsnitt eller sugklocka fast barnet sen vid födseln inte uppvisar några tecken på syrebrist. Ingreppen som innebär ökade risker för mor och barn skulle potentiellt ha kunnat undvikits utan att utsätta barnen för ökad risk för syrebrist genom att använda sig av kompletterande metoder såsom till exempel skalpblodprovtagning. Sedan CTG infördes i förlossningsvården har ingreppen ökat och fortsätter att öka i världen.

Under själva förlossningen, under värkarna, utsätts fostret för syrebrist som går över. Det sker i samband med att blodflödet från moderkakan via navelsträngen till fostret nästintill upphör under livmoderns kontraktioner. Mellan värkarna när livmodern slappnar av återgår blodflödet till det normala igen. Om värkarna är för frekventa eller fostrets reserver begränsade kan fostrets ämnesomsättning påverkas

negativt, och då ökar koncentrationen av vätejoner och mjölksyra i fostrets blod. Så när CTG larmar om misstänkt syrebrist hos fostret, kompletterar förlossningsläkaren med skalpblodprovtagning för att få mer information om fostrets syresättning under förlossningen och kan ingripa där det behövs. Vid skalpblodprovtagning, tar man ett litet blodprov från fostrets huvud och analyserar det med hjälp av en laktatmätare alternativt analyserar vätejon koncentrationen, pH (negativa logaritmen av vätejoner) i en stationär blodgasmaskin. Sänkta pH eller förhöja laktat värden är ett tecken på syrebrist och förlossningen påskyndas. Dock är majoriteten av värden normala och förlossningen kan i stället fortsätta, trots att CTG har larmat. Om man inte hade tillgång till metoden skulle troligtvis ingreppen öka.

Laktatmätaren man använder är en liten handhållen dosa så kallad patient nära analys (PNA) och man får resultatet inom en minut inne på förlossningsrummet. Det vill säga man behöver inte skicka blodprovet till laboratoriet för att analyseras vilket annars är vanligt förekommande i sjukvården. Den stora fördelen med PNA är att den bidrar till snabbare kliniska beslut i handläggningen. Metoden har använts sedan 90-talet och idag används den i Sverige i ungefär var åttonde förlossning och i varierande utsträckning i Europa och Australien.

Det har kommit nya apparater på marknaden men inga som har utvärderats tillräckligt för att man ska kunna använda dem säkert i förlossningsvården. De olika laktatmätarna har också olika mätvärden, så innan man börjar använda en ny apparat måste den studeras grundligt i prestanda, säkerhet och vilket gränsvärde man ska använda.

Genom en marknadsanalys fann vi en ny laktatmätare StatStrip Lactate® som var designad för sjukhusvård. Många av de tidigare laktatmätarna har varit skapade för att utvärdera fysiska prestationer i idrottsmedicin. Den krävde också mindre blod för analys och analyserade blodprovet snabbare. Vidare hade den också inbyggda formler för att justera för olika ämnen och koncentrationen på blodet som annars kan ge felvärden på laktatmätningen. Eftersom fostrets blod är mer koncentrerat än vuxnas blod tror vi att den korrigeringen är viktig, då det annars skulle felaktigt kunna ge ett alldeles för lågt laktat värde och därmed risk att uppseglande syrebrist missas.

Den andra sekundär diagnostiska metoden vi undersökte heter Skalpstimulerings test och är en välkänd metod. Om CTG larmar för syrebrist gör man då Skalpstimuleringstest som går ut på, att man genom att peta på barnets huvud under förlossningen får en reaktion på CTG. Om man då får en uppgång i hjärtfrekvens (acceleration) tolkas det som att fostret är väl syresatt och man kan avvakta med interventioner. Tidigare har det gjorts ett fåtal och fram för allt små studier av metoden. Trots det används den frekvent runt om i världen fram för allt i USA men även i Sverige.

Delarbete 1: Lactate Pro^{TM}2 for measurement of fetal scalp blood lactate during labour – proposing new cut-offs for normality, preacidemia and acidaemia: a cross-sectional study

I det första delarbetet undersöktes en uppföljare till LactatePro®(LP) som heter LactatePro2®(LP2). Men det visade sig att den hade helt andra mätvärden än LP. Gränsvärdet för att ingripa i förlossningen låg mycket högre än den tidigare apparaten. För LP2 rekommenderar vi gränsvärde för normalt laktat <6,3 mmol/L och förhöjt laktat >7,1mmol/L. Det är lägre gränsvärden än vad Svensk Förening för Obstetrik och Gynekologi (SFOG) rekommenderar. Vi fann också att LP2 vid upprepade mätningar av samma bloddroppe uppgav för stor spridning i resultaten. Vi bedömde därför att den inte var tillräcklig säker för att användas i förlossningsvård och började söka efter en ny apparat.

Delarbete 2: Effectiveness of fetal scalp stimulation test in assessing fetal wellbeing during labour, a retrospective cohort study

I det andra delarbetet undersökte vi en annan kompletterande metod till CTG som kallas foster stimulerings test. I ett stort material fann vi att metoden inte är tillförlitlig i utdrivningsskedet av förlossningen. Det verkar som att det inte finns någon koppling till om man får en acceleration eller ej till hur barnet är syresatt i den fasen. Dock behövs fler studier kring denna metod för att utröna om den är tillförlitlig eller ej. Men vi rekommenderar att den används med försiktighet i utdrivningsskedet eller inte alls.

Delarbete 3: Reliability of the point-of care analyser "StatStrip® Xpress^{TM}" for measurement of fetal blood lactate

I det tredje delarbetet genomgick StatStrip Lactate® apparaten utförliga prestandatest i samarbete med Laboratoriemedicin vid Skånes Universitets sjukhus och är den första laktatmätaren som blivit godkänd dvs ackrediterad av laboratoriemedicin. Den tidigare laktatmätaren har inte legat under laboratoriemedicins ansvar och därmed inte blivit lika strikt kontrollerad. Apparaten jämfördes mot en stationär blod-gas maskin och visade generellt lite lägre värden men med tillförlitliga mätningar. Vi kunde därmed studera den vidare i förlossningsvården.

Delabete 4: Proposed cut-off for fetal scalp blood lactate in intrapartum fetal surveillance based on neonatal outcomes: A large international prospective observational study

I det fjärde delarbetet studerade vi vilken nivå av laktat som vid mätningar med StatStrip® Lactate mätare var ett lämpligt gränsvärde för ingripande i förlossning. Eftersom syrebrist under förlossningen är ovanligt krävdes ett stort antal prover för att kunna räkna ut ett säkert gränsvärde. Från 3334 födande kvinnor där ett onormalt CTG mönster hade gett anledning att ta ett skalpblodprov kunde vi baserat på hur barnen mådde vid förlossningen och om de uppvisade några tecken på syrebrist i navelsträngsblodet vid födseln ta fram ett gränsvärde för ingripande för Statstrip Laktat® mätare. Tidigare studier har baserats på jämförelser av gränsvärden för behov av påskyndande av förlossningen med skalpblodprovtagning med mätning av pH. Vad vi känner till är denna studie den största som gjorts för att identifiera gränsvärden för intervention på skalpblodprov och med så många prover tagna nära inpå förlossningen. Laktatmätaren kunde med stor säkerhet förutse i skalpblod om barnet hade tecken på syrebrist vid födelsen. Ett gränsvärde på ≥5.2 mmol/L föreslogs för användande av StatStrip® Lactate under förlossningen.

Avhandlingen nyhetsvärde

Studierna i denna avhandling belyser följande:

- Gränsvärdet för förhöjt laktat mätt med LactatePro2® >7,1 mmol/ L och det är ett lägre gränsvärde än vad som rekommenderas av SFOG. Däremot bedömdes LP2 inte vara tillräckligt tillförlitlig att användas i förlossningsvård då upprepade mätningar av samma bloddroppe gav för spridda resultat.
- Sambandet mellan laktat mätt i skalpblod och laktat mätt i navelsträngsblod blev starkare ju närmre förlossningen skalpblodprovet togs.
- Skalpstimuleringstest är enligt vår studie inte tillförlitligt i utdrivningsskedet av förlossningen och fler studier behövs för att avgöra om metoden kan användas i öppningsskedet.
- StatstripLactate® mätare överensstämde väl med större robustare mätinstrument och hade tillförlitliga mätningar i fosterblod.
- För första gången har vi tagit fram ett gränsvärde för ingripande under förlossning för skalpblodprov med laktat, baserad på tecken på syrebrist i navelsträngsblod och på det nyfödda barnets mående vid födseln.
- Det är också den största studien som gjorts på skalpblodprovtagning samt på prover tagna i nära anslutning till födelsen. StatstripLactate® kunde med stor säkerhet i skalpblod förutse om barnet hade tecken på syrebrist vid födelsen
- För mätning av laktat med StatstripLactate i fosterskalpblod rekommenderar vi gränsvärde ≥5,2 mmol/L.

Introduction

The goal with intrapartum fetal monitoring is to discover signs of hypoxia at an early stage to allow for timely and appropriate intervention to avoid adverse neonatal outcomes. At the same time, the methods should also safely rule out hypoxia to allow labour to continue without unnecessary obstetrical interventions. The obstetrical dilemma is that we have two patients in one, where there is a fine balance on the scale between the best for the mother and what is best for the baby. To save the fetus from critical labours, we sometimes put the mother at increased risk of complications due to the clinical interventions. More research in the field is requested to keep interventions during labour at optimal levels especially since interventions also are associated with risks for the mother and the fetus (1–3).

Intrapartum fetal hypoxia accounts for a high percentage of the perinatal deaths and long-term neurological sequelae, both of which have a significant negative impact on the families and on health-care professionals (4).

The most commonly used method, for fetal monitoring during labour, cardiotocography (CTG) has been criticized for leading to unnecessary interventions, where the fetus at birth is vigorous, despite an alarming CTG pattern. To improve the diagnostic precision of CTG and reduce the false positives, secondary complimentary tests are used, although to a different extent around the world (1). Fetal scalp blood sampling is frequently used in Europe and Australia, whereas fetal scalp stimulation test is primarily recommended and used in the United States. Both tests are mentioned in national and international guidelines despite that the level of evidence is questionable, especially for the fetal scalp stimulation test (1,5–7). Scalp blood sampling is performed for analysis of pH or lactate. Fetal stimulation test is based on the assumption, that the healthy fetus will react with an increase in heartrate when the scalp is stimulated.

The internationally recognised point of care lactate meter for fetal scalp blood lactate measurement, Lactate Pro is no longer in production and therefore there is an urgent need to find a new safe device to allow for the method to continue (8).

Fetal acid-base balance and metabolism in pregnancy and labour

In the uterus, the fetus is totally dependent on the maternal respiration and circulation for the perfusion and gas exchange across the placenta as well as the umbilical and fetal circulation for the supply of oxygen and nutrients and the elimination of carbon dioxide and waste products(9).

The fetus features unique adaptations to ensure that the supply of oxygen exceeds its metabolic demands in the uterus. This in turn prepares the fetus with a considerable margin for adequate oxygenation for the strainful labour. At the onset of labour, the fetal-maternal gas exchange is affected, even in normal labour due to the uterine contractions and compression of the umbilical cord. The uterus contractions decrease the maternal uterine blood flow leading to reduced placental perfusion, which in turn affects the gas exchange (10,11). The healthy fetus can cope with this intermittently reduced gas exchange, as long as it is not too severe or persistent (12). The placental perfusion is normally restored between contractions and the fetus gets a chance to restore the oxygenation and eliminate the carbon dioxide. Acute hypoxia in short episodes is physiological for labour as a result of the uterus´s contractions and compression of the umbilical cord. In fact, a certain level of acidosis is considered normal and stimulates the baby to take its first breath at birth (13).

The umbilical cord and the gas exchange across placenta

From the maternal circulation across the placenta, oxygenated blood is pumped through the single umbilical vein into the fetal circulation. Simultaneously deoxygenated blood with a higher carbon dioxide concentration is pumped back by the fetal heart through the umbilical arteries to the placenta and the maternal circulation, where excess CO_2 is eliminated by the mothers breathing (14). Therefore, blood gas values measured in the umbilical arteries provide the most accurate information of fetal acid base status at birth (15). Near term, the maternal blood flow to the uterus is 500 mL/minute.

The pH is defined as the negative logarithm of the hydrogen ion (H+) concentration. Therefore, the relationship between pH and H^+ concentration is logarithmic and not linear. As the concentration of H^+ increases pH decreases. The pH is a measure of the degree to which a solution is acidic or alkaline.

To aid the fetal-maternal gas exchange several mechanisms increase the fetal oxygenation and elimination of carbon dioxide (CO_2). H^+ and CO_2 easily cross the placenta. For instance, the fetal haemoglobin has a higher affinity for O_2 than the maternal haemoglobin, which facilitates the fetal uptake of oxygen across the

placenta. Likewise, the carbon dioxide easily diffuses across the placenta to the maternal side since the maternal haemoglobin has a higher affinity for carbon dioxide than fetal haemoglobin. In addition, the fetus has a higher haemoglobin concentration than the mother.

For the importance of cellular functions, the pH level is tightly regulated in the extracellular fluid. Acids are buffered to neutralize the pH mainly by plasma bicarbonate (HCO_3^-) and hemoglobin in the erythrocytes. Bicarbonate binds to hydrogen ion and the result is water and carbon dioxide, which easily diffuses across the placenta to the maternal circulation and lungs. (Figure 1) CO_2 has a greater permeability across the placenta than O_2 (16). If the buffering capacities are exhausted the pH decreases as well as bicarbonate.

Base excess/deficit is defined as the amount of acid or base required to restore pH to 7.40 at pCO_2 5.3kPA at 37ºC at the actual saturation of blood expressed in mmol/L (17). It is a calculated measurement of the buffering capacity expressed in mmol/L. An elevated base deficit measured in the blood is a sign of the buffering mechanisms.

Fetal metabolism

The fetus is dependent on the maternal supply of energy. The major energy substrate is glucose accounting for 70-80% of the fetal energy requirements but alternative substrates such as lactate, ketoacids, amino acids and fatty acids are also sources of energy (18). Glucose diffuses easily across the placenta to the fetus by facilitated diffusion. The fetus has a lower glucose concentration than the mother which aids this process. Energy is produced intracellularly by the metabolism of glucose and glycogen through the glycolytic pathway forming pyruvate. When sufficient oxygen supply, pyruvate, enters the mitochondria and is further metabolised by the Citric Acid Cycle generating maximal energy with 36 Adenosine triphosphate (ATP), water and 6 CO_2. The produced carbon dioxide (CO_2) affects the hydrogen ion concentration (H+) by the following equation, where the equilibrium is shifted to the right.

Figure 1. $CO_2 + H_2O \Longleftrightarrow H_2CO_3 \Longleftrightarrow H^+ + HCO_3^-$

In the undisturbed fetus this reaction goes back and forth intra and extracellular several times until CO_2 is eliminated across the placenta to the maternal circulation and does not affect the pH (17). H+ can also be cleared across the placenta.

When disturbed gas-exchange across the placenta the carbon dioxide is accumulated leading to increased concentration of H+. Furthermore, the insufficient oxygen supply result in that pyruvate, is instead metabolised anaerobically by lactate dehydrogenase, generating lactate and less energy due to the formation of only 2 ATP. Therefore, the hypoxic fetus generates much less energy through anaerobic metabolism of glucose compared to normal aerobic metabolism.

$$\text{Pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{Lactate} + NAD^+$$

Lactate is the major end product of anaerobic metabolism. The lactate production does not cause metabolic acidosis, since the production of lactate consumes two protons, in fact therefore, it retards acidosis (19,20). With lactate production, nicotinamide adenine dinucleotide (NAD+) is produced which supports continued ATP generation from glycolysis. A high concentration of lactate intracellularly does not lower the pH in the cell. However, as the concentration of lactate increase intracellularly, the lactate is transported across the cell membrane from the cell to the extra cellular fluid (21). This occurs together with a hydrogen ion to maintain the ion charge equilibrium across the cell membrane (21). Therefore, the concentration of hydrogen increases and thus leads to further lowering the pH extracellularly in the blood.

The emerging accumulation of hydrogen ions and the depletion of buffering mechanisms eventually result in metabolic acidosis. If severe lack of oxygen or prolonged exposure, this will eventually lead to cell death (22,23).

If oxygen supply is restored lactate can be reconverted into pyruvate by lactate dehydrogenase and pyruvate can enter the Citric Acid Cycle for optimized metabolism. To an extent lactate can cross the placenta to the maternal circulation but the major elimination of lactate is through this reconversion. Some of the lactate is also thought to be metabolised in the placenta (24,25).

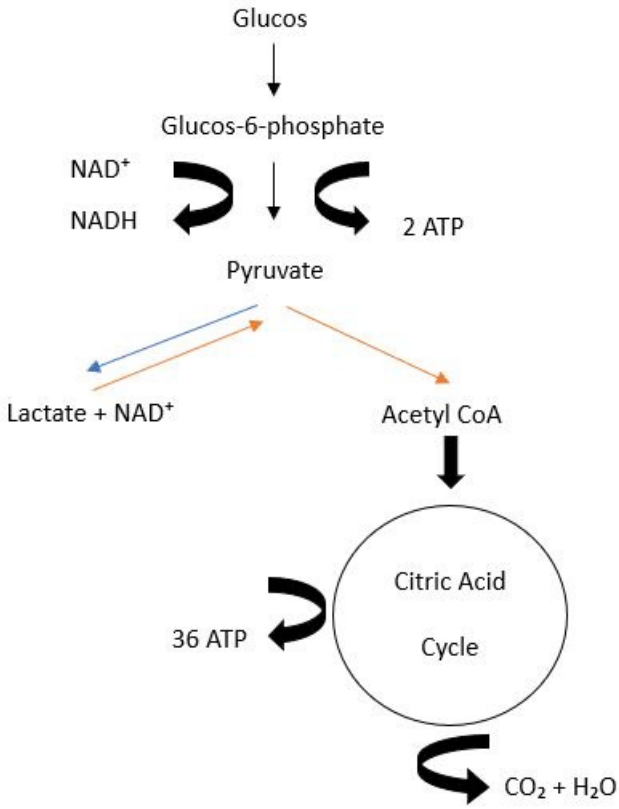


Figure 2. Schematic illustration of aerobic and anaerobic metabolism, blue arrow represent anerobic metabolism and red arrow aerobic metabolism

During the third trimester the healthy fetus prepares for the strenuous labour by converting excess energy substrate into glycogen which is stored in the fetal liver, heart, and skeletal muscles. In the event of fetal hypoglycaemia, glycogen phosphorylase is activated, and glycogen is metabolised into glucose. In contrast, the premature, the growth restricted fetuses or fetuses with prelabour dysfunction of the placental have not been able to build up the glycogen storage. A lower glycogen store limits their ability to produce energy by anaerobic metabolism. The placental dysfunction also leads to inadequate ability to restore the impaired gas exchange between the contractions and therefore the growth restricted fetus has a higher risk of intrapartum acidosis as well as and can more rapidly progress to metabolic acidosis (26–28).

Development of fetal acidosis

Impairment of the fetal-maternal gas exchange will result in the development of acidosis due to carbon dioxide retention and tissue hypoxia with the production of lactate (with concomitant hydrogen ion production) and carbonic acids. These two mechanisms occur in parallel and result in increasing H+ concentration and thus pH is lowered. Cord compression and reduced blood flow in the myometrium and placenta due to increasing contractions in labour are common reason for reduced CO_2 elimination and thus lowered pH (17).

Acidaemia is defined as an increased hydrogen ion concentration in the blood, whereas acidosis is increased hydrogen ion concentration in the tissue. *Respiratory acidosis*, is lowered pH, due to carbon dioxide accumulation and is harmless if short duration (12,29). In contrast, long lasting or severe hypoxia leads to a further decrease in pH and an increase in base deficit (when the buffering mechanisms are depleted) and increased lactate which results in *metabolic acidosis*, with risk of impaired cellular function causing damage to vital organs (23). The low pH deranges the proteins regulating the cell membrane transport mechanisms and thus the cell function (21).

Severe hypoxia can be caused by unpredictable acute catastrophic obstetrical events such as cord prolapse, placental abruption or uterine rupture(12). These are rare, the vast majority (75%) instead, occur gradually in labour as a result of the uterine contractions (30).

The fetuses compensatory defence mechanisms with sustained hypoxia

If oxygen supply falls the healthy unborn child can withstand the hypoxia by excellent and fascinating defence mechanisms. The labour induces a surge of stress hormones mediated by sympathicus whereby adrenalin and noradrenalin are released. They induce glycolysis of stored glycogen and an increase in the heart rate whereby the fetal-placental perfusion increases and aid the O_2 delivery and CO_2 elimination (17). The next protective mechanism is the activation of peripheral chemoreflexes (31,32). As hypoxic blood enters the fetal circulation the chemoreceptors increase blood pressure by peripheral vasoconstriction, which leads to the redistribution of blood flow to critical organs such as the brain, heart and adrenal glands, called Brain sparing (27,31,32). Further the parasympathicus is triggered by a carotid chemoreflex, which causes a rapid fetal heart rate deceleration presumed to reduce myocardial oxygen consumption and allows increased transit time of erythrocytes through tissue beds, including the placenta for improved gas exchange (33). The shift to anaerobic metabolism depletes the energy stores much faster since much less ATP is produced and an energy-saving mechanism by the

fetus, is to reduce movements. When anaerobic reserves are exhausted and cardiac glycogen is depleted, this causes impaired myocardial contractility. If hypoxia is further sustained eventually a progressive systematic hypotension gradually occur causing cerebral ischaemia and neural cell injury (31). Also, other organs are also affected such as the heart, liver, kidneys and the new-born will show multiorgan failure (34). In the worst case, although rare, the injuries lead to death.

Lactate from discovery to use in obstetrics

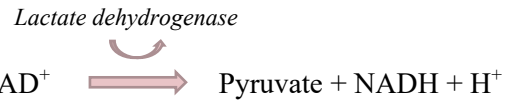
Lactic acid and Lactate

Lactic acid was discovered in 1780 by a Swedish chemist named Carl Wilhelm Sheele, from sour milk. Lactic acid is carboxyl acid and dissociates to form lactate and a hydrogen proton (H+).

The lactate concentration varies in different blood compartments with the highest concentration in plasma. Plasma lactate concentration, is 50% higher than in the erythrocytes and 30% higher than in capillary whole blood (35). A high correlation (r=0.99) between capillary blood lactate and plasma lactate has been shown(35).

Glycolysis and glycogenolysis in the fetal liver induced by fetal catecholamines, result in the production of pyruvate. Increased pyruvate concentrations led to lactate production. Under normal conditions there is a steady state between lactate and pyruvate 10-15:1 (17). Therefore, during labour even under aerobic conditions, a certain amount of lactate is produced in the fetus (36,37). The ratio of lactate/pyruvate is increased with hypoxia (17). Thus, lactate in fetal blood could theoretically increase with high doses of maternal glucose infusion but for this to occur the glucose concentration must exceed 8.3 mmol/L (37). Continuous maternal intravenous glucose infusion during labour was shown not to affect the lactate levels in fetal scalp blood or cord acid-base balance (38,39).The majority of lactate is eliminated through reconversion of lactate to pyruvate by lactate dehydrogenase. Pyruvate can then enter the Citric cycle intracellularly in the mitochondria for optimal energy production. For that process to occur, oxygenation must be restored.

Figure 3.



Lactate can be transported across the placenta together with a hydrogen ion and this occurs in the direction with the lowest hydrogen concentration, which is to the maternal side (24). Although this process is slower than carbon dioxide elimination across the placenta (17) The maternal lactate level is 20-30% lower, which facilitates the lactate diffusion across the placenta (25). The accumulation of lactate in the fetal blood, however, occurs when the production of lactate exceeds its clearing mechanisms.

When fetal distress, lactate measured in fetal blood is considered mainly to originate from the fetus (25,36,40,41). Furthermore, fetal anaerobic metabolism is likely to be the main source for the fetal lactate increase and not from the mother, since the fetal maternal lactate gradient is positive in cases with fetal distress as opposed to normal labour this gradient is negative and FBS lactate correlate significantly to umbilical cord artery lactate (25,36,40,42).

In the first stage the lactate production is constant and there is no correlation to the cervical dilation (42,43). However, in the active part of second stage lactate increase in fetal and maternal blood, and more rapidly in the mother. The fetal lactate increased in scalp blood was 0.032 mmol/L per minute pushing in the second stage (which equals 2 mmol/L per hour) in a study (40). Another recent study reported a smaller increase of only 0.025 mmol/L per minute pushing and that the correlation between the lactate value in FBS and number of minutes pushing had a poor corelation of (R=0.1) (44).

Lactate through oxidative metabolism is also an important energy substrate for the fetus. It has been suggested that lactate produced by the astrocytes support oxidative metabolism in cortical neurons (45). Since lactate does not cross the blood-brain barrier easily, blood-borne lactate is not considered a significant source (45). However, lactate levels in magnetic resonance imaging correlate strongly to lactate in arterial cord blood at birth and is a useful predictive marker (46,47). A review concluded that deep grey matter Lactate/NAA is the most accurate quantitative MR biomarker within the neonatal period for prediction of neurodevelopmental outcome after neonatal encephalopathy. This may be a useful parameter in early clinical management decisions and as a surrogate end point in clinical trials that evaluate novel neuroprotective therapies (47).

Even the uterus produces lactate as a result of the intensive contractions (48,49). With the increasing activity in the uterus and decreased blood flow in the

myometrium the acid load in the myometrium will increase and if there is insufficient oxygen lactate is produced. Intermittent acidification in the myometrium is thought to be a normal phenomenon in labour (48). Interestingly, for women suffering dysfunctional labour, it has been suggested that increasing acidification in the myometrium underlies dysfunctional labour (50). The measuring of lactate in amniotic fluid could be an interesting predictor of the course of labour in primiparous for improved diagnostics of dystocic labours (51,52).

Measurement of lactate is also a well-established, marker within prehospital, intensive and sepsis care for hypoxia caused by impairment of circulation and tissue perfusion (53,54). The use of Point of care lactate measurements is growing.

Experimental animal studies showed that when induced hypoxia in fetuses there was a strong association between subcutaneous measured lactate to lactate measured in the brain, central circulation and cord blood (55–58). Lactate measured in central fetal arterial blood correlated strongly to BD (R=0.95) and pH (R=0.86) (59). Furthermore, it has been demonstrated that increases in subcutaneous lactate levels preceded the increase in lactate level and pH decrease in brain tissue. Thus, it has been suggested that lactate is an earlier marker of hypoxia than pH. Subcutaneous lactate levels significantly increased 2-3 minutes after the asphyxic period (56). When exposed to intermittent total umbilical cord occlusion (duration one minute) lactate increased at a rate of 0.35 mmol/L per minute of occlusion (59)(60). At recovery lactate normalized at a rate of 0.04 mmol/L per minute (59). Corresponding to a recovery rate of 2.4 mmol/L per hour. Recently it was shown in a rat model that lactate levels measured in subcutaneous fluid collected by a continuous micro-dialysis probe closely reflected central plasma lactate levels upon transient de-oxygenation (R=0.89). The microdialysis probe they used for the lactate measurement was integrated into a fetal scalp electrode, which enabled continuous measurement of lactate subcutaneously (58).

The possibility to analyse lactate in fetal scalp blood during labour has been reported since the 1970´s but the method required large amounts of blood 150-200 µL and sampling was difficult to succeed (61,62). It was therefore deemed too impractical to be used in clinical practice despite promising results. It was not until the 1990´s the method gained a new landmark in clinical practice, due to the new test strip method for lactate measurement, requiring very small amounts of blood for analysis (42,63).

Asphyxia

Asphyxia comes from Greek and means pulselessness and birth asphyxia refers to a condition where the newborn is severely affected by hypoxia. It can occur before, during and after labour. The main goal of intrapartum surveillance is to prevent birth asphyxia i.e., asphyxia evolving during labour. Although it is rare, when it occurs, it can lead to serious neurological disability or death and evidently has tremendous impact on the individual, the family and, labour staff.

In the literature various definitions of asphyxia are used as outcome measures, which complicates the comparisons of results. Since there is no international consensus on the optimal outcome value to assess intrauterine asphyxia in the newborn it remains debatable. Fetal asphyxia can be described as a condition of impaired blood gas exchange leading to progressive hypoxemia and hypercapnia with a significant metabolic acidosis (64). According to US Task Force and ACOG´s updated edition from 2019, "*Neonatal Encephalopathy and Neurological Outcome"* to determine, that an acute hypoxic-ischemia event occurred within close temporal proximity to labour and delivery, contributed to neonatal encephalopathy a multidimensional assess is performed and include:

1.) Apgar Scores less than 5, at 5 and 10 minutes.

2.) Fetal umbilical artery acidemia of pH <7.0 or BE ≥12 mmol/L

3.) Neuroimaging evidence of acute brain injury seen on Magnetic Resonance Imaging.

4.) Presence of multisystem organic failure: can include renal injury, hepatic injury, hematological abnormalities, cardiac dysfunction, metabolic derangements and gastrointestinal injury or a combination of these.

5.) No evidence of other proximal or distal factors that could be contributing factors.

Therefore, the incidence of birth asphyxia varies upon the definition employed. An extensive Danish study recently reported an incidence of birth asphyxia (defined as pH<7.0 or Apgar scores at five minutes <7) of 0.6%. The Swedish pregnancy quality register reported in 2019 that the proportion of newborns with Apgar <7 at 5 min in term (≥37+0 gestational weeks) infants was 1.2% in 2019 (65).

Use of Apgar Score in the assessment of the new-born

Apgar Score was invented and first published by Virginia Apgar in 1953(66). Apgar scores provide valuable information about the clinical status of the newborn judged at one, five and ten minutes after birth. The Apgar Score consists of five parameters, which happens to be acronym of the founder: activity (A), pulse (P), Grimace, reflex

irritability (G), appearance/skin color (A) and respiration (R). The Apgar Score quantitates clinical signs of neonatal depression where each parameter is evaluated and given points 0-2, which sum up to 0-10 at the given point of time. The Apgar Score evaluation is a cheap test of the clinical status of the newborn and is used globally. The major advantage with the Apgar Score is that almost every newborn is evaluated, and it has been said that more or less every newborn has been looked at through the eyes of Virginia Apgar (67).

Table 1. Apgar Score System.

Parameter	Score 2	Score 1	Score 0
Pulse/Heart rate	>100 beats per minute	<100 beats per minute	Absent
Respiration	Vigorous cry	Slow, irregular. Weak cry	Absent
Muscle tone	Active	Flexed limbs	Absent
Reflex irritability	Prompt response to stimuli	Minimal response to stimuli	Floppy, no response
Colour	Completely pink	Body pink, blue extremities	Blue, pale

Normal: 7-10, Moderately depressed: 4-6, Needs immediate resuscitating: 0-3
Assessment at one, five and ten minutes after birth

First minute Apgar Score parameter is particularly valuable to decide the need for new-born resuscitation at birth, whereas the five- and ten-minutes Apgar Scores evaluate the neonate´s response to resuscitation. The five minutes Apgar Scores are associated with short and long term neurological outcomes are often used as a proxy for asphyxia and as a research outcome parameter of poor neonatal outcome (68–73). Strong association to negative long term cognitive effects as evaluated in school results have been found in large epidemiological studies (69,72).

Even though, low Apgar Score in most neonates are likely to be due to hypoxia and acidaemia, depressed vital signs may also be due to other reasons, including medications given to the mother, respiratory distress, malformations and therefore the scoring system should not be used as a proxy for asphyxia (70,74). If the new-born has a low first minute Apgar Score and has received neonatal interventions this will also affect the five and ten minute Apgar Score and therefore not only represent intrauterine acidaemia (75). A high degree of interobserver disagreement also exists and due to the above, the value of low Apgar Scores as a research endpoint has been questioned (76–78).

Apgar scores and the association to umbilical cord blood acid base values are modest and vary in different studies, not all new-borns with low Apgar Scores have acidosis and vice versa (68,79,80). Likewise, there is a modest correlation between Apgar Scores and fetal scalp blood lactate (81–83).

Umbilical cord blood gas analysis in the assessment of the new-born

James *et al.* 1958 first recognized that umbilical cord blood gas analysis could give an indication of asphyxia at birth. Interestingly, Virginia Apgar was also the last author of this article.

Skåne university hospital, was the first clinic in Sweden to introduce routine sampling in all new-borns at birth in 1981 (84). In most labour wards in Sweden, it is routine to analyse cord blood gases in every new-born despite the clinical condition at birth. However, in other clinics an indication is required such as pathological CTG, meconium-stained water, the use of FBS during labour etc or the baby is born in a poor condition (85). According to the Swedish pregnancy register 2019, 82.3% of all babies had umbilical cord blood analysis (65). For babies with a low (<4) five minutes Apgar Score this number was less than 74%.

Cord blood provides useful information about the intrauterine oxygenation prior to birth. The results give important feedback to staff about the interpretation of fetal monitoring in labour. In addition, they serve as quality assurance of the labour clinic and are an important objective outcome measure in research and cases of litigation (84). A normal blood-gas strongly indicates against that the adverse outcome was caused by intrapartum asphyxia(84,86). However, the results lack the information of occurrence of acidosis during pregnancy.

However, analysing and interpreting cord blood gases requires good technique and knowledge of pitfalls (1,87,88). It is therefore important to be aware of the many physiological and methodological factors that can influence the readings. Blood sampling from both the cord artery and vein in the umbilical card is carried out immediately after delivery and before the baby´s first cry (1). Sampling from both vessels is recommended in order to validate the sample and identify the arterial and venous sample correctly, so as to avoid sample mix-up (12). The arterial sample reflects the fetus acid-base status and the venous is the blood from the placenta.

Since 2008 it is routine in Sweden to sample from the unclamped cord. Before that, the cord was double clamped directly after birth so that the acid base status would not be altered by ongoing placenta metabolism and gas exchange (89). Cord blood samples are affected by sampling in unclamped cord with a significant decrease in pH and increase in pCO_2 and lactate. This is probably caused by a phenomenon called hidden acidosis where metabolites in the peripheral veins are flushed out in the central circulation when the neonate´s circulation is restored (89–91) Therefore, to ensure the measurement of the correct acid-base status of the new-born it is important to sample the cord blood as soon as possible after birth. The results are also affected by time from sampling to analysis and this is why a time limit of 15 minutes is recommended (87).

Fetal acidosis in cord blood

There is no international consensus upon the definition of acidosis with suggestions varying from pH <7.00 to <7.20 in arterial umbilical cord blood (80,92,93). At the university hospital in Skåne, the definition for acidosis used is pH <7.10 which, is based on below the mean value -2SD of pH in the population (94). More severe acidosis is considered when pH reach <7.05 (12). However, in the range 7.0-7.05 most neonates The acid base values and lactate in cord blood are also affected by gestational age, which is thought to be due to increasing fetal metabolism and aging of the placenta by progressing gestation and gestational age adjusted reference values have shown to have a better predictive value of neonatal outcome (95–98). It is important to note that pH is on a logarithmic scale and not linear, which is why a fall in pH with 0.1 units gives a rise of H^+ of different magnitude at different pH levels. For instance, from a pH 7.30 to a pH 7.20, H^+ concentration rise with 13mmol/L as compared to from a pH 7.0 to a pH 6.90, the increase of H^+ is the double (5,12). This is, why the evaluation of the degree of acidosis with pH is more difficult than with a linear measurement such as BD or lactate.

Fetal metabolic acidosis in cord blood

Furthermore there is no consensus on the definition of metabolic acidosis at birth, level of pH, or if BD_{ecf} should be used or pH alone (12,80,99–101). BD is added to pH to distinguish between respiratory and metabolic acidosis. Of note, BD is not an analyte but a calculated value expressed in mmol/L from equations using pH, pCO2 and hemoglobin (fixed value or measured)(102). Different equations exist in different blood gas machines, which will provide diverging results(96,103). Different compartments of fluids used such as base deficit in extracellular fluid $BD_{ecf,}$ or base deficit in blood Bd_{blood}, also provides different results, the latter resulting in higher values (96).

It is generally agreed that with metabolic acidosis there is a risk of adverse neonatal outcome (64). ACOG define MA by pH <7.0 and BD >12 mmol/L (93). The definition of MA as pH <7.05 and BD_{ecf} >12mmol/L has been widely used in large studies such as the Swedish STAN study and the RCT comparing FBS with lactate or pH (although they did not specify compartment measured) (104,105). 40% of those with pH<7.05 had BD_{ecf} above >10 mmol/L (12). Furthermore, according to Low *et al.* only BD_{ecf} >12 mmol/L was required for the diagnosis of MA with an incidence of 2% in their population (64). FIGO on the other hand, recommends the use of pH <7.0 and BD_{ecf} >12mmol/L but recently however, suggested lowering the limit to pH<7.05+BD_{ecf} >10 mmol/L and to include lactate >10 mmol/L as an alternative to BD (9).

The use of lactate in umbilical cord and new-born blood as a predictor of neonatal outcome is supported by several other studies (98,106–108). Lactate >10 mmol/L

in arterial cord blood has proven to be more closely associated with neonatal outcome and the need for Neonatal intensive care (NICU) than BD especially when gestational age adjusted reference values were employed (97,98). Among acid base parameters, gestational age adjusted arterial cord lactate showed the highest predictive ability to identify 5-minute Apgar score <7 with AUC 0.79(98). Lactate measured in arterial blood at 30 minutes of life showed a strong predictive ability for moderate and severe neonatal encephalopathy(109). Lactate is a linear measurement of the degree of metabolic acidosis, which in turn correlate to an adverse neonatal outcome (101,110) By using lactate instead of BD some of the methodological confounding could possibly be reduced(98).

In a large Swedish case control study the prevalence of MA defined as 7.05+BD >12mmol/L was 0.68% and 0.38% for pH <7.0 (111). MA occurred more frequently in nulliparous than parous women (111). In a selected cohort with indication for fetal scalp blood sampling the prevalence of MA (7.05+BD >12 mmol/L) was reported to 3.6% (105). Not all newborns with MA have a clinical impaired condition at birth or at later follow-up(112). Fetal death and neurological sequelae increase after severe cord artery acidosis at birth pH <7.0 (80,92,113) In a large Swedish study no cases with HIE occurred with umbilical arterial pH >7.0(111).

It has been reported that 40-50% of metabolic acidaemia is due to suboptimal care, thus preventable (114,115). The main reasons for suboptimal care leading to metabolic acidosis have been identified as a failure of appropriate action upon signs of fetal distress and injudicious use of oxytocin (114). The use of oxytocin is commonly associated with preventable adverse events during labour (114).

Hypoxic Ischemic Encephalopathy

Severe intrapartum asphyxia can lead to short and long-term neurological damage. Short term neurological injury occurring within 48 hours from birth is referred to as Hypoxic Ischemic Encephalopathy (HIE) (116,117). The diagnosis requires confirmation of metabolic acidosis in the umbilical cord blood or in the new-born blood, together with low Apgar scores at 5 and 10 minutes, and early Magnetic resonance Imaging with signs of cerebral oedema (118). HIE has an estimated incidence of 1.5 per 1000 live births (119).

HIE is classified into three stages, mild, moderate or severe, according to the clinical signs and symptoms by the grading system by Sarnat and Sarnat (117). Mild (grade 1) is characterised by hyper alertness, irritability, jitteriness and a normal electroencephalogram (EEG). Moderate (grade 2) is characterised by obtundation, hypotonia, strong distal flexion and occasional multifocal seizures. Severe (grade 3) is associated with coma. Permanent neurological damage is rare in cases with mild HIE and most infants recover without any sequels, whilst moderate and severe are

strongly associated with long term neurological morbidity and mortality (118,120). The incidence of Hypoxic ischemic encephalopathy (HIE) grade 2 and 3 was reported 0.7 per 1000 term newborns in Sweden(65).

The neuronal injury caused by severe acidosis develops in two phases, whereby the initial ischemic phase is characterized by hypoperfusion and ischemia in areas of the brain leading to cell death. The second phase, the reperfusion phase occurs after 2-6 hours and leads to further cell death in the affected areas of the brain. Treatment with therapeutic hypothermia has been shown to mitigate the second phase and limit the neuronal damage but requires early diagnosis to initiate treatment in a referral center and with a narrow therapeutic window <6 hours from birth (121).

Long term neuronal damage could lead to the development of cerebral paresis or cognitive and neuromotor deficits (118,120). However, intrapartum asphyxia accounts for only 10-20% of cerebral paresis cases (118,122–124).

Fetal monitoring during labour

Cardiotocography

Fetal Cardiotocography (CTG) is the main method for fetal surveillance in high and middle-income countries and became available for clinical use in 1968 (125). The CTG interpretation model was derived from empirical observations of CTG recordings during human labour by Hon and Hess in the 1950s (126,127) The CTG enabled continuous electronic recording of the fetal heart rate with simultaneous recording of the uterine contractions. CTG is commonly used and has provided important knowledge of the fetal condition during labour. The main goal of introducing CTG was to prevent intrapartum fetal death, which initially was shown by the method (128,129). Before the introduction of CTG in Sweden in the 1970s the perinatal mortality was 15 per 1000 new-born (130). The perinatal mortality at term as of today is 1.5 per 1000 new-born, although it is uncertain to what extent CTG has contributed to this reduction (65).

However, since the introduction of CTG into labour care, the interventions have increased and the benefits from fetal surveillance have been questioned(131,132). In the last Cochrane review 2017, it was concluded that continuous CTG during labour is associated with a reduction of the incidence of neonatal seizures, but has no impact on Apgar scores, cerebral palsy, or perinatal mortality despite an increase in operative births. The majority of the trials included, compared continuous CTG to intermittent auscultation by Pinards stethoscope or ultrasound Doppler velocimetry. There are no RCTs comparing CTG to no surveillance at all. The true

prevalence of acidosis is unknown and would also be unethical to study in human fetuses. It is also difficult to compare the use of CTG with different obstetrical guidelines and interpretation models used in various trials (133). Furthermore these studies were carried out in the 1970s to early 1990s where equipment, clinical experience, and interpretation criteria were very different from current practice, and they were underpowered to evaluate differences in major outcomes (9,134). Nonetheless, a large American observational study from 2011 showed that the use of CTG during labour was associated with significantly lower early neonatal and infant mortality as well as reduced number of infants with five minutes Apgar scores less than 4 and neonatal seizures (135). A fall in perinatal mortality by the use of CTG has also been reported by other studies (136–138). Still, CTG is associated with a high intra and interobserver variability and the second most common indication for caesarean section is due to non-reassuring or indeterminate CTG tracing (139–141).

The CTG has a high negative predictive value for fetal distress and it is generally agreed that a normal tracing is a reassuring sign of fetal wellbeing and oxygenation (5,9,75,85). It was reported that 94% of those new-borns with a normal CTG had umbilical arterial blood pH >7.20 (75). In another study, for the outcome pH <7.15 a sensitivity of 97%, specificity 84%, positive predictive value 37% and negative predictive value of 99.5% was reported (142).

In the first stage of labour 50% of CTG may be classified as abnormal depending on classification system used (143). Pathological patterns are less common. In a previous study we found that among neonates with 5minutes Apgar score >9, 18% had a pathological CTG pattern during labour (70). Due to the intensified uterus contractions in the second stage, the fetus is at increased risk of hypoxia (9,144). Despite this, the scientific literature about second stage CTG patterns, is poor (145,146). During this phase, the interpretation of the CTG recording is further complicated by maternal moves and pushing leading to incomplete recordings or lack of recordings (145). In addition, it was shown in a study that the occurrence of unclassifiable CTG traces were significantly more common among the fetuses with metabolic acidosis (cord artery pH 7.0+ BD >12) (144).

According to Swedish guidelines, intermittent CTG monitoring every second hour is recommended in low risk labours in first stage (5,147). If non reassuring CTG then continuous registration is adopted. In second stage and in high risk labours continuous CTG monitoring is recommended (5).

The FIGO guideline for CTG interpretation, by an international consensus panel in 2015, aimed to reduce the interobserver disagreement (148). The interpretation model was modified to the Swedish system and has been in use since 2017 (5). Despite that none of these models had previously been validated they were introduced into clinical practice directly (149,150). Compared to the previous model

used in Sweden (which was a modification of the Figo guideline 1987) and the new modified FIGO, a validation study showed significantly less sensitivity for cord artery pH <7.10 , a fall from 94.5% to 76.7% in first stage and for second stage the sensitivity decreased from 87% to 50% (149,150).

Secondary tools to assure fetal wellbeing

Since the drawbacks with cardiotocography it has therefore been suggested that CTG should, only be used as a screening method for hypoxia and the diagnosis of acidaemia should in most cases, be confirmed by fetal scalp blood sampling before intervention (151). There is a growing body of evidence and awareness by delivery staff of the increased risks with interventions that could lead to both physical and psychological harm (65,152–154) Delivery by caesarean section (CS) is an increased risk of bleeding, infections, surgical complications and thrombosis for the mother. There is also a higher risk for adverse outcomes in subsequent pregnancy compared with vaginal birth. A primiparous delivering by caesarean also have an increased risk of operative delivery in subsequent pregnancies (155). Multiple CSs are associated with a higher risk of maternal morbidity and mortality (156). Additionally, infants born by CS have different hormonal, physical, bacterial, and medical exposures (such as intrapartum antibiotics and uterotonics) and are exposed to more short-term risks, which range from altered immune development, allergy, atopy, asthma, and reduced diversity of the intestinal gut microbiome, compared with those born vaginally (156). Furthermore, vacuum extraction has a more than fourfold risk of complicated perineal tears (65,154). Obstetrical interventions due to suspect fetal distress can also be a negative experience leading to secondary fear of birth in proceeding pregnancy (152,153).

Since the introduction of CTG, the intervention rates have increased. Based on data from 121 countries, a trend analysis showed that between 1990 and 2014, the global average CS rate increased from 6.7% to 19.1% (157)(158). The reason for this is multifactorial and complex but could partly be due to unnecessary interventions as a result of the low positive predictive value of CTG.

The two most commonly used secondary tools attempted to reduce the false positive rate of cardiotocography are fetal stimulation test and fetal scalp blood sampling with either pH analysis or lactate analysis(1). Fetal scalp sampling is mostly used in Europe and Australia whereas the fetal stimulation test is primarily recommended in American guidelines (5–7,159).

In Sweden, FBS with lactate is used in most obstetric units, but FSS is also recommended in clinical guidelines (5,160). FBS with pH has been routinely used in Swedish clinics since the beginning of the 80´s and may have contributed to

significantly reducing caesarean sections in the 80´s (42). The caesarean section rate has since then increased, but the Northern countries remain among those countries with lowest section rates compared to other high income countries (155,157).

Despite the fact that there is a lack of randomized controlled studies comparing CTG in conjunction with FBS to CTG alone, emerging evidence from observational studies has shown that FBS decreases operative deliveries and caesarean sections (161–164). This is supported by the Cochrane review on fetal scalp blood sampling, NICE guidelines and FIGO guideline on adjunctive technologies although they call for further studies on the subject (1,2,6). Others have shown in a subgroup analysis between trial, the use of CTG in conjunction with FBS with pH compared to studies with only CTG, that the use of FBS significantly reduces neonatal acidosis but instead instrumental deliveries are increased (165).

Early studies on FBS used as a secondary tool to CTG suggest improved neonatal outcomes (62,166). Still, there is only one RCT from 1979 that compared the use of continuous CTG monitoring with or without fetal scalp blood sampling and its effect on the rate of caesarean section (167). Unfortunately, the study was unpowered with only 230 in each arm, to show any significant differences. Several retrospective observational studies have thereafter shown a decrease in caesarean section with the use of FBS with pH in conjunction to CTG (166,168–170). Others have shown a reduction in acidosis (umbilical artery pH<7.0) OR 0.55 and low 5-minute Apgar Scores <7 OR 0.71 in combination with an increase in spontaneous births(162). A Danish review showed a decrease in emergency caesarean section and vacuum extraction rates from 8.2% and 8.5% to 7.9% for both, when FBS increased from 3.8 to 6% in a six year period (163). The authors concluded from the literature review that it seems that the use of FBS in conjunction with CTG reduces operative delivery and possibly even neonatal asphyxia.

Among other secondary tests to CTG such as near-infrared spectroscopy and continuous pulse oximetry have not shown to significantly reduce interventions nor improve neonatal outcomes (171,172). Analysis of fetal ECG together with CTG has been evaluated in randomised trials and a meta-analysis by the Cochrane institute concluded that with the use of STAN, the rates of instrumental vaginal deliveries and FBS were lower than with CTG only, whereas the rates of severe metabolic acidosis, neonatal encephalopathy or caesarean section did not differ significantly (173).

Invention of fetal blood sampling

The method of fetal scalp blood sampling was invented by Saling, in 1962, in Berlin, which was actually before CTG was established (174). When CTG was introduced into clinical practice, Saling et al. advocated for the combined routine fetal

monitoring with CTG in combination with FBS if CTG was abnormal and later FBS was adopted as a secondary tool to CTG.

The Saling Technique is still used in the same way today (174). Initially pH was used and the limits for normal ranges were based on the evaluation of 77 cases with undisturbed parturients. These results were confirmed by others (175,176). In 1967 normal values were established in a larger cohort with particular attention to the range compatible with the clinically unimpaired condition of the new-born. From 1500 fetuses selected by indication for FBS (which in this study was meconium-stained water, found by amnionscopy or ruptured membranes or alteration or fall in fetal heartbeat registered by Piquard´s stethoscope), 306 vigorous new-borns (by means of vigorous clinical state by Salings scoring system) were selected. From this the mean +/-2 SD was used to set the reference value and the lower limit of 7.24 was considered prepathological and below 7.20 as pathological (177). These reference values are in use for FBS-pH to date. Interestingly, Saling et al found that the mean value before the onset of labour was 7.305 and during labour pH increased until cervix dilation of 5-8 cm 7.348 and thereafter decreased in the second stage.

Ingemarsson and Arulkumaran later found similar normal pH ranges but concluded that a critical evaluation of the acid-base balance is necessary, since in most cases, the abnormal acid-base balance is transient and of a respiratory, harmless type without concomitant fetal distress (176).

Fetal Scalp Stimulation Test

Fetal scalp stimulation test (FSS) is based on the assumption that the healthy fetus will react with an increase in heartrate when the scalp is stimulated and is therefore, recommended to be used when non-reassuring CTG by several guidelines and obstetrical societies (1,5,7,85). Fetal stimulation test was first described by Sontag in 1936 (178). There are four methods for fetal stimulation tests described in the literature: vibroacoustic stimulation, Allis clamp pinching, digital stimulation or puncture of the scalp for fetal scalp blood sampling (FBS) (179). Most frequently the digital stimulation is used. In the late 80´s the test became more widely used after American obstetricians recommended fetal blood sampling to be abandoned since they claimed that FBS did not lower the frequency of instrumental deliveries (180–182). However, FBS was already at the time used infrequently, in approximately 2 % of all labours.

There is one metanalysis on FSS-test from 2002 based on 11 articles on the different stimulation test (six studies on scalp punction and two on digital stimulation). Despite few and small studies presenting likelihood ratios with wide confidence intervals the method was recommended (179). The metanalysis concluded that Intrapartum stimulation tests appeared to be useful to rule out fetal acidaemia in the

setting of a non-reassuring FHR pattern. However, because these tests were less than perfect, caution was advised and fetal scalp pH should be determined whenever possible after a positive stimulation test (lack of acceleration) (179).

Lately the FSS test has been questioned since the evidence for the method is low with a few and small observational studies and there are no randomized trials (51,60). However, others argue that the FSS-test is safe and there is a randomized controlled trial ongoing in Ireland comparing CTG in conjunction with FSS-test compared to CTG in conjunction with FBS-pH (183).

The pioneers of point of care measurement of lactate

In the early nineties a Swedish research group introduced a new test strip method for lactate measurement Lactatecard, a prototype for LactatePro™(LP). The new method required only 20µL and the result was presented within 60 seconds (63). Previous methods for lactate measurement had required at least 150µL and consequently had only been used for research purposes and not in clinical practice (184). This test strip method had been developed to evaluate athletes performance in sports medicine (185). The method showed good correlation to the reference method measured in plasma (Monotest: Boeringer Mannheim, Germany) R=0.94 in 24 fetal scalp blood samples. Also correlation between the two methods in arterial cord blood was good R=0.95 (63). In normal labours at term with normal CTG recordings and vigorous new-borns, fetal scalp blood lactate was measured with the test strip method and the mean lactate was 1.7-1.84 (SD 0.5-0.8mmol/L) (43,184).

Thereafter, a later version of the lactate prototype that required only 5 µL blood and showed a significant difference $p<0.001$ in median FBS lactate between normal labours and labours with fetal distress (according to CTG), median value and 5th and 95th percentiles 1.24 (0.36/2.9) respectively 1.82 (0.4/4.02)(42). FBS scalp blood lactate correlated to simultaneously analysed scalp blood pH R=-0.43. From the same cohort the correlation between FBS lactate sampled within 60 minutes from birth (N=103) and cord artery lactate was R=0.65 (41).

In a retrospective study on all patients with indication for FBS due to ominous CTG pattern 1993-1998 the reference value for intervention and the predictive value of FBS with LP was established. Kruger´s study was a well conducted and large retrospective study where, for the first time, the predictive ability of FBS lactate was showed for adverse neonatal outcomes. The predictive ability for lactate for adverse neonatal outcomes was generally better with higher sensitivity than FBS-pH but not significant. However, the study raises some concerns since the reference values were chosen by applying the already accepted reference values based on percentiles for pH and the cohorts were not comparable (166). The 25th percentile for pH was found to be 7.21 (which was close to the recommended reference value of 7.20) and

corresponded to the 75th percentile for lactate of 4.8 mmol/L. The cohort from Saling et al. contained vigorous new-borns, whereas in the Kruger study the cohort was selected by including only women with a non-reassuring CTG. Further, they did not report the time from FBS to delivery, which means that cases with hours between FBS and delivery might have been included in the analysis. The outcome measures used in the study (HIE, pH<7.0 and BD>16) may also have been too severe. There were also two different lactate meters used, LP and a protype that was calibrated differently, which may also have biased the results. LP is the most studied POC lactate meter and the cut-off >4.8 mmol/L is internationally recognized (2).

FBS pH or lactate?

To measure pH or lactate in FBS is open to debate. Two RCT´s have compared FBS pH with FBS lactate. The first RCT concluded that lactate measurement in fetal scalp blood to be a method that required significantly less time, fewer incisions, and lower failure rates than sampling for pH. Furthermore, there was no significant difference between the lactate and pH subgroups in mode of delivery or neonatal outcome (186). A cut-off of 3.08 mmol/L measured with lactate card (a prototype to LP) was used for intervention, compared to the intervention cut-off for pH <7.20. The above cut-off corresponded to the 99th percentile in the population and corresponded the LP value of 4.2 mmol/L (63,187).

In 2008, these results were confirmed in a larger Swedish multicentre RCT with LP and the cut-off 4.8 mmol/L compared to pH with the cut-off <7.21 with 1496 patients in each arm (105) The only significant difference was a higher sampling failure rate in the pH group compared to lactate. Among those with FBS samples below/above the cut-off for intervention (lactate ≤4.8; pH >7.20) within one hour of birth, there were no new-borns with pH<7.0 in the lactate arm, whereas in the pH group there were six cases, suggesting that lactate can safely rule out severe acidaemia.These results were confirmed in a secondary analysis to be equal in the second stage of labour (188).

Several studies report a higher predictive ability with FBS lactate than pH, in addition that lactate seems to be an earlier marker of hypoxia (8,56,105,189).

A prospective Danish study found in contrast that FBS with Lactate Scout™ would lead to more instrumental deliveries, without a decrease in severe metabolic acidosis. However, they did not use a cut-off, specific for that device, which may have affected the results (190).

Lactate and pH are not totally comparable since they measure different things. PH is also more fluctuant since hydrogen ions are more easily transported across the placenta than lactate. PH alone, cannot discriminate between type of acidaemia; respiratory or metabolic (176). Furthermore, cord compression and intermittent

impaired gas-exchange over the placenta caused by uterine contraction in normal labour can lead to transient impairment of carbon dioxide exchange resulting in increased hydrogen ions and thus a decrease in pH that is also physiological (176). These conditions are harmless if they do not persist too long and are quickly resolved after birth, as the baby breathes, and the accumulated carbon dioxide is eliminated(64).

In an observational study it was shown that 43% of FBS pH samples were inconsistent with a greater variation than 0.038 (the acceptable maximum analytical difference by the laboratory in the study) when double analysed, and the reliability of the test was therefore questioned. In 16% the difference crossed the decision making threshold (191).

The cord pH as well as FBS pH correlation to cord lactate is also moderate (81,192) and in a study the agreement for lactate and pH values for R^2 were between 0.3 and 0.45, suggesting that only 30–45% of the variance in lactate values can be attributed to changes in pH why that they are not comparable and probably measure different things (193). Others report the false reassurance of hypoxia with FBS pH(194). Recently, the predictive ability of FBS-pH to predict cord artery pH<7.05 and five minute Apgar Sore <7 was shown to equal 0.59 and 0.55 respectively (195).

FBS lactate is superior to pH in sampling failure, with more than tenfold more sampling failures with pH(81,105,186). This is due to the larger amount of blood required for analysis. In addition, pH cannot be analysed bedside, which is why analysing problems, such as having a long distance to the analysing instrument or blood clotting in the tube, is also a contributing factor. A FBS pH sample also takes longer time and more repetitions of incisions to obtain a sample leading to long time intervals from sampling to result and making a decision to intervene (186,191,196).

FBS lactate as a secondary tool to CTG

The method gained increasing popularity in the 90´s when the new test strip method was introduced and required only 5 µL of blood (63). Since then, there are several POC lactate meters on the market, all differently calibrated and hence have different cut-offs for intervention. LP is the most studied device for use in fetal scalp blood sampling and the internationally accepted cut-off for intervention is 4.8 mmol/L (8). Fetal scalp blood with measure of lactate is recommended and supported by several societies (1,2,5,6).

Scalp blood lactate sampled within 60 minutes to birth is associated to arterial umbilical cord blood acid-base values with the best correlation to lactate (R= 0.48-0.65) and BD (0.258-0.51) and moderate inverse corelation to pH (-0.21- - 0.38) (41,81,82,197). Although the time limit of 60 minutes from FBS to birth may be considered too long to expect higher associations. Also, different brands of point of

care devices and blood gas machined measure lactate differently since no gold standard exist. In addition, lactate concentrations differ in various compartments and are therefore not entirely comparable (35). The moderate corelation of FBS lactate to cord pH could be explained by the fact that they measure different thing, Although, FBS pH showed a correlation to cord pH of 0.40-0.42 and there was a significant relationship between scalp pH and scalp lactate ($r = –0.56$, $p = 0.001$)(81,197).

There is an association between FBS lactate and CTG patterns, where late or severe variable decelerations combined with tachycardia were the most frequent pattern with elevated lactate levels(198). The opposite was found for isolated reduced variability and the absence of accelerations during labour that had no increased prevalence of acidaemia (198,199).

Since growth restricted fetuses lack sufficient glycogen reserves it was hypothesized that they would not have the ability to produce lactate in response to hypoxia during labour. However, it has been shown that the growth restricted fetuses had higher levels of lactate in fetal scalp blood and umbilical cord blood and that the ability to produce lactate as a response to hypoxia was intact (200,201). Also, fetuses with accelerated growth/in large for gestational age have shown to have an intact ability to produce lactate in fetal scalp blood and umbilical cord blood as a response to sustained intrapartum hypoxia (200,202).

FBS lactate and the association to low five minute Apgar Scores is poor ($r=0.18$) (81,82). On the other hand, as mentioned earlier, Apgar scores do not only represent acidosis but a generally depressed condition at birth that could be due to other causes as well.

The method of fetal scalp blood sampling has been criticised for being invasive but the puncture to obtain a small drop of blood for lactate measurement is comparable to the application of a scalp electrode for continuous CTG and the method is also well tolerated by the women (203–205). Fetal complications from FBS with LP are rare, even in the event of succeeding vacuum extraction (81,198).

The normal reference values for vigorous new-borns with normal CTG in the second stage was reported to 1.1-5.2 mmol/L (the mean +/- 2 SD) measured with LP. This raised the question whether different cut-offs should be used in the first and second stages?

With the use of oxytocin or epidural, the mean lactate values have been found to be significantly higher (44). A theory presented by the authors was the hypothesis of a negative effect of exogenous oxytocin on the fetal circulation, which theoretically, could lead to disturbed and decreased cerebral circulation and the development of acidosis, Primiparas also have significantly higher FBS lactate values than multiparous but this could not be explained by a longer pushing time. (44).

Risk factors for a lactate value measured by LP >4.8mmol/L at FBS were reported to be the result of minor language barriers, active bearing down, and maternal hight <155 cm(206). Interestingly, the study could not show an increased risk with induction of labour, the use of oxytocin, fetal gender or night-time fetal blood sampling.

FBS with lactate is frequently used in Sweden and has been reported to be performed in 10.5% of all deliveries (206). Of women undergoing FBS 8.8% had lactate levels above the recommended cut-off for intervention and hence only 1% of all labouring women were delivered due to elevated FBS lactate levels (198). Other studies report 9.5-12% elevated values depending on device, and which cut-off was employed (82,207). The various frequencies are probably explained by, that local traditions and level of experience, which affect the frequency of FBS (208). Different CTG interpretations models may also influence the number of tracings classified as non-reassuring and hence the frequency of FBS(149,150).

A normal FBS lactate has been reported to have no false negatives for acidosis (pH<7.0)(105,189,209). In addition high negative predictive values of 98-100% have been shown to predict outcomes such as umbilical cord artery pH ≤7,10, pH ≤7.10+BD≥12mmol/L and pH≤7.00+BD≥12mmol/L (189,209). This implies that the method can safely rule out sustained hypoxia during labour.

Although, it is important to be aware that the opposite, false positives, can occur if contamination of the sample with amniotic fluid occurs since it contains high levels of lactate (37,210). Further a high haematocrit can give false low readings of lactate in whole blood (211,212). Scalp oedema have been found to result in lower lactate values (Unpublished data Wiberg) whereas others have found no difference (also unpublished data(37)).

Despite the evidence from observational studies for FBS lactate, there is still no randomized study comparing the use of only CTG to the use of CTG in adjunction with FBS lactate, that has shown any reduction in intervention rates. The Flamingo trial was recently published but was clearly underpowered to be able to show any differences in caesarean section rates (213).

Long-term follow up studies on use of fetal scalp blood lactate measurement during labour and the outcome of the children are still scarce even though the method has been frequently used since the 1990´s. Until now there is only one 4 year follow up from the cohort from the Swedish RCT in 2008. For the children who had higher levels scalp lactate were shown to have an increased probability of fine motoric and cognitive dysfunction at four years of age. Importantly, this was not true for the children with low levels of lactate at fetal blood sampling (214).

Even, if FBS with lactate in conjunction with CTG can identify emerging intrapartum acidosis to allow timely intervention, this is not the case in obstetrical

catastrophes such as placental abruption, cord prolapse, uterine rupture or severe chorion amnionitis. Such events require immediate interventions and should not be delayed by fetal blood sampling (8,105,214).

Since LP has ceased in production new devices have been suggested and with new cut-offs for intervention (207). So far only one study derived device specific cut-offs for neonatal outcomes but it only included 140 patients and therefore did not have the power to show the predictive ability for more severe adverse neonatal outcomes (215). Instead, new cut-offs have been suggested by converting the internationally accepted cut-off for FBS pH or LP (159,207,216–219). Frequently the time intervals from FBS to birth have been too long or not specified. Others report logistical analysing problems such as samples had to be sent to a central laboratory for analysing (8,81,218–220).

The new lactate meter SSLX showed a strong association to lactate values measured in fetal blood simultaneously analysed by stationary blood gas machines (R= 0.81-0.97) (216,221), Unlike the previous POC lactate devices it adjusted for haematocrit interference, which showed a closer agreement to stationary blood gas lactate values as compared to LP (212).Previously suggested cut-toffs were found in the range 5.0-7.0 (159,193,216–218).

The rationale for this thesis was that the most studied lactate meter for use in fetal scalp sampling LactatePro™ had ceased production and there was an urgent need to find an alternative. Since CTG has a low positive predictive value for fetal hypoxia, secondary tools to cardiotocography are essential, to identify at an early stage, fetuses with hypoxia that would benefit from timely intervention to avoid injury – and with a more precise identification of fetuses at risk for hypoxia interventions can hopefully be reduced. Two different lactate meters were evaluated. We also studied fetal scalp stimulation test since this test is recommended in the U.S, as an adjunctive tool to CTG instead of fetal scalp blood sampling.

Aims

The primary aim of this thesis was to search for a new reliable POC to replace LactatePro™ after the production was discontinued and to publish cut-offs for that specific device. Secondary, to study the predictive values for Fetal Scalp Stimulation Test.

I: Propose cut-offs in fetal scalp blood for LactatePro2™ based on the comparison of lactate values measured with LactatePro™ and LactatePro2™.

II: To investigate whether accelerations of the fetal heart in response to fetal scalp stimulation (FSS) while performing fetal blood sampling (FBS) could be used as a good predictor of fetal well-being and fetal scalp lactate < 4.2mmol/l. For women with 20 min from FBS to delivery we also wanted to study if the FSS test could rule out a pathological low pH in umbilical cord blood.

III: To evaluate the reliability of a new POC lactate meter. A prospective quality study where StatstripXpress® lactate meter was compared to lactate measurements with ABL 800.

IV: In a large multicentre study with >3500 labouring women find the cut-off for StatStripXpress® and StatStrip lactate® meter to rule out fetal hypoxia based on neonatal outcomes.

Materials and Methods

Measurements of lactate

There is no gold standard for lactate measurement and hence various stationary blood gas machines measure lactate differently (222). The concentration of lactate also varies depending on which compartment of fluid is measured why direct comparisons between lactate measured in different blood compartment is not directly comparable (35).

Fetal scalp blood (FBS) lactate can be measured by point of care devices, which has the major advantage of only requiring small blood volumes and rapidly delivering the result. FBS lactate can also be measured in stationary blood gas machines with the disadvantage of requiring large blood volumes, which is difficult to obtain sufficiently from the fetal scalp and hence the sampling failure is too high to be clinically useful. In the stationary blood gas machine ABL 800 (Radiometer, Copenhagen), lactate is measured in plasma. In point of care devices, lactate is measured in whole blood. Lactate is measured by amperometry in ABL 800, Stat Profile® PRIME™ CCS Analyzer (Nova Biomedical, Waltham, US) LactatePro™, LactatePro2™ and StatstripXpress®/Statstrip® Lactate meter (SSLX) (Nova Biomedical, Waltham, US) whereby lactate is converted into pyruvate and hydrogen peroxide, which is then oxidized (223,224). The resulting electric current measured is then proportional to the lactate level in mmol/L.

The measurement of lactate is affected by interferences of haematocrit, paracetamol, bilirubin, acetaminophen, ascorbic and uric acid(54). In addition, cord blood and new-borns have higher haematocrit values, which is why this interference could be substantial in fetal scalp blood (225). Theoretically, a high haematocrit in fetal blood could mask an increasing lactate concentration when lactate is measured in whole blood by POC devices. ABL 800 instead measures lactate in plasma and therefore it is not affected by haematocrit interference (223).

Before introducing a new device into clinical practice, the analytical performance of the device must be evaluated. The bias is the percentage of deviation from the reference method. In our study ABL 800 was set as the reference method. The correlation to the reference method is generally studied as well as the agreement. The analytical precision and variance by examining the coefficient of variation (CV). In addition, preanalytical and analytical process errors must be considered.

Cord blood

The procedure

Paired cord blood samples are routinely collected directly after delivery and before the baby's first cry on unclamped cord in marked A (arterial) or V(venous), in 2 mL preheparinised plastic syringes (Radiometer). The artery is first sampled since it empties quickly and therefore most difficult to sample. After removal of the needle, syringes are emptied for air bubbles, closed, and analysed within fifteen minutes by the stationary blood gas analyser.

Laboratory analysis

The labour staff are trained and certified by Biomedical analysts to analyse the cord blood correctly. The blood gas instrument is situated in the labour ward for easy access and quality checks are run by staff from the hospital laboratory on a regular basis. The Automated Blood Laboratory (ABL) 800 is a mini-laboratory with optional wet chemistry and blood gas determinations such as pH, pCO_2, pO_2, BD_{ecf}, HCO_3^-, Hct, Hb, electrolytes, glucose and lactate and the analysing time for a sample is approximately three minutes for a full blood gas status (223). Base deficit (BD_{ecf}) (the reciprocate value of BE_{ecf}) is calculated in the machine for extra cellular. The ABL 800 is a robust instrument commonly used worldwide both in the clinics and for research purposes.

The Stat Profile® PRIME™ CCS Analyzer (Nova Biomedical, Waltham, US) is also a robust automated blood laboratory for measurement of pH, pCO^2, pO^2, BD_{ecf}, HCO_3-, Hct, Hb, electrolytes, glucose, and lactate. In paper 4, this blood gas machine was used for FBS-pH measurements and cord blood gases at birth in one of the centra. To ensure the two BGAs were in agreement, cord blood was double analysed simultaneously by the two instruments. No significant differences in measurements of pH, pCO2 and lactate were found. Base Excess (BEecf) was calculated in the machine. (226)

Fetal scalp blood measurement with lactate or pH

Indication

There is an indication for FBS when the CTG is non reassuring or pathological.

Contraindication

Contraindications include rapidly deteriorating CTG or severely pathological tracing. FBS should be avoided if there is risk of vertical transmission or risk of fetal coagulopathy.

The procedure

Fetal scalp blood was sampled according to the standard procedure by Saling (174). Through an amnion scope, the fetal scalp was carefully wiped to remove contamination products and punctured to a depth of no more than 2 mm. Ideally the scalp was wiped once again to ensure removal of contamination product such as fetal tissue products and fat as well as amniotic fluid that can interfere with the result (220). Sampling should be performed on a proper blood drop and not from smeared blood on the scalp. Capillary blood was collected in pre-heparinized plastic capillary tubes containing up to 80 µL. The blood was blown out or tapped from the syringe and thereafter analysed bedside with lactate by the point-of-care device LP or with pH (Stat Profile Prime Analyzer) as the primary methods. In the first and fourth study the blood was measured simultaneously, from the same blood drop by LP2 or SSLX. Gloves should always be used when handling blood products but even when handling the test strips gloves are important, since sweat (contains lactate) from fingers could otherwise alter the analysing results.

LP was calibrated for every 25th analysis with a control test-strip and SSLX was calibrated daily with a test solution.

Guidelines for clinical use of FBS lactate and pH

Internationally recommended cut-offs for FBS lactate measured by LP are: lactate level < 4.2 mmol/L = normal, 4.2–4.8 mmol/L = pre-acidaemia and > 4.8 mmol/L = acidaemia (8).

For FBS pH <7.20 was considered pathological (177).

If pre-acidaemia, repeat measurement within 20-30 minutes. If pathological value, delivery is expediated (5).

When evaluating the FBS result for clinical decision making the obstetrician must also consider the progress of labour, the fetal reserve, the severity, and the rate of deterioration of the CTG pattern.

Pitfalls

Samples contaminated by amniotic fluid, fetal tissue, admixture of maternal blood or meconium may affect values. It remains uncertain whether Scalp oedema affects the measurements.

A limitation in the method is that it depicts the fetal metabolic status at that certain time point. If CTG patterns remains non reassuring the FBS must be repeated. Rapid changes in gas exchange can occur, especially in the second stage.

Analysis by different POC devices

All the POC lactate meters measure lactate in whole blood by amperometry but are completely differently calibrated.

LactatePro™ (Arkray, Japan) (LP), measures lactate in 5µL of whole blood, with an analysis time of 60 seconds. It is calibrated for every 25th analysis with a control test strip. According to the manufacturer the SD in adult blood is 0.07 mmol/L and the coefficient of variation (CV) is 3.2% for LP.

LactatePro2™ (Arkray, Japan) (LP2)(227), measures lactate in 0.5µL of whole blood, with an analysis time of 15 seconds. LP2 measures in the ranges 0.5-25 mmol/L. It is calibrated for every 25th analysis with a control test strip. For LP2, the SD is 0.2–0.7 mmol/L and the CV 2.9–4.3% in adult blood. Operation ranges are: temperature 15–40 °C.

Statstrip® Lactate™ and Statstrip® Xpress (Nova Biomedical, Waltham, US) (SSLX) (224) measure lactate in 0.6µL of whole blood, analysis time 13 seconds. SSLX measures lactate in the range 0.3-20 mmol/L. Unlike the previous POC´s, it is designed for hospital use and has the advantage that interferences of haematocrit, paracetamol, bilirubin, acetaminophen, ascorbic and uric acid are eliminated by algorithms. The POC lactate meter presents in two versions although equally calibrated, StatStrip® Xpress™ and StatStrip® Lactate, with the latter having the ability of real time transfer directly to the electronic medical system. This is an important issue in patient safety to minimize human typing errors and patient mix up. Operation ranges are: temperature 15–40 °C (59–104 °F), altitude up to 4500m (15,000 ft), humidity 10–90% and a haematocrit value within 20–65%.

Figure 4. Statstrip® Xpress

Statistical analyses

Statistical analyses were performed using SPSS 23-26.0 (SPSS, Chicago, IL, USA) and Graph Pad Prism, La Jolla, California.

Comparisons of groups

To assume the appropriate statistical method the distribution of the data must be known. From a histogram the distribution of the data can be shown. When data is normally distributed the sample is centralized around the mean and equally distributed around it. Parametric tests are applied for comparisons. The data is presented with the mean and the standard deviation. The standard deviation (SD) is a measurement of how much the values in a population differ from the mean.

If skewed distribution, the data is presented with the median together with percentiles or quartiles. Non-parametric tests are applied for comparisons.

The range express the minimum and maximum values of the data distribution.

For comparisons of groups the following tests were used in the studies. For comparisons of means a parametric test such as Student´s T-test was used. Ratios were analysed and compared by Chi-square test or Kruskal-Wallis test. Fisher's test/The Chi-square test was used for comparing frequencies or proportions between

two or more unrelated groups. Kruskal-Wallis test is a non-parametric test used for comparisons between three or more groups.

Group comparison of continuous skewed variables was performed with a non-parametric test such as Mann-Whitney U. Mann-Whitney U test can be used when comparing two unrelated groups. Non-parametric tests are based on rankings and on fewer assumption why they are more robust on skewed distribution. If possible, a parametrical test should be used as it is preferred to a non-parametrical test.

Two-tailed statistics were performed for comparisons of groups and a P value of <0.05 was considered statistically significant. For two-tailed tests the null hypothesis is that the difference between the two groups is zero.

Confidence interval (CI) is a given range, most commonly 95%, within which the true value lies. A larger sample size provides a narrower confidence interval.

Simple Linear regression analysis

By simple linear regression analysis, the association between a numerical outcome and a numerical exposure can be illustrated.

The equation of the regression line is as follows:

$$y = \beta 0 + \beta 1 x$$

β0 and β1 are the parameters or the regression coefficients of the linear regression, where β0 is the intercept (the value of y when x =0) and β1 is the slope of the line (the increase in y for every unit increase in x).

The correlation coefficient (R) is a measure of the strength of the linear relation. The correlation coefficient is always a number between -1 and +1 and equals zero if there is no linear association between the variables. The larger its absolute value the closer association. The maximum value of 1, is obtained if the points in the scatterplot lie exactly on a straight line. The opposite occurs if high values of y tend to go with low values of x and the correlation coefficient is thereby negative. Pearson correlation coefficient is commonly used.

If the data is not normally distributed, a non-parametrical measure of rank correlation can be used called Spearman rank correlation.

Coefficient of determination (R^2) is the correlation coefficient squared, which is the proportion of the variation (%) in the dependent variable that is predictable from the independent variable. In other words, the percentage of the variation that can be attributed to changes in one variable affecting the other variable for instance exposure and outcome or comparison of two measuring instruments or two different variables.

Bland Altman plot

Linear regression analysis studies the relationship between one variable and another but not the agreement. When comparing two measuring methods it is important to know that a high correlation does not imply that the two methods agree. Therefore a Bland Altman plot (228) is used to assess the comparability between two clinical measuring methods, the extent of agreement (228). It is a way to evaluate a bias between the mean differences of two different measuring instruments, and an agreement interval within which 95% of the differences of the second method, compared to the first one lies is employed. If the differences are normally distributed, then approximately 95% of differences will lie within this range. Despite a perfect correlation there could still be a bias. The difference between the measurements is plotted against the mean of the two methods. The extent of agreement, within 95% limits of agreement, corresponds to the mean +/- 2 standard deviations.

Systematic bias

The *systematic bias* is the mean difference between the two measuring methods (the new method and the reference method) and reveals if there is tendency to be higher or lower than the true value. It is then for the investigators to decide whether the methods are sufficiently in agreement for the new one to replace the old.

Precision

The precision of a measuring method is how precise the instrument can replicate the measurements. This is calculated by the Coefficient of variation, (CV%). For accurate measurements for an instrument or device, low CV values are preferred. A CV<5% is generally considered as a good CV value.

$$CV = \frac{SD}{Mean}$$

Diagnostic tests

A test´s diagnostic properties can be described by its sensitivity, specificity, positive and negative predictive values which are calculated by crosstabulation.

Sensitivity- is the proportion of diseased identified with a positive test = a/(a+c)

Specificity- is the proportion with no disease correctly identified as such with a negative test = d/(b+d)

Positive predictive value- is the proportion of those who tested positive and truly have the disease, "rule in" =a/(a+b)

Negative predictive value- is the proportion of those who tested negative and truly have no disease, "rule out" =d/(d+c)

	Disease	**No disease**	**Sum**
Test positive	True positive - a	False positive - b	a+b
Test negative	False positive - c	True negative - d	c+d
Sum	a+c	b+d	

Likelihood ratios (LR) can also be used to describe the test-properties of a test. An advantage is that unlike sensitivity, specificity, positive and negative predictive values, likelihood ratios are independent of the prevalence of the outcome.

Positive likelihood ratio (LR+) = Sensitivity/ (1- specificity)

Negative likelihood ratio (LR-) = (1- sensitivity)/ specificity

The likelihood ratio is considered significant when the 95% confidence does not cross one. A positive LR greater than 10 or a negative LR less than 0.1 have great potential to alter clinical decisions (229).

Reference values

To set a reference value it is recommended to include at least 120 reference individuals (55). From a healthy population the reference value is set by the mean and +/- 2SD if normally distributed. This will result in a lower and upper limit of normality. If skewed distribution the median and percentiles are employed. The percentiles can vary but commonly used are $10/90^{th}$. Additionally, quartiles can be used. However, reference values are a statistical demarcation of normality and pathology and it needs to be shown if there is an associated to an increased risk for an adverse outcome.

ROC-curves

The Receiver operator characteristic (ROC) curve is a plot of the sensitivity against 1- specificity for different binary outcome variables. The area under the receiver operator curve (AUC), predicts the ability i.e., the performance of the diagnostic test to identify the disease. The outcome with the highest predictive ability will give the most optimal sensitivity and specificity. If the test for a certain outcome has an area of one it would mean that the test has 100% sensitivity and 100% specificity. In

contrast, *Line of no effect* is AUC 0.5 i.e., a test with a value less than 0.5 is not considered a useful diagnostic tool.

From the ROC curve, the optimal cut-off statistically is the shortest distance from one. The ROC curve presents a plot of different point estimates of cut-offs and is a sort of trade-off of sensitivity and specificity. As sensitivity increase, specificity decrease. Depending on what is valued the most important for a certain test, a high sensitivity or a high specificity, the most optimal point estimate can be chosen. For instance, a severe outcome that cannot be missed require a higher sensitivity with the drawback of a lower specificity which, leads to more false positives.

Cut-off

Cut-offs can be derived from, for example analysing the results from ROC curves and is a value set by expert in relation to the adverse outcome, intervention and sometimes also health economics (21).

In fetal surveillance the cardiotocography can be seen as the screening method with high sensitivity for hypoxia. It requires secondary tests to improve its specificity. The secondary test is a type of diagnostic test, but in this case, it should not diagnose severe hypoxia, but instead at an earlier stage identify the risk of severe hypoxia to prevent the development of disease. Since severe hypoxia is a serious outcome, the secondary methods should safely rule out hypoxia and an optimal secondary test would therefore have a low likelihood ratio for adverse outcome. The positive likelihood ratio is in this case therefore not the key issue.

Describing the statistical methods, the following references were used, Kirkwood Essential Medical Statistics 2003 and Internet Medicine Diagnostic Tests “Medicinsk statistik – diagnostiska tester” Ludvigsson 2017.

Ethical approval

Paper 1 was approved by the Regional Ethics Committee in Copenhagen, Denmark (H-6-2014-FSP-013), The Danish Data Registry (HEH-2014-075) and Regional Ethics Committee of Karolinska Institute, Stockholm, Sweden (2016/1723-32).

For paper 2 the Regional Ethics Committee in Copenhagen, Denmark, regarded the study as a register study and deemed no need for written consent (H-6-2014-FSP-016).

Paper 3 and 4 was approved by the Regional Medical Ethics Committee in Lund, Sweden (2016/1038) and the Western Sydney Local Health District Human Research Ethics Committee AU RED LNR/18/WMEAD/413.

Paper-specific Materials and Methods

Paper 1: Use of Lactate ProTM2 for measurement of fetal scalp blood lactate during labor – proposing new cut-offs for normality, preacidemia and acidaemia: across-sectional study

This observational study was carried out at Copenhagen University in Herlev, Denmark, and Söder Hospital, Karolinska Institute, Stockholm, Sweden, from November 2013 to May 2014.

The inclusion criteria were labouring women with singleton in cephalic presentation, >33 weeks of gestational age, no contraindications for FBS, a non-reassuring CTG or a significant event with automated analysis of fetal electrocardiogram (ST-waveform analysis (STAN^{TM}, Neoventa Medical, Gothenburg, Sweden)).

In case of a non-reassuring CTG or a significant STAN-event, interpreted by the doctor on call, FBS was performed by standard technique according to the clinical guidelines. Only lactate values measured with LP were used in the clinical management. When indicated, fetal blood sampling was repeated. From the same capillary, one drop of blood was analysed with LP and LP2 at the same time.

FBS samples taken within 60 min before delivery were included in the correlation analysis between pH and lactate values in cord blood. Umbilical cord blood samples were taken immediately after delivery on unclamped cord and analysed within 15 min by a stationary blood gas analyser ABL 800. Obstetric and neonatal data were routinely entered into the electronic records (Copenhagen: OPUS, H-EPJ, Sweden: Obstetrix, Siemens AB).

To calculate the CV for LP2 in umbilical cord blood, repeated analysis of lactate (10 times in the same blood drop within 5 min) was performed from five different cord blood samples with various lactate levels.

Statistical analyses

The correlation between various variables was calculated by linear regression analysis with 95% prediction interval. Bland–Altman plot was used to investigate a possible relationship between the discrepancies between the lactate values by the two devices. Limits of agreement and conversion equations were calculated by performing a linear regression with the difference between the measurements of the two methods as dependent variables and the mean value of the methods as independent (230). Conversion equations between the two methods were calculated from the results of the regression. From the conversion equations, new reference values for normality, preacidemia, and acidaemia for LP2 based on LP were

generated. Sensitivity and specificity with 95% CI for normality and acidaemia were calculated for comparison between the two devices.

Paper 2: Effectiveness of fetal scalp stimulation test in assessing fetal wellbeing during labor, a retrospective cohort study

A retrospective study at Copenhagen University in Herlev, Denmark. This study included women in active labour with an indication for FBS due to a non-reassuring CTG (suspicious or pathological trace) or a significant STAN event (ST-waveform analysis of the fetal electrocardiogram, STAN®, Neoventa Medical, Gothenburg, Sweden) were enrolled if the inclusion criteria was obtained. In the actual study the cohort was divided into three groups corresponding to the FBS to-delivery time, Group 1: ≤ 20 min, Group 2: 21–59 min and Group 3: ≥ 60 min. In the original study the indication for FBS was based on the CTG interpretation (in Denmark the FIGO classification from 1987 is used for CTG classification) by midwives and doctors on call. To classify a CTG tracing at least 20 min readable registration is obligatory. Therefore, we choose to re-assess the CTGs for up to 30 min before FBS in order to define the baseline and for the fetal response (acceleration) to scalp stimulation (wiping and puncture) up to 5 min after FBS. An acceleration could only be defined if the baseline was definable before FBS and if there was an increase in the fetal heart rate by at least 15 beats per minute for more than 15 seconds (148,231) . The FSS-test was regarded positive when no acceleration was seen and negative when an acceleration could be identified as described in previous publications on the subject (179). The CTGs were re-interpreted by one of the authors (F.S.), during November 2017 until June 2018. The appraiser was blinded to the FBS result, delivery mode and neonatal outcome. FBS was performed by the doctor on call by the standard technique previously described. According to the guidelines, the FBS should be repeated after 20 min if the measured lactate value was ≥4.2 mmol/L and the CTG pattern persisted non-reassuring (5,232). If the lactate value was > 4.8 mmol/L expediated delivery was recommended. Umbilical cord blood was sampled from unclamped cord directly after birth and analysed within 15 minutes by ABL 800.

Statistical analyses

Ratios were analysed and compared by Chi-square test or Kruskal-Wallis test. Group comparison of continuous variables was performed with Mann-Whitney U. For scalp lactate the whole cohort was included in the analysis, whereas for the umbilical cord blood gases (UCBG) only women delivered within 60 min from FBS to delivery were included. Crosstabulation was used to calculate sensitivity, specificity, and likelihood ratios. Likelihood ratios are often used to compare the diagnostic value of a test due to their independence of the prevalence. The likelihood

ratio is considered significant when the 95% CI does not cross one. A two-tailed p-value of less than 0.05 was considered statistically significant. Analyses were performed using SPSS 25.0 (SPSS, Chicago, IL, USA).

Paper 3: Reliability of the point-of care analyzer "StatStrip® Xpress™" for measurement of fetal blood lactate

This study was a prospective quality study. The first part was carried out from March until July 2016, and the second part from September 2016 until October 2018 at the delivery department, Skåne University Hospital, Sweden.

Paired cord blood samples were routinely collected directly after delivery and before the baby's first cry in preheparinised plastic 2 mL syringes. After removal of the needle, syringes were emptied for air bubbles, closed, and analysed within five minutes by the stationary blood gas analyser ABL800™. Simultaneously with analysis by ABL800 ™, the residual blood in the syringe was tested in duplicate or triplicate by the point-of-care device StatStrip®Xpress™.

For the second part of the study scalp blood was collected from 324 fetuses showing a suspicious or pathological CTG-tracing and analysed 2-3 times from the same blood drop with SSLX.

Statistical analysis

Correlation coefficients were calculated by simple linear correlations with 95% prediction interval. Accuracy, bias, and discrepancies of the different methods were assessed by Bland-Altman plot, Kruskal-Wallis test, and Student's t-test. All P-values were two-sided and P-values below 0.05 were considered significant. Graph Pad Prism, La Jolla, California was used for statistical analysis.

Paper 4: Proposed cut-off for fetal scalp blood lactate in intrapartum fetal surveillance based on neonatal outcomes: a prospective observational study

This prospective observational multicentre study was conducted from January 2016 to March 2020 at seven different maternity clinics in Sweden (three regional clinics: Helsingborg, Ystad and Kristianstad) and four tertiary clinics, Skåne University Hospital, Sahlgrenska University Hospital, Söder Hospital and one in Australia, Westmead Hospital, Sydney.

Inclusion criteria were indication for fetal scalp blood sampling due to suspicious or pathological CTG patterns in labour, singleton pregnancy ≥35+0 gestational weeks (according to ultrasound dating in the first or second trimester), vertex

presentation, and no contraindication for FBS. When indicated, FBS was performed by the standard procedure described by Saling. For clinical decision making, the scalp blood was primarily analysed by LP, except at Sahlgrenska University Hospital where LP and/or pH was analysed (pH analysed by Stat-Profile-Prime-Analyzer, Nova Biomedical, Waltham, US). Simultaneously, from the same blood drop, the lactate level was measured by StatstripLactate or Statstrip Xpress (SSLX).

If the blood drop was too small for both tests, analysing of only LP or pH was performed. The sampling time and results were noted in the medical record. If FBS was repeatedly assessed from the same fetus, only the last value was entered into the database. Paired umbilical cord blood was sampled from all new-borns on unclamped cord directly after delivery in pre-heparinized syringes and analysed within fifteen minutes by stationary blood gas analysers (BGA) in the labour units (ABL800, Radiometer, Copenhagen, Denmark or Stat-Profile-Prime Analyzer). For both BGAs the Base Deficit was calculated in extracellular fluid (BD_{ecf}).

Obstetric and neonatal outcome variables were retrieved from the electronic medical records (Obstetrix, Cerner) and entered retrospectively into the database. LP was calibrated for every 25th analysis with a control test-strip and SSLX was calibrated daily with a test solution. The primary outcome was metabolic acidosis (MA) in cord blood defined as pH < 7.05 and BD_{ecf} > 10mmol/L and/or lactate > 10mmol/L (9,109). If arterial samples were missing, venous samples were used with the same cut-offs as arterial. Since venous pH values are usually less acidotic than arterial, venous levels meeting cut-off criteria for arterial samples are evidently pathological (233). Secondary outcome measures included alternative combinations of the blood gas parameters, Apgar scores (AS) and various clinical neonatal outcomes: neonatal intensive care unit admission (NICU), neonatal resuscitation interventions, such as continuous positive airway pressure therapy (CPAP), bilevel positive airway pressure (BiPAP) or ventilation. The correlation between scalp blood lactate and umbilical artery blood pH/lactate was determined in relation to the time interval 0-15 minutes, 0-25 minutes, 0-30 minutes, and 0-60 minutes from FBS to delivery to define the optimal time-limit for cases to be included in the calculation of the suggested cut-off for intervention.

Statistical analysis

The incidence of metabolic acidosis varies between 1.3% to 5.7% and with wide confidence intervals. For this reason, it was not reasonable to perform a power calculation for this study. Based on the study of Wiberg-Itzel et al., a sample size of 3000 women was chosen to achieve a sufficiently large number of the predefined outcomes for the calculations in a reasonable timeframe (105).

Receiver Operating Characteristic (ROC) curves with the respective areas under the curve (AUC) were calculated for the relevant outcomes. Spearman rank correlation

coefficients were calculated. Kruskal-Wallis or Fisher´s exact test was used when appropriate. To investigate a possible relationship between the discrepancies in values obtained by either the two BGAs or POCs linear regression and one sample T-test before a potential Bland-Altman plot was constructed. Analyses were performed using SPSS 26.0 (SPSS, Chicago, IL, USA). For the calculation of sensitivity, specificity, positive (LR+) and negative likelihood ratios (LR-), with their 95% confidence intervals, Medcalc.org was used.

Results and Comments

Paper I

Use of Lactate Pro™ for measurement of fetal scalp blood lactate during labor – proposing new cut-offs for normality, preacidemia and acidemia: a cross-sectional study

Since LP had ceased production there was an urgent need to find a replacement. LP had up until now been used in most labour clinics in Sweden. In this study the updated version LactatePro2™ (LP2) was studied and investigated to be a possible replacement in FBS lactate measurement in fetal monitoring during labour. New cut-offs for intervention were derived from conversion of the previous cut-offs for LP.

Results

Seven hundred and one fetal scalp blood samples were analysed simultaneously with LP and LP2 from 466 women in active labour. LP-lactate values ranged from 0.9 to 10.3mmol/L (median 2.8) and LP2-lactate values from 1.2 to 13.3 mmol/L (median 4.1) with consistently higher values when measured with LP2. The two lactate meters correlated closely with a correlation coefficient of r=0.92 (95% CI: 0.91-0.93, p<.0001), although the difference in absolute values increased linearly with increasing lactate concentration as shown by the Bland Altman Plot. From the linear model and the corresponding regression coefficients, the conversion equations were calculated.

Relationships between methods:

LP2-LP1 = 0.03+0.39 (LP2+LP1)/2

Conversion equations:

LP1 = -0.02 + 0.68 x LP2 (SD= -0.09-0.07 x LP2)

LP2 = 0.03 + 1.48 x LP1 (SD= 0.16 + 0.17 x LP1)

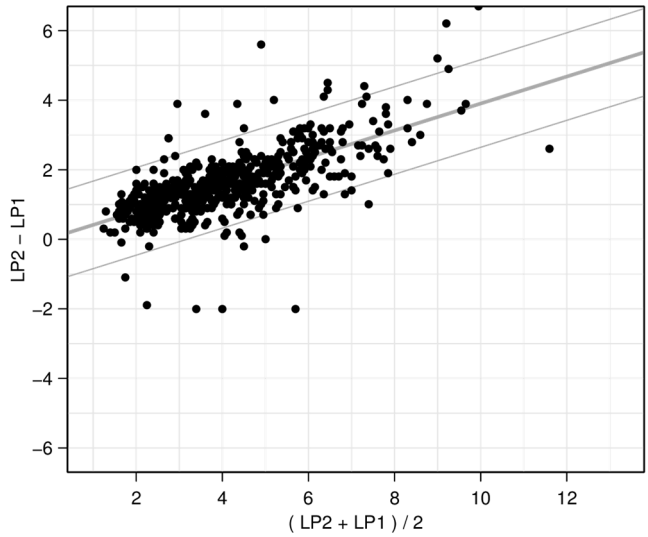


Figure 5. Bland-Altman plot showing the agreement between the two different devices.

The recommended cut-offs for normality and acidaemia for LP were converted using the conversion equation, revealed that LP2-lactate <6.3 mmol/L corresponded to LP lactate <4.2 mmol/L for preacidemia with a sensitivity, respectively, a specificity of 0.789 (95% CI: 0.712, 0.853) and 0.980 (95% CI: 0.965, 0.99) in relation to LP cut-offs. LP2-lactate >7.1 mmol/L corresponded to LP-lactate >4.8 mmol/L for acidaemia with a sensitivity of 0.803 (95% CI: 0.691,0.888) and a specificity of 0.959 (95% CI 0.940, 0.973) in relation to LP cut-offs.

The recommended rate of intervention differed with the devices cut-off with 12% pathological FBS lactate with LP1 and 10 % for LP2. A previous study recommended a similar conversion equation based on 69 paired FBS lactate samples and resulted in the cut-off for acidaemia of > 7.3mmol/L (207). They also found a lower intervention frequency when LP 2 was used. Compared to their results our suggested cut-off had a better sensitivity but slightly lower specificity for the outcome acidaemia defined as LP1 >4.8mmol/L. The sensitivity calculated by our algorithm was (0.803 (95% CI: 0.691, 0.888) versus 0.761 (95% CI: 0.645,0.854)) and the specificity with our algorithm (0.959 (95% CI: 0.940, 0.973) versus 0.975 (95% CI:0.959,0.985)).

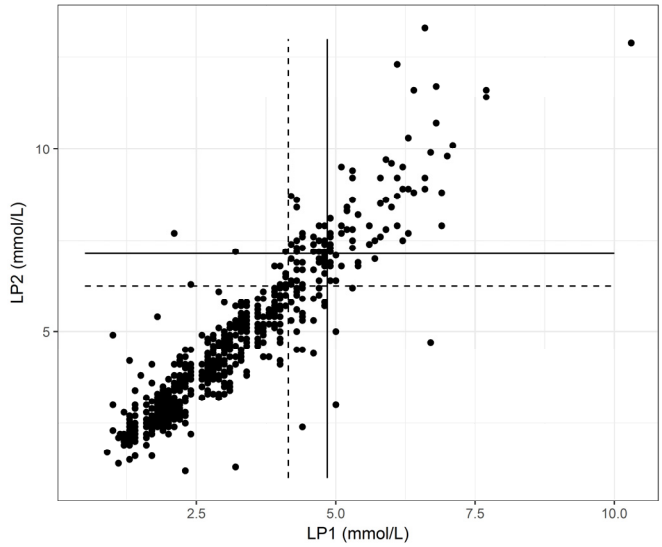


Figure 6. Scatter plot with different cut-offs for preacidemia and acidaemia.

The correlation between lactate values measured with LP and LP2 to pH in artery umbilical cord blood (within 60 minutes N= 327) were significant and equalled for both devices LP: r=0.18 (p<0.002, 95% CI: 0.29, 0.07), LP2: r=0.18 (p<0.002, 95% CI: 0.28, 0.06). There was a positive significant correlation to lactate in umbilical artery cord blood for both devices with a stronger correlation for LP than for LP2 (r = 0.38, p<0.0001, 95% CI: 0.24-0.50), respectively, r = 0.33, p<0.0001, 95% CI: 0.19-0.46).

The inter-relationship of FBS-lactate measured by LP2 and lactate in umbilical cord blood was dependent on the time from FBS to delivery: within 0-15 min, r=0.43 (95% CI: 0.16-0.63), 16–30 min, r=0.25 (95% CI: 0.04-0.43). Between 31 and 60 min, there were too few samples to allow analysis.

The CV for LP2, was calculated from five different cord blood samples with ten repeated measurements, with lactate levels ranging from 3.5 to 11.2 mmol/L. The CV varied between 4.2% and 23.4% implying a too low reproducibility.

Table 2: Coefficient of variation for five cord blood samples with different lactate concentrations. Coefficient of variation (SD/mean=CV %)

Mean lactate concentration (mmol/l)	3.5	5.2	6.9	9.6	11.2
Number of measurements	10	10	10	10	10
Standard deviation (SD)	0.3	0.5	0.5	0.4	2.6
Coefficient of variation (CV%)	8.6	9.6	7.2	4.2	23.2

Comments

In this study we defined the new reference values for LP2. LP2-lactate <6.3 mmol/L corresponded to LP lactate <4.2 mmol/L for preacidemia and LP2-lactate >7.1 mmol/L corresponded to LP-lactate >4.8 mmol/L for acidaemia. These values are slightly lower than previously reported from a similar conversions model for LP2. However, our study included nearly ten times as many measurements (207). Another study found LP 2 intervention threshold to be equivalent to 5.3 mmol/L, calculated by receiver-operating characteristic analysis with the outcome LP >4.8 mmol/L (159).

For the lactate concentration of 6.9 mmol/L, which is the closest value to the newly recommended cut-off value, the CV was 7.2% and similar results were found by Birgisdottir et al (207). This, low reproducibility could lead to a high risk of, misinterpretation of results. In a clinical situation, with a lactate value close to the cut-off for acidaemia, 6.9 mmol/L the true value can be, somewhere between 6.4 and 7.4 mmol/L, where both the false too low or too high lactate value can affect further management of labour, in a negative way. The obstetrician must therefore be aware of this bias.

Furthermore, we found the inter-relationship of FBS-lactate measured by LP2 and lactate in umbilical cord blood was dependent on the time from FBS to delivery. This finding was perhaps not surprising since it is evident that the longer time the fetal scalp blood sample is taken before birth, theoretically, the less the association to the outcome will be. But the fact that previous studies had published correlations for FBS Lactate to umbilical artery cord pH and lactate with variable results (r=0.48-0.65) raised the question if this time limit was reasonable? (41,81) In 60 minutes before delivery several factors can influence the results of the umbilical cord blood. Especially in the second stage where the fetus is exposed to the highest risk of hypoxia and consequently asphyxia can evolve rapidly.

LP and LP2 are designed for the use in adult athletes but adult whole blood and fetal blood have different physiological features. Fetal cord blood has a higher haematocrit value compared with adult blood (234). The reference range for haematocrit at birth among term neonates is 42–65% as shown in a study which is both a wider range and higher values than adults (225). Lactate levels measured in whole blood depend on the haematocrit value (211,212). In a study by Professor Niels Fogh Andersen, Copenhagen, (unpublished data), three test tubes were filled with adult venous whole blood. The haematocrit was manually increased from (1) 47% to 66%, (2) 39% to 59%, and (3) 43% to 71%. When lactate was measured by LP, a decrease was observed. The observed differences were a decrease by 42%, 34%, and 45% respectively. Consequently, one can fear that measurements of lactate with LP or LP2 can eventually mask a fetal acidaemia since a high haematocrit value leads to false low lactate values measured.

The new knowledge of the low reproducibility of LP2 and the importance of haematocrit adjustment for accurate measurement of lactate in whole blood led us to search for a new POC device for lactate measurement in fetal scalp blood. In the meantime, we also wanted to evaluate another secondary method to CTG frequently used namely fetal scalp stimulation test.

Paper II

Effectiveness of fetal scalp stimulation test in assessing fetal wellbeing during labor, a retrospective cohort study

Fetal scalp stimulation test is recommended by several obstetrical societies but the observational studies behind these recommendations are small and not up to date suggesting the need to conduct a new larger study. All previous studies apart from one had compared the FSS test to FBS pH and not FBS lactate (179,199).

Results

In this study of 385 women with non-reassuring CTG and indication for FBS we showed that:

1.) For FSS test the test properties for detecting a fetal scalp lactate LP ≥4.2 mmol/L were: sensitivity 79% (95% CI:69.4–86.6%) specificity 42.7% (95%CI:36.9–48.7%), LR + 1.38 (95% CI:1.19–1.59) and LR- 0.49 (95% CI:0.33–0.74).

2.) When maternal baseline characteristics such as maternal age, gestational age, induction of labour, fever during labour, epidural anaesthesia, oxytocin augmentation and repeated FBS were compared between those with a positive and a negative FSS test, there was no significant difference. However, there was a tendency towards more women having a negative test i.e., no acceleration when the labour was stimulated by oxytocin ($p = 0.051$).

3.) When the cohort was divided by the FBS-to-delivery time; 128 women in Group 1; ≤ 20 min, 117 women in Group 2; 21–59 min and 140 women in Group 3 > 60 min there were significant differences in the number of positive/negative test between the three groups ($p < 0.000$). In Group 1 93% of women were delivered vaginally (Table 3).

4.) There was no significant difference in level of scalp lactate or umbilical cord blood gas values between those with a positive versus a negative FSS test. In contrast, for Group 2, 73.5% were delivered vaginally and for that group there was a significant difference in the level of FBS lactate and arterial umbilical BE.

5.) The sensitivity for FSS test for the outcomes scalp lactate ≥4.2 mmol/L and ≥ 4.8 mmol/L were better within 20 min from FBS to delivery if compared to the whole cohort.

6.) In Group 1 (≤20 minutes) the (LHR+) for prediction of acidaemia i.e., lactate ≥4.2 mmol/L or lactate ≥4.8 mmol/L or umbilical artery pH ≤ 7.10 given a positive test were: 0.94 (95% CI 0.8–1.1), 0.85 (95% 0.7–1.0) and 0.98 (95% CI 0.8–1.2), respectively. The (LHR-) were for the same parameters 1.38 (95% CI 0.6–3.15), 2.17 (95% CI 0.97–4.84) and 1.09 (95% CI 0.4–2.95), respectively.

7.) A negative FSS test for fetal acidaemia was present in 36 % in the whole cohort but only in 15.6% in the group ≤ 20minutes from FBS to labour. In Group 1 both the negative and positive likely hood ratios were not significant with confidence intervals crossing one, LR+ 0.94 (95%CI:0.81–1.10) and LR- 1.38 (95% CI:0.61–3.15).

Table 3. Scalp lactate, UCBG and Apgar score < 7 at 5 minutes in 385 women with need of FBS during delivery. The cohort is divided by time from FBS to delivery and in positive and negative test results i.e., no versus an acceleration on CTG at FBS. The UCBG are not shown for women with ≥ 60 minutes from FBS to delivery. Medians with [range]

	No acceleration (Positive test)	**Acceleration (Negative test)**	**p value**
FBS to delivery ≤ 20 min (n = 128)	108 (84%)	20 (16%)	
Scalp lactate mmol/L	4.2 [1.6-7.7]	4.4 [1.9-7.0]	0.66
pH	7.2 [6.99-7.34]	7.2 [7.06-7.31]	0.790
A-pCO_2 (kPa)	7.48 [4.68-13.6]	8.12 [5.18-10.2]	0.408
A-BE	-6.8 [-17-0.8]	-6.1 [-12-(-2)]	0.829
A-lactate mmol/L	7.5 [3.6-12]	6.3 [4.5-9.1]	0.748
5 min AS < 7	3	0	NA
FBS to delivery 21 – 59 min (n = 117)	69 (59%)	48 (41%)	
Scalp lactate mmol/L	3.2 [1.1-6.8]	2.3 [1.0-6.4]	0.012
pH	7.23 [7.04-7.32]	7.22 [6.99-7.35]	1.00
A-pCO_2 (kPa)	7.31 [4.38-11]	7.88 [5.09-11.1]	0.472
A-BE	-5.95 [-17-1.4]	-4.15 [-10.8-7.3]	0.044
A-lactate mmol/L	5 [2.6-10.0]	6.5 [2.9-8.9]	0.609
5 min AS < 7	2	0	NA
FBS to delivery ≥ 60 min (n = 140)	68 (49%)	72 (51%)	
Scalp lactate mmol/L	2.1 [1-5]	2.1 [1.1-4.2]	0.911

UCBG: umbilical cord blood gases, FBS: fetal blood sampling, Min: minutes, A: artery umbilical cord blood, pCO_2: partial pressure of CO_2, BE: base excess, NA: not applicable.
Mann-Whitney test for continuous data, Fisher's exact test for nominal data.

Comments

In this study we demonstrated that the LHRs for both ruling in and out fetal acidaemia by scalp stimulation test is poor. The scalp lactate values, and the umbilical cord blood gases were remarkably similar between the fetuses, despite a positive or negative FSS test. Neither were there any differences in baseline characteristics between the groups of positive or negative FSS tests. An interesting finding, however, when oxytocin augmentation was used, there was a tendency to more fetuses responding with an acceleration upon stimulus. One explanation for this could be an extraordinary release of the stress hormones through the stimulus of sympathicus or a lower concentration of natural oxytocin and that adrenalin/noradrenalin mitigates the effect of parasympathicus (148,199,235–237).

FSS-test can be practiced by vibrio acoustic stimulation, digital scalp stimulation, puncture, or Allis clamp pinching, where the two latter methods have been questioned due to the painful procedure, since pain normally results in a decrease in vagal tone (by parasympathicus) directly followed by an increase of sympathicus. In case of hypoxia, the autonomic nervous system seems to fail, resulting in only activation of parasympathicus (182,238). Therefore, we attempted to come across this issue by gently sweeping/cleaning before puncture. By that, we would expect an increase in heart rate before a possible decrease in the vagal tone.

It is generally agreed upon that a test with a LR+ greater than 10 or a LR- less than 0.1 have the potential to alter clinical decisions (229). We found a considerably low LR+ of 1.38 and unsatisfying high LR- of 0.49. In the group of women delivered shortly after FBS the likelihood ratios were non-significant with LR+ 0.94 and LR- of 1.38. Our results differed significantly from most of the previously published results included in the meta-analysis. However, these studies were all based on a small number of cases and mostly with wide 95% confidence intervals. Our results were similar to those found in the Swedish study by Holzman et al. in 2016 (179,199,204,239). That study is based on a cohort of 1070 women (with indication for FBS due to non-reassuring CTG) where the authors showed a LR+ of 1.15 and a LR- of 0.14 for the test properties of FSS compared to FBS with lactate. Another explanation why our results differed could be the measurements of FBS-pH rather than-FBS lactate in Holzman's and our study. Still the results deviated where we found a much lower LR- especially in group one. Perhaps in our study there was a larger proportion of women in the second stage.

The stage of labour could also possibly affect the FSS test. Except from two studies, we were not able to assess the stage of the labour the FSS/FBS was performed and this why we analysed the whole cohort independently of which stage in labour the FBS was performed. An interesting finding was that, in the group delivered within 20 minutes from the FBS, 93% of the women were delivered vaginally assuming that they were in the second stage of labour at the time when FBS was performed.

In this group the LR+ was 0.94 and LR- 1.38 implying that the test could not alter clinical decision making in any direction in second stage. Commonly, FBS is not recommended in the second stage and our belief is that most obstetricians instead expedite delivery if CTG deteriorates during that phase. Although, there is a trend towards more use of FBS even in the second stage (188). If the majority of previous studies are based on performance of the FSS tests during the first stage or early in the second phase before pushing, the fetus will be less acidotic compared to the active second stage and could therefore have improved the results (240). In the present study 84% had a positive FSS test in the group within 20 minutes to births whereas for 21-59 minutes to birth the result was 59% and for ≥60 minutes to birth the percentage was lowered to 49%. At the same time, in all three groups, there were no significant differences in median FBS lactate value between those with, or without, an acceleration. Further, during the second stage the fetal head and eye bulbuls are exposed to extreme pressure from surrounding tissues. It is likely that the fetus becomes desensitized to pain by an increased release of endorphins and therefore is unable to react to a pain stimulus on its way through the birth canal (241). Not only pressure on the eye bulb, but also natural oxytocin and augmentation with artificial oxytocin activates parasympathicus and this is why it seems that the absence of accelerations during second stage is an unspecific sign not related to hypoxia (1,148,199,235–237).

An optimal secondary test to CTG requires a better sensitivity and a much lower negative likelihood ratio in order to detect acidaemia and safely rule out acidaemia in labour to be able to intervene appropriately without the risk of adverse neonatal outcomes. In our study the FSS test did not correspond to these properties and was particularly not useful in second stage. We cannot exclude that FSS test is an alternative to FBS in the first stage of labour, but the absence of provoked accelerations in the second stage seems to be a normal phenomenon, why the FSS test must be used with caution in this stage. However, these findings need to be confirmed in larger studies.

Paper III

Reliability of the point-of care analyzer “StatStrip® Xpress™” for measurement of fetal blood lactate

As demonstrated (paper I) LP2 had not shown convincing reproducibility in analysing fetal blood lactate, we initiated the search for a new device. A market analysis revealed that Statstrip®Xpress™ (SSX) was the only point of care lactate meter designed for hospital use. Previous POC lactate meters were all originally developed for athletes

in sports medicine. SSX also had abilities of reducing interfering factors of importance for analysis of lactate in whole blood and had been used increasingly in prehospital emergency care and intensive care units (53,242). Effect of haematocrit on lactate measurements had shown that LactatePro™ measured lactate in cord blood lower with increasing haematocrit whereas Statstrip and the stationary blood gas machine remained stable (212). In this study we evaluated its performance of SSX compared to the stationary blood gas analyser ABL 800™.

Results

In this study cord blood samples were collected from 112 patients. 101 arterial and 111 venous cord blood samples were of sufficient volume to be analysed successfully by ABL800™ for pH, pCO2 and pO2 and for repeated measurements with SSX.

We found that there were no differences between the correlation coefficients of ABL800™ artery lactate and SSX-artery lactate R=0.96 versus ABL800™ venous lactate and SSX-venous lactate R=0.94 and therefore the ABL800™ artery and venous lactate values were merged for further calculations. The correlation between the composite (arterial and venous samples) ABL800™ lactate and SSX-lactate was R=0.95 and agreement R^2=0.90.

Absolute SSX-lactate values were lower compared to values measured by ABL800™. The bias (the mean difference between the two methods) was significant, and increased in absolute values, but decreased in percentages, from −0.79 mmol/L (−21.1%) to −1.68 mmol/L (−15.1%) for low to high lactate values ($p < 0.05$).

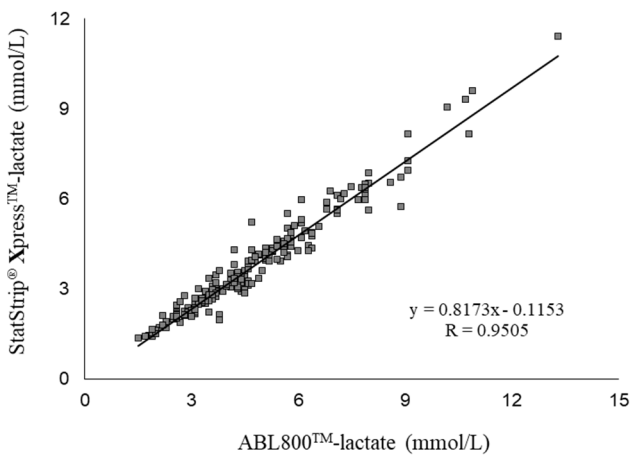


Figure 7.The correlation between lactate values in umbilical cord blood measured by SSX and ABL 800.

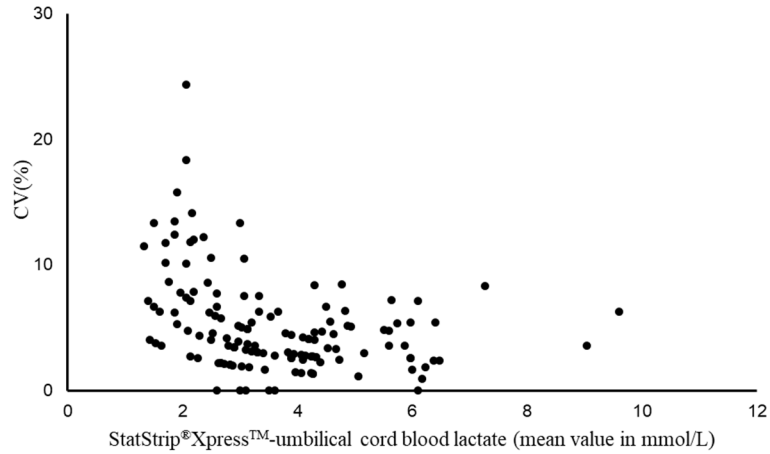


Figure 8.CV for cord blood lactate analysed by SSX

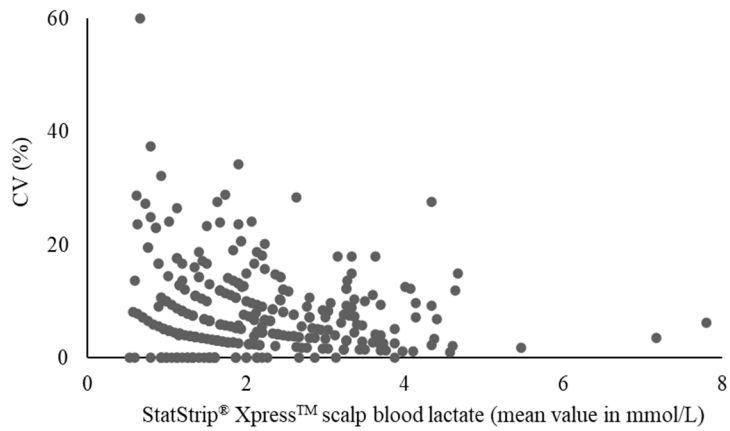


Figure 9. CV for scalp blood analysed by SSX

The mean CV in umbilical cord blood (N=140) samples was for low lactate values ≤3 mmol/L, 7.1%, whereas for lactate values >3 mmol/L the mean CV was 3.8%. There was no statistical difference between repeated measurements of the same blood drop with SSX (p=0.75) (Figure 8).

The mean CV for fetal scalp blood lactate (N=321) measured by SSX was for lactate values ≤3 mmol/L 8.4%, whereas with values >3 mmol/L the mean CV was 6.8% (Figure x). There was no statistical difference between repeated measurements of the same blood drop with SSX (p=0.11) (Figure 9).

The correlations between umbilical cord SSX- and ABL800™-lactate values correlated similarly to the measured acid-base values (pH, pCO^2, pO^2, BD_{ecf},

HCO_{3-}, Hct, Hb, glucose). PH, HCO_{3-} and BD_{ecf} showed the best correlations to lactate with a stronger correlation in arterial blood. In contrast, there was a poor correlation between SSX lactate and haematocrit and glucose in cord blood.

Comments

To the best of our knowledge, this was the first study to evaluate the reliability and reproducibility of StatstripXpress® in fetal blood. We found that SSX lactate had an excellent correlation and agreement to the reference method, R=0.95 and R^2=0.90 in agreement with previously published results (216,221). The bias (the mean difference between the two methods) was significant and increased from −0.79 mmol/L (−21.1%) to −1.68 mmol/L (−15.1%) for low to high lactate values ($p < 0.05$)

Even though the reference method and the POC device both analyse lactate by amperometry they measure lactate in different compartments, plasma respectively whole blood, which in fact entails that the absolute values are not totally comparable (35). However, the bias to the reference method is not the main issue in this context. The cut-offs for SSX used in clinical practice must be derived from the lactate meter and related to the clinical outcome and not to values originated from a BGA or approximation of previously accepted cut-offs.

In a setting lacking a BGA, as in low-income countries, the use of SSX could be an appropriate alternative to easily assess the lactate levels in the new-borns. By adjusting the suggested reference values for lactate in cord blood, those neonates who will benefit from observation and care could be predicted (97,243). In centres with routine sampling on all new-borns, it is observed that in cases with Apgar Score <4 at five minutes, there is a tendency towards a lower frequency of successful analysis of cord samples than if vigorous new-borns (65). This is probably due to the fact that it is more difficult to sample the cord when the baby suffer from asphyxia since the cord becomes flaccid (177). Also, when an asphyxiated baby is born, it is a very stressful clinical situation where all the focus is on resuscitation of the new-born and hence cord blood sampling could be missed. Another reason can be blood clots in the syringe that hinder the analysis. Therefore, sampling and analysing lactate with SSX could perhaps even be used in high income countries as an alternative when cord blood analysis fails? (244)

The coefficient of variation in scalp blood was higher compared to umbilical cord blood. For lactate values more than 3 mmol/L the CV was 3.8% for cord blood and 6.8% fetal scalp blood. Heinis et al. found the CV in scalp blood for StatStrip lactate at 7.5 mmol/L to equal 5% although based on 37 fetal scalp blood samples (221). Similar CV for cord blood lactate of 3.99% was found for LP (222).

The difference in CV between fetal scalp blood and cord blood can be explained by several factors; 1) the scalp blood was mainly double analysed whereas the

umbilical cord blood was triple analysed 2) the cord blood was analysed in a standardised procedure by one person whereas scalp blood was analysed by various doctors 3) the umbilical cord blood is sampled by injection of a needle directly into a vessel without the risk of contamination, whereas the scalp blood is sampled by puncturing the skin to access capillary blood with the risk of contamination of amnion fluid and fetal tissue, for example fat.

By the small amount of blood (0.6 μL) used for the measurement, variations in the blood composition will automatically have an impact on the result. Based on our results, we therefore highlight the importance of carefully cleaning the scalp before performing a FBS, to sample from a good drop of blood and not to scrape the scalp for blood. When lactate values close to the cut-off for intervention are measured, a safety procedure could be to double analyse the same blood sample. In case of a variation of more than 7% between the results, we recommend repeating the scalp sample for a new analysis.

Until now, the point of care measurement of fetal scalp lactate has not been supervised by the laboratory but instead by the labour ward. Since this study was published, the Statstrip lactate meter was accredited by laboratory medicine Skåne and there is ongoing collaboration for the laboratory to assume the quality assurance of the procedure. Theoretically, with increased quality assurance and education on the procedure, the preanalytical errors of fetal scalp blood analysing will hopefully decrease, which would also improve the CV.

Umbilical cord SSX- and ABL800™-lactate values correlated similarly to the measured acid-base values and the strongest correlations were found for PH, HCO3– and BD_{ecf}, suggesting that lactate is an excellent parameter for metabolic acidosis. SSX-lactate concentrations were not significantly associated with haematocrit, most likely due to the algorithms in SSX that corrects for haematocrit interference Furthermore, there was no correlation between SSX lactate and glucose, an important finding supporting that maternal hyperglycaemia has no association to fetal lactate production.

Paper IV

Proposed cut-off for fetal scalp blood lactate in intrapartum fetal surveillance based on neonatal outcomes: a prospective observational study

We had previously shown that SSX was a reliable and attractive alternative to LactatePro for use in fetal scalp blood sampling. In this large prospective study, we aimed to investigate the predictive ability of fetal scalp blood lactate measured by Statstrip Xpress/Statstrip Lactate (SSLX), and for the first time define the optimal cut-off for intervention based on neonatal outcomes. Since intrapartum asphyxia is rare, a large cohort was required.

Results

In this observational study, 3334 women with FBS during labour due to non-reassuring CTG were included for analysis. Of all the women, who had FBS during labour, 48.8% had spontaneous vaginal delivery. 16.7% had a pathological lactate value with LP >4.8 mmol/L, which meant that 83.3% had a normal value which allowed labour to continue., Totally 16.1% were delivered by instrumental vaginal delivery for fetal distress and 18.5% by caesarean section for fetal distress. Metabolic acidosis occurred in 4.8% and the frequency of Apgar score <7 at five minutes after birth was 2.6%.

The study showed that, the mean difference between LP and SSLX was non-significant 0.17 mmol/L ($p = 0.11$). LP and SSLX lactate values showed a strong linear association, $R=0.94$.

The maternal and neonatal characteristics were divided in two cohorts, depending on the time interval between FBS to delivery. For most of the parameters, there were significant differences between the two cohorts, though for MA, low AS and need for neonatal intervention, the differences were not significant.

A majority of FBS 62.7%, were carried out in the second stage of labour.

The correlations between SSLX and umbilical arterial blood pH and lactate were dependent on the time from FBS to delivery with the optimal correlations in women 0-25 minutes from FBS to delivery, where R represent the correlation coefficient: R-pH = -0.30 (95% CI: -0.38 - (-0.22)) and R-lactate = 0.57 (95% CI: 0.51-0.64). (Table 4) Therefore, ROC analysis of FBS lactate levels and neonatal outcome variables were performed only on cases delivered within 25 minutes of FBS (N=799).

Table 4. The association between FBS lactate and umbilical cord artery lactate and pH, for different time intervals from FBS to birth.

Time (min) interval from FBS to birth	Correlation coefficient Lactate (95% CI)	N	Correlation coefficient pH (95% CI)	N
0-60	0.51 (0.46-0.56)	1057	-0.20 (-0.26-(-0.15))	1282
0-30	0.55 (0.48-0.62)	599	-0.28 (-0.35- (-0.21))	714
0-25	0.57 (0.51-0.64)	478	-0.30 (-0.38 - (-0.22))	566
0-15	0.57 (0.46-0.66)	216	-0.26 (-0.38-(-14))	252

The areas under the curves (AUC) and different optimal cut-off levels for lactate for different outcomes, with corresponding sensitivity, specificity, negative and positive likelihood ratios are presented in table 5.

Fetal scalp blood lactate measured by SSLX, showed an excellent ability to predict metabolic acidosis. The AUC for metabolic acidosis was 0.87 (95% CI: 0.77-0.97), sensitivity 82.4% (95% CI: 56.6-96.2), specificity 80.1% (95% CI: 76.0-83.7) with the optimal cut-off ≥5.7mmol/L. The highest predictive ability was found for metabolic acidosis defined as pH <7.05 and BD_{ecf} ≥12 mmol/L with AUC 0.97 (95% CI:0.92-1.0) The optimum cut-off varied between 3.6 mmol/L to 5.8 mmol/L for the various outcome variables. From these outcome variables and the expected invention rates, we recommend the cut-off ≥5.2 mmol/L for intervention.

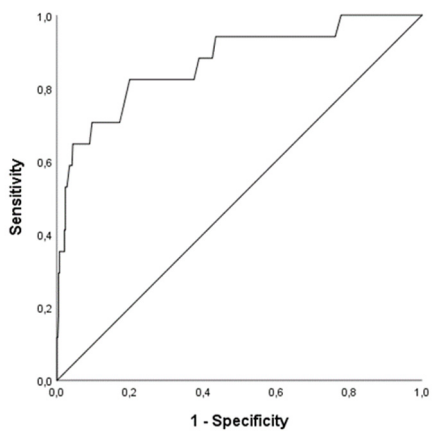


Figure 10. The AUC for Fetal scalp blood lactate measured by StatstripLactate®/StatstripXpress® MA (pH < 7.05 + (BD_{ecf} > 10mmol/L and/or lactate > 10mmol/L was 0.87 (95% CI 0.77-0.97).

Table 5. Area under the ROC curve (AUC) for lactate measured by the StatstripLactate®/StatstripXpress® Lactate system within 25 minutes from scalp blood sampling to delivery (N=799). The optimal cut-off lactate value with highest accuracy (maximal sensitivity and specificity) and the likelihood ratios are presented for different neonatal outcome variables.

Outcome	Cases	Non-cases	AUC (95% CI)	Optimal cut-off lactate value	Sensitivity (%)	Specificity (%)	Positive LR (95%CI)	Negative LR (95%CI)
Metabolic acidosis (MA)	17	437	0.87 (0.77-0.97)	5.7	82.4 (56.6-96.2)	80.1 (76.0-83.7)	4.1 (3.1-5.5)	0.2 (0.1-0.6)
pH < 7.0	7	534	0.83 (0.68-0.97)	4.6	85.7 (42.1-99.6)	60.9 (56.6-65)	2.2 (1.6-3)	0.2 (0-1.4)
pH < 7.10	83	459	0.72 (0.66-0.78)	4	75.9 (65.3-84.6)	53.2 (48.5-57.8)	1.6 (1.4-1.9)	0.5 (0.3-0.7)
pH < 7.15	205	353	0.67 (0.62-0.71)	3.6	73.7 (67.0-79.6)	49.9 (44.5-55.2)	1.5 (1.3-1.7)	0.5 (0.4-0.7)
pH < 7.05 + BD_{ecf} ≥ 12mmol/L	7	528	0.97 (0.92-1)	5.8	100 (59.0-100)	81.0 (77.3-84.1)	5.2 (4.4-6.2)	0.0 (-)
pH < 7.05 + Lactate > 10mmol/L	16	455	0.87 (0.76-0.97)	5.6	81.3 (54.4-96)	78.9 (74.9-82.6)	3.9 (2.9-5.2)	0.2 (0.1-0.7)
pH < 7.10 + Lactate > 8mmol/L	59	412	0.78 (0.72-0.84)	4.5	78.0 (65.3-87.7)	63.1 (58.3-67.8)	2.1 (1.8-2.5)	0.4 (0.2-0.6)
pH < 7.15 + Lactate ≥ 7mmol/L	152	313	0.72 (0.67-0.77)	4.2	69.1 (61.1-76.3)	62.6 (57-68)	1.9 (1.6-2.2)	0.5 (0.4-0.6)
pH < 7.10 + composite outcome	36	505	0.76 (0.67-0.85)	4.8	72.2 (54.8-85.8)	65.7 (61.4-69.9)	2.1 (1.7-2.7)	0.4 (0.3-0.7)
AS < 4 at 1-minutes	37	761	0.76 (0.68-0.84)	4.5	78.4 (61.8-90.2)	60.1 (56.5-63.6)	2 (1.6-2.4)	0.4 (0.2-0.7)
AS < 7 at 5-minutes	22	776	0.74 (0.63-0.86)	5.2	72.7 (49.8-89.3)	71.8 (68.5-74.9)	2.6 (2-3.4)	0.4 (0.2-0.8)

MA: pH < 7.05 and (BDecf > 10 mmol/L and/or lactate > 10mmol/L), ROC: receiver operating characteristic, LR: Likelihood Ratio, BDecf: Base Deficit in extracellular fluid mmol/L, Composite outcome: one or more of the following, admission to neonatal intensive care unit continuous positive airway pressure therapy, bilevel positive airway pressure, manual ventilation or Apgar score (AS) < 7 at 5 minutes.

We found a poor correlation between the number of minutes of pushing and the lactate values measured by SSLX, R=0.24 and R^2=0.06. Women who had a fever during labour (>38 degrees Celsius) had significantly higher lactate values than those without a fever.

From Sahlgrenska University Hospital we obtained cases with simultaneously measured FBS pH and SSLX values. Due to the small number of cases within 25 minutes from FBS to birth (n = 41), ROC curves for the predictive ability of pH respective lactate for MA were extended to include cases within 60 minutes (n = 208). The AUC-MA for scalp blood pH was 0.47 (95% CI: 0.26-0.67) and for scalp SSLX lactate 0.66 (95% CI: 0.49-0.82).

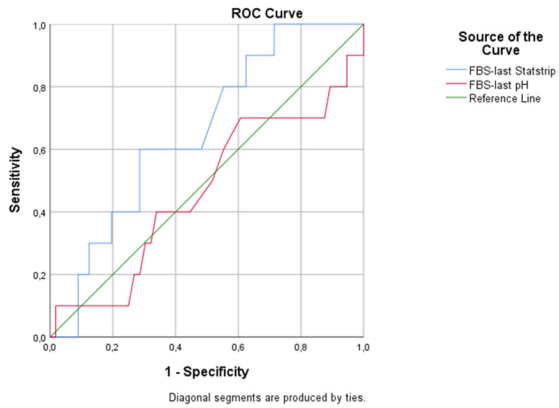


Figure 11. The AUC for simultaneasly measured Fetal scalp blood pH and lactate measured by StatstripLactate®/ StatstripXpress® for the outcome MA (pH < 7.05 + (BDecf > 10mmol/L and/or lactate > 10mmol/L was 0.87 (95% CI 0.77-0.97). From Sahlgrenska University Hospital N=208.

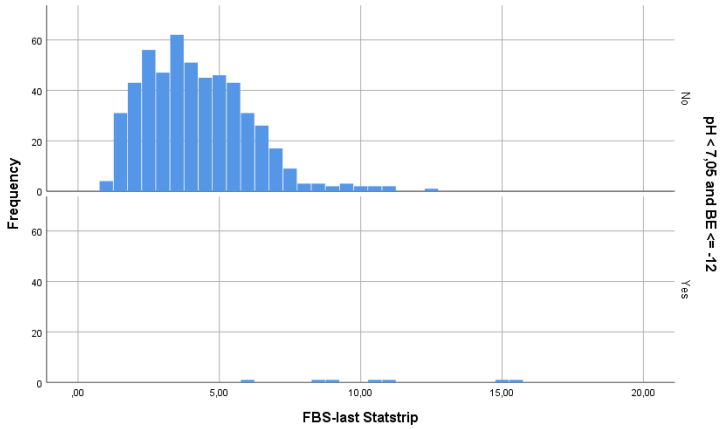


Figure 12. Histogram showing the distribution of SSLX FBS lactate values and the outcome pH <7.05 and BE ≤ -12mmol/L

Comments

From this large observational study, we proposed a new cut-off for acidaemia in scalp blood lactate during labour to ≥5.2 mmol/L for StatStripLactate® and StatstripXpress®. To our knowledge this is the largest study on fetal scalp blood lactate and most importantly we used samples taken close to labour and based the cut-offs for intervention on neonatal outcomes. Previous studies on fetal scalp blood lactate, have compared the lactate value to the established reference value for FBS-pH of <7.20 or Lactate Pro 4.8 mmol/L, and often the time intervals from sapling to delivery were not specified or were very long (8,193,216,217,220). We showed that

the association, between FBS lactate and cord artery lactate improved as the time interval from FBS to birth decreased, and this is why we chose to include, only those FBS within 25 minutes of birth. Furthermore, lactate and pH are comparable, since they measure different things, where lactate is the end product of anaerobic metabolism and pH is a measurement of acidosis. Lactate is a linear measurement of the degree of metabolic acidosis, whereas pH cannot discriminate between respiratory acidosis and metabolic acidosis, the latter strongly associated to poor neonatal outcome (30).

Depending on which cut-off used, the sensitivity and specificity will differ for the different outcomes and the expected intervention rate. A lower cut-off will naturally yield a higher intervention rate, since more samples will be judged as pathological, with a higher sensitivity but with the trade off a lower specificity. In contrast, a higher cut-off, will lead to a lower intervention rate due to fewer pathological values, with a lower sensitivity but improved specificity. The argument for the chosen cut-off of 5.2mmol/L, is the balance between obtaining the best sensitivity and specificity for common recognized prognostic factors of intrapartum asphyxia. By increasing the cut-off to more than 5.2 mmol/L, the sensitivity will decrease for AS <7 at 5 minutes and for the composite outcome. On the other hand, by choosing a lower cut-off than 5.2 mmol/L, potentially the intervention rate will be unnecessarily high. We have previously shown, that the mean value for LP + 2SD equals 5.2 mmol/L in the second stage, although it is not known, whether that cut-off is associated with an increased risk for adverse outcomes (44). It has been previously shown that the risk for disability at 4 years, increases with increasing scalp blood lactate levels (214).

A major issue in this study, was to decide which neonatal outcome measure to be used for the test. The outcome parameter could not be too severe, such as hypoxic ischemic encephalopathy. Instead, the method should identify, the fetuses at risk early enough to allow for timely intervention to avoid adverse perinatal outcomes. There is no ideal outcome variable, specifically indicating intrapartum asphyxia. Analysing cord blood, provides the clinician with the most objective and accurate measurement of the metabolic status of the new-born, although the majority of babies with deteriorated cord blood gases will be vigorous and manifest no obvious short- or long-term neurological sequelae (112,113). There is no international consensus of the definition of fetal metabolic acidosis (MA) in cord blood, which compared to respiratory acidosis, is a serious threat to the cell function (12,34,80,245). The ACOG definition of metabolic acidosis, is pH < 7.0 + BD_{blood} > 12 mmol/L, whereas the FIGO guideline uses a threshold of pH < 7.05 + BD_{ecf} >10mmol/L or lactate > 10mmol/L, because an association with adverse neonatal outcome is recognized at that level (9,93,97,98,109). The lactate value in cord blood, correlates with the lactate concentration in the fetal brain, which in turn is an established marker for the severity of cell damage and thereby, for the degree of

hypoxic ischemic encephalopathy (246–248). Lactate, in contrast to BD, is not a calculated entity, significantly dependent on the compartment used for calculation, but a measured entity (96). This supports the use of lactate in the definition of MA.

It has previously been shown that lactate, increase in second stage by 0.025-0.032 mmol/L per minute of pushing. However in this study, pushing in second stage was a poor association to increased lactate levels, where only 6 % of the changes in lactate where found to be attributed to pushing time (40,249). Interestingly in women who had a fever during labour, the fetus had significantly higher FBS lactate values. The raises the question of the impact of maternal fever on FBS lactate values and are they reliable in that case? It is known that bacterial infection can induce lactate production in the leucocytes and in sepsis hypoperfusion of the tissues lead to increased lactate levels in the blood (21,53).

It is important to emphasize that, the FBS lactate level will reflect the metabolic status of the fetus, at that certain timepoint, depending on the individual fetal reserve and intensity of the uterus contractions, the fetal metabolic status may therefore rapidly deteriorate. Consequently, comparing the FBS-lactate value to the fetal outcome will always be biased by the time-lag from FBS to delivery. This elucidates the importance of using FBS values, sampled close to birth, for setting the intervention cut-off.

There were too few FBS-pH to allow a comparison to SSLX prediction ability, but within 60 minutes the AUC for MA-BD_{ecf} was unsatisfactory, similar to a recent study (195). The cord pH as well as FBS pH correlation, to cord lactate is also poor (23,35) and in a study the agreements for lactate and pH were between 0.3 and 0.45, suggesting that only 30–45% of the variance in lactate values can be attributed to changes in pH (36).

In this study, SSLX had poor correlation to Apgar Scores, at one and five minutes after birth, which is in line with previous studies for both FBS lactate and pH (81,82). Apgar Scores are, therefore, probably too unspecific for early metabolic acidaemia and the prediction ability of SSLX was also lower.

The main limitation was, that despite the routine to take cord samples on all newborns, not all cases had a successful and complete analysis from both vessels and with lactate. The most common problem was that only one sample was obtained, which most likely is venous since it is more easily sampled. In asphyxic neonates the cord blood is often difficult to sample due to poor blood volume in the cord vessel, which could have biased the results (65,177). This occurs more often in the arteries due to low fetal left side ejection fraction. It the vein value is low the artery is lower or equal.

Another limitation was, despite the large number of patients included, that since we intervened on pathological LP lactate values, the numbers of adverse outcomes were low, resulting in relatively wide confidence intervals regarding the sensitivity.

In conclusion, scalp blood lactate measured by SSLX had an excellent ability to predict metabolic acidosis and pH < 7 in umbilical cord blood. From the ROC analysis, based on neonatal outcomes, we suggest the scalp blood lactate cut-off for intervention to be ≥5.2mmol/L when using the StatstripLactate®/StatstripXpress® Lactate system.

Conclusions

This thesis highlights the importance of using device specific cut-offs for measurement of lactate and to be able to safely use fetal scalp stimulation test further studies are required.

The following conclusions are based on the findings from the original studies included in this thesis:

I. We propose the following cut-offs for LP2 scalp lactate: < 6.3 mmol/L = normal, 6.3–7.1 mmol/L = pre-acidaemia, > 7.1 mmol/L = acidaemia. However, LP2 cannot be recommended as a reliable tool to assess intrapartum fetal well-being due to its high coefficient of variation, and since it does not adjust for the haematocrit value. The correlation between LP2 lactate and cord artery lactate was stronger for samples taken closest to delivery.

II. There is an association between the fetal ability to react to a scalp stimulus and the fetal metabolism. However, we found the efficiency of FSS test too poor to rule in or rule out fetal hypoxia. Therefore, we recommend using the FSS test with caution, especially during the second stage where absence of accelerations also after provocation seems to be a normal phenomenon.

III. Assessment of fetal blood lactate concentration is easy and quickly performed with Statstrip Xpress. The lactate meter had an excellent correlation to the reference method. The POC has an acceptable precision in fetal blood.

IV. Scalp blood lactate has an excellent ability to predict metabolic acidosis From the ROC analysis, based on neonatal outcomes, we suggest the scalp blood lactate cut-off for intervention to be ≥5.2mmol/L when using the StatstripLactate®/StatstripXpress® Lactate system.

Future Perspectives

Even though fetal scalp blood sampling with lactate is a familiar method in most clinics in Sweden, a disadvantage has been that the device has not been accredited by the clinical laboratories and hence no requirements for education before using the method. Statstrip Lactate meter is now accredited by the regional laboratory in Skåne and the aim is to educate the staff before implementation of the new device into clinical practice. This will lead to better quality of the analysis and will hopefully reduce pre- and analytical errors.

Although several observational studies have shown a decrease in intervention rates when FBS is used in conjunction with CTG, there is a lack of randomized controlled trials to measure its efficacy. An RCT would increase the level of evidence for the method and hopefully more women around the world could benefit from the use of FBS with fewer interventions.

There is also a lack of long-term follow up of children who underwent fetal scalp blood sampling during labour. To our knowledge there is only one 4 year follow up study (214). Also, more long-term follow up studies are needed to prove the value of the test. We plan a long-term follow up from this cohort.

The use of continuous lactate measurement integrated in fetal scalp electrode is an interesting upcoming research field (58,250). By the use, of a continuous measurement of lactate, the shortcoming of point of care measurement, that it only reflects the metabolic status of the fetus at a certain time point and thus if alarming CTG pattern persists must therefore be repeated. Since severe CTG patterns of severe hypoxia precede the rise in the lactate production, for instance bradycardia, the use of continuous lactate meters cannot replace CTG, but could definitely be a future important tool for early detection of hypoxia and has the potential to reduce acidosis during birth (250).

Unsatisfactory success rate of paired umbilical samples has raised the question, if POC devices can be used to measure lactate in cord blood when there is insufficient blood amount for blood gas machines analysis?

The association of lactate in fetal scalp and cord blood and fever need further attention and studies to elucidate the relation.

Financial Support

The studies in this thesis and the work with the thesis was supported by research grants from Region Skåne, Sweden (REGSKANE-823551, REGSKANE-285871 and REGSKANE-632511)

The FBS Lactate Study (Paper two and four) were partly funded by grants from LÖF LÖF (Landstingens Ömsesidiga Försäkringsbolag, a national Swedish insurance company whose main task is to insure public financed health care providers). By our request we received Statstrip lactate meters and test strips from Nova Biomedical for the studies. Zoegas foundation Helsingborg supported the fourth study. Forskning och utveckling (FOU) Helsingborg Hospital also supported writing the thesis.

The second paper received Open Access funding provided by Lund University.

Nova Biomedical kindly provided the SSLX lactate meters and test sticks for study 3 and 4.

The funders had no influence on the study designs, conduction of studies, data collection, interpretation of results or writing manuscripts/thesis.

Acknowledgements

The work with the studies and writing the thesis was conducted during a five-year period in parallel with my clinical work as an Obstetrician. This would not have been possible to achieve without the help of others. Thank you, to all the women and their neonates that participated in the studies. I would like to express my special gratitude to:

First of all, I would like to thank my tutor and dear friend Associate Professor, Nana Wiberg, from the bottom of my heart. It has been a fantastic journey and honour to work with you! I am so grateful having been given this opportunity, for all the knowledge that you generously shared and for your patience with me in my learning process. You gave me detailed feed-back and constructive criticism of all aspects of the projects. I admire your knowledge and endless energy. Thank you!

My co-tutors Associate Professor Andreas Herbst, who also introduced me to research, and Associate Professor Karl Kristensen for your valuable input and guidance.

My co-writers, Ylva Carlsson, Rim Berggren, Mandy Wang, Theresa McGee, Eva Wiberg-Itzel, Farzaneh Shakuori, Christina Vinter and Helen Edwards for fruitful discussions and valuable input.

Kristina Persson, Associate Professor for sharing your knowledge in laboratory medicine with me and valuable input as co-writer in paper 3.

Per-Erik Isberg for invaluable statistical support and co-writer.

Professor Göran Lingman, former head of the Department in Lund, for giving me the opportunity to work in the amazing field of obstetrics.

Johanna Wagenius, head of Department in Helsingborg, for being supportive in the work with my studies and thesis.

The Staff at the Skåne University Laboratory- for their enthusiasm to help me finding all those missing cord blood samples.

Madeleine Leiding, Christel Johansson and Lou Kruse for helping out with data entry and for your positive attitudes and enthusiasm for the study.

Midwives, assisting nurses and colleagues in Lund and Helsingborg for helping me out in different ways in the projects and for being such nice colleagues. Your encouragement meant a lot to me!

My fantastic and supportive colleagues during my residency “The Red Room” Anna Bonnevier, Lotten Darlin, Malin Sundler, Arnfridur Henrysdottir and Sigurlaug Benedictsdottir, thank you for always being there for me and for all the tears and laughs.

My great friends and neighbours who cheered me up and helped me when I mostly needed it and gave me new perspectives.

Richard Hogan for language review and encouragement.

My parents and extended family, especially my mother Gunilla, for always believing in me, being encouraging, and teaching me to never give up! You were always there for advice and support.

My grandmother Nancy, who always had all the time in the world for me when I was a child.

My dear sisters, Joanna, Clara, Siobhàn and Olivia for being the best sisters and always being encouraging, bringing new perspectives and for great laughs!

Cristian, the love of my life, for being loving, understanding and supportive throughout the whole process and taking care of the kids. Especially when I left you to go to my parent´s house or when I was locked away in the study to write my thesis. At the same time, you managed to run the building project to extend the house. I love you!

My fantastic children Oliver, Oscar and Fabian, for being you and for being understanding when I had to work so much. You give me so much energy and inspiration! I look forward to catching up some time with you! I love you!

References

1. Visser GH, Ayres-de-Campos D. FIGO consensus guidelines on intrapartum fetal monitoring: Adjunctive technologies. Int J Gynaecol Obstet. 2015 Oct;131(1):25–9.
2. East CE, Leader LR, Sheehan P, Henshall NE, Colditz PB, Lau R. Intrapartum fetal scalp lactate sampling for fetal assessment in the presence of a non-reassuring fetal heart rate trace. Cochrane database Syst Rev. 2015;5(3):CD006174.
3. Carbonne B, Pons K, Maisonneuve E. Foetal scalp blood sampling during labour for pH and lactate measurements. Best Pract Res Clin Obstet Gynaecol. 2016;30:62–7.
4. Ayres-de-Campos D. Intrapartum fetal surveillance. Vol. 30, Best practice & research. Clinical obstetrics & gynaecology. Netherlands; 2016. p. 1–2.
5. SFOG/LÖF. CTG utbildning [Internet]. Available from: http://ctgutbildning.se/index.php
6. National Institute for Health and Care Excellence. Fetal blood sampling during labour - NICE Pathways [Internet]. 2018 [cited 2019 Nov 25]. Available from: https://pathways.nice.org.uk/pathways/intrapartum-care/fetal-blood-sampling-during-labour#content=view-node%3Anodes-taking-and-interpreting-sample
7. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum Fetal Heart Rate Monitoring: Nomenclature, Interpretation, and General Management Principles. Obstet Gynecol [Internet]. 2009 Jul [cited 2019 Mar 11];114(1):192–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19546798
8. Kruger K, Hallberg B, Blennow M, Kublickas M, Westgren M. Predictive value of fetal scalp blood lactate concentration and pH as markers of neurologic disability. Am J Obstet Gynecol. 1999;181(5 I):1072–8.
9. Ayres-de-Campos D, Arulkumaran S. FIGO consensus guidelines on intrapartum fetal monitoring: Physiology of fetal oxygenation and the main goals of intrapartum fetal monitoring. Int J Gynecol Obstet [Internet]. 2015 Oct 1 [cited 2020 Oct 25];131(1):5–8. Available from: http://doi.wiley.com/10.1016/j.ijgo.2015.06.018
10. Malcus P, Gudmundsson S, Marsál K, Kwok HH, Vengadasalam D, Ratnam SS. Umbilical artery Doppler velocimetry as a labor admission test. Obstet Gynecol. 1991 Jan;77(1):10–6.
11. Li H, Gudmundsson S, Olofsson P. Uterine artery blood flow velocity waveforms during uterine contractions. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2003 Dec;22(6):578–85.
12. Westgate J, Garibaldi JM, Greene KR. Umbilical cord blood gas analysis at delivery: a time for quality data. BJOG An Int J Obstet Gynaecol. 1994;101(12):1054–63.

13. James LS, Weisbrot IM, Prince CE, Holaday DA, Apgar V. The acid-base status of human infants in relation to birth asphyxia and the onset of respiration. J Pediatr [Internet]. 1958;52(4):379–94. Available from: http://www.sciencedirect.com/science/article/pii/S002234765880058X
14. Blechner JN. Maternal-fetal acid-base physiology. Clin Obstet Gynecol. 1993 Mar;36(1):3–12.
15. DAWES GS, MOTT JC, WIDDICOMBE JG. The foetal circulation in the lamb. J Physiol. 1954 Dec;126(3):563–87.
16. Gurtner GH, Traystman RJ, Burns B. Interactions between placental O2 and CO transfer. J Appl Physiol. 1982 Feb;52(2):479–87.
17. G R. Perintal Acid-Base Balance. Studentlitteratur; 1988.
18. Rao PNS, Shashidhar A, Ashok C. In utero fuel homeostasis: Lessons for a clinician. Indian J Endocrinol Metab. 2013 Jan;17(1):60–8.
19. Robergs RA, Ghiasvand F, Parker D. Biochemistry of exercise-induced metabolic acidosis. Am J Physiol - Regul Integr Comp Physiol. 2004;287(3 56-3):502–16.
20. Berend K, Duits AJ. The role of the clinical laboratory in diagnosing acid-base disorders. Crit Rev Clin Lab Sci. 2019 May;56(3):147–69.
21. Theodorsson E. Laurells Klinisk Kemi. 2018.
22. Low JA. Determining the contribution of asphyxia to brain damage in the neonate. J Obstet Gynaecol Res. 2004 Aug;30(4):276–86.
23. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol [Internet]. 1997;177(6):1391–4. Available from: http://www.sciencedirect.com/science/article/pii/S0002937897700802
24. Piquard F, Schaefer A, Dellenbach P, Haberey P. Lactate movements in the term human placenta in situ. Biol Neonate. 1990;58(2):61–8.
25. Piquard F, Schaefer A, Dellenbach P, Haberey P. Is fetal acidosis in the human fetus maternogenic during labor? A reanalysis. Am J Physiol. 1991 Nov;261(5 Pt 2):R1294-9.
26. Wassink G, Bennet L, Davidson JO, Westgate JA, Gunn AJ. Pre-existing hypoxia is associated with greater EEG suppression and early onset of evolving seizure activity during brief repeated asphyxia in near-term fetal sheep. PLoS One. 2013;8(8):e73895.
27. Turner JM, Mitchell MD, Kumar SS. The physiology of intrapartum fetal compromise at term. Am J Obstet Gynecol. 2020 Jan;222(1):17–26.
28. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. N Engl J Med. 1999 Apr;340(16):1234–8.
29. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obstet Gynecol. 1994 Apr;170(4):1081–7.
30. Low JA, Pickersgill H, Killen H, Derrick EJ. The prediction and prevention of intrapartum fetal asphyxia in term pregnancies. Am J Obstet Gynecol. 2001;184(4):724–30.

31. Lear CA, Wassink G, Westgate JA, Nijhuis JG, Ugwumadu A, Galinsky R, et al. The peripheral chemoreflex: indefatigable guardian of fetal physiological adaptation to labour. J Physiol. 2018 Dec;596(23):5611–23.
32. Giussani DA. The fetal brain sparing response to hypoxia: Physiological mechanisms. Vol. 594, Journal of Physiology. Blackwell Publishing Ltd; 2016. p. 1215–30.
33. Giussani DA, Spencer JA, Moore PJ, Bennet L, Hanson MA. Afferent and efferent components of the cardiovascular reflex responses to acute hypoxia in term fetal sheep. J Physiol. 1993 Feb;461:431–49.
34. Low, James A CP and DEJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obs Gynecol. 1994;170(4):1081–7.
35. Foxdal P, Sjödin B, Rudstam H, Östman C, Östman B, Hedenstierna GC. Lactate concentration differences in plasma, whole blood, capillary finger blood and erythrocytes during submaximal graded exercise in humans. Eur J Appl Physiol Occup Physiol. 1990;61(3–4):218–22.
36. Suidan JS, Wasserman JF, Young BK. Placental contribution to lactate production by the human fetoplacental unit. Am J Perinatol. 1984 Jul;1(4):306–9.
37. Nordström L. Fetal scalp and cord blood lactate. Best Pract Res Clin Obstet Gynaecol. 2004 Jun;18(3):467–76.
38. Nordström L, Arulkumaran S, Chua S, Ratnam S, Ingemarsson I, Ph D, et al. CONTINUOUS MATERNAL GLUCOSE INFUSION DURING LABOR : EFFECTS ON MATERNAL AND FETAL GLUCOSE AND LACTATE LEVELS. 1995;12(5):357–62.
39. Piquard F, Hsiung R, Schaefer A, Haberey P, Dellenbach P. Does fetal acidosis develop with maternal glucose infusion during normal labor? Obstet Gynecol. 1989 Dec;74(6):909–14.
40. Nordström L, Achanna S, Naka K, Arulkumaran S. Fetal and maternal lactate increase during active second stage of labour. Br J Obstet Gynaecol. 2001;108(3):263–8.
41. Krüger K, Kublickas M, Westgren M. Lactate in scalp and cord blood from fetuses with ominous fetal heart rate patterns. Obstet Gynecol. 1998;92(6):918–22.
42. Nordström L, Ingemarsson I, Kublickas M, Persson B, Shimojo N, Westgren M. Scalp blood lactate: a new test strip method for monitoring fetal wellbeing in labour. Br J Obstet Gynaecol. 1995;102:894–9.
43. Nordström L, Ingemarsson I, Persson B, Shimojo N, Westgren M. Lactate in fetal scalp blood and umbilical artery blood measured during normal labor with a test strip method. Acta Obstet Gynecol Scand. 1994 Mar;73(3):250–4.
44. Wiberg N, Källén K. Fetal scalp blood lactate during second stage of labor: determination of reference values and impact of obstetrical interventions. J Matern Neonatal Med. 2017;30(5).
45. Pellerin L, Pellegri G, Bittar PG, Charnay Y, Bouras C, Martin JL, et al. Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. Dev Neurosci. 1998;20(4–5):291–9.

46. Cahill A, Macones G, Smyser C, López J, Inder T, Mathur A. Umbilical Artery Lactate Correlates with Brain Lactate in Term Infants. Am J Perinatol. 2016 Oct;34(06):535–40.
47. Thayyil S, Chandrasekaran M, Taylor A, Bainbridge A, Cady EB, Chong WKK, et al. Cerebral Magnetic Resonance Biomarkers in Neonatal Encephalopathy: A Meta-analysis. Pediatrics [Internet]. 2010 Feb 1;125(2):e382 LP-e395. Available from: http://pediatrics.aappublications.org/content/125/2/e382.abstract
48. Wray S. Insights into the uterus. Exp Physiol. 2007 Jul;92(4):621–31.
49. Wray S, Alruwaili M, Prendergast C. HYPOXIA AND REPRODUCTIVE HEALTH: Hypoxia and labour. Reproduction. 2021 Jan;161(1):F67–80.
50. Quenby S, Pierce SJ, Brigham S, Wray S. Dysfunctional labor and myometrial lactic acidosis. Obstet Gynecol. 2004 Apr;103(4):718–23.
51. Wiberg-Itzel E, Pembe AB, Järnbert-Pettersson H, Norman M, Wihlbäck A-C, Hoesli I, et al. Lactate in Amniotic Fluid: Predictor of Labor Outcome in Oxytocin-Augmented Primiparas' Deliveries. PLoS One. 2016;11(10):e0161546.
52. Murphy M, Butler M, Coughlan B, Brennan D, O'Herlihy C, Robson M. Elevated amniotic fluid lactate predicts labor disorders and cesarean delivery in nulliparous women at term. Am J Obstet Gynecol [Internet]. 2015 Nov 1;213(5):673.e1-673.e8. Available from: https://doi.org/10.1016/j.ajog.2015.06.035
53. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Vol. 43, Intensive Care Medicine. Springer Berlin Heidelberg; 2017. 304–377 p.
54. Toffaletti JG. Blood lactate: biochemistry, laboratory methods, and clinical interpretation. Crit Rev Clin Lab Sci. 1991;28(4):253–68.
55. Kastendieck E. Lactate in fetal tissue during hypoxia ; correlation to lactate , pH and base deficit in the fetal blood. Eur J Obstet Gynecol Reprod Biol. 1988;29:61–71.
56. Engidawork E, Chen Y, Dell'Anna E, Goiny M, Lubec G, Ungerstedt U, et al. Effect of Perinatal Asphyxia on Systemic and Intracerebral pH and Glycolysis Metabolism in the Rat. Exp Neurol [Internet]. 1997;145(2):390–6. Available from: http://www.sciencedirect.com/science/article/pii/S0014488697964827
57. Amer-Wåhlin I, Nord A, Bottalico B, Hansson SR, Ley D, Maršál K, et al. Fetal cerebral energy metabolism and electrocardiogram during experimental umbilical cord occlusion and resuscitation. J Matern Neonatal Med. 2010;23(2):158–66.
58. Tigchelaar F, Groen H, Westgren M, Huinink KD, Cremers T, van den Berg PP. A new microdialysis probe for continuous lactate measurement during fetal monitoring: Proof of concept in an animal model. Acta Obstet Gynecol Scand. 2020;99(10):1411–6.
59. Frasch MG, Mansano RZ, Gagnon R, Richardson BS, Ross MG. Measures of acidosis with repetitive umbilical cord occlusions leading to fetal asphyxia in the near-term ovine fetus. Am J Obstet Gynecol [Internet]. 2009;200(2):200.e1-200.e7. Available from: http://dx.doi.org/10.1016/j.ajog.2008.10.022

60. De Haan HH, Gunn AJ, Williams CE, Gluckman PD. Brief repeated umbilical cord occlusions cause sustained cytotoxic cerebral edema and focal infarcts in near-term fetal lambs. Pediatr Res. 1997 Jan;41(1):96–104.
61. Yoshioka T, Roux JF. Correlation of fetal scalp blood pH, glucose, lactate and pyruvate concentrations with cord blood determinations at time of delivery and cesarean section. J Reprod Med. 1970 Nov;5(5):209–14.
62. Simmons SC, Lieberman B. The combined use of cardiotocography and fetal blood sampling in monitoring the fetus in labour. J Obstet Gynaecol Br Commonw. 1972 Sep;79(9):816–20.
63. Nordstrom L, Institutet K, Shimojo N, Westgren M, Institutet K. Fetal scalp and umbilical artery blood lactate measured with a new test strip method. 1992;99(April):307–9.
64. Low JA. Intrapartum fetal asphyxia: Definition, diagnosis, and classification. Am J Obstet Gynecol [Internet]. 1997;176(5):957–9. Available from: http://www.sciencedirect.com/science/article/pii/S0002937897703855
65. The Swedish Pregnancy register, annual report 2019 [Internet]. [cited 2020 Oct 20]. Available from: www.graviditetsregistret.se
66. APGAR V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg. 1953;32(4):260–7.
67. Skolnick AA. Apgar quartet plays perinatologist's instruments. Vol. 276, JAMA. United States; 1996. p. 1939–40.
68. Ruth VJ, Raivio K. Perinatal brain damage : predictive value of metabolic acidosis and the Apgar score. 1988;297(JULY).
69. Stuart A, Otterblad Olausson P, Källen K. Apgar scores at 5 minutes after birth in relation to school performance at 16 years of age. Obstet Gynecol. 2011 Aug;118(2 Pt 1):201–8.
70. Hogan L, Ingemarsson I, Thorngren-Jerneck K, Herbst A. How often is a low 5-min Apgar score in term newborns due to asphyxia? Eur J Obstet Gynecol Reprod Biol. 2007;130(2).
71. Thorngren-Jerneck K, Herbst A. Low 5-minute Apgar score: a population-based register study of 1 million term births. Obstet Gynecol. 2001 Jul;98(1):65–70.
72. Tweed EJ, Mackay DF, Nelson SM, Cooper S-A, Pell JP. Five-minute Apgar score and educational outcomes: retrospective cohort study of 751,369 children. Arch Dis Child Fetal Neonatal Ed. 2016 Mar;101(2):F121-6.
73. Razaz N, Cnattingius S, Persson M, Tedroff K, Lisonkova S, Joseph KS. One-minute and five-minute Apgar scores and child developmental health at 5 years of age: A population-based cohort study in British Columbia, Canada. BMJ Open. 2019;9(5):1–9.
74. Freeman JM, Nelson KB. Intrapartum asphyxia and cerebral palsy. Pediatrics. 1988 Aug;82(2):240–9.
75. Gilstrap LC 3rd, Hauth JC, Hankins GD, Beck AW. Second-stage fetal heart rate abnormalities and type of neonatal acidemia. Obstet Gynecol. 1987 Aug;70(2):191–5.

76. O'Donnell CPF, Kamlin COF, Davis PG, Carlin JB, Morley CJ. Interobserver variability of the 5-minute Apgar score. J Pediatr. 2006 Oct;149(4):486–9.
77. Bovbjerg ML, Dissanayake M V., Cheyney M, Brown J, Snowden JM. Utility of the 5-Minute Apgar Score as a Research Endpoint. Am J Epidemiol. 2019;188(9):1695–704.
78. Rüdiger M, Rozycki HJ. It's Time to Reevaluate the Apgar Score. JAMA Pediatr. 2020 Apr;174(4):321–2.
79. Sykes GS, Molloy PM, Johnson P, Stirrat GM, Turnbull AC. Fetal distress and the condition of newborn infants. Br Med J (Clin Res Ed). 1983 Oct;287(6397):943–5.
80. Goodwin TM, Belai I, Hernandez P, Durand M, Paul RH. Asphyxial complications in the term newborn with severe umbilical acidemia. Am J Obstet Gynecol. 1992;167(6):1506–12.
81. Ramanah R, Martin A, Clement MC, Maillet R, Riethmuller D. Fetal scalp lactate microsampling for non-reassuring fetal status during labor: A prospective observational study. Fetal Diagn Ther. 2010;27(1):14–9.
82. Borruto F, Comparetto C, Treisser A. Prevention of cerebral palsy during labour : role of foetal lactate. 2007;
83. Iorizzo L. Proposed cut-off for fetal scalp blood lactate in intrapartum fetal surveillance based on neonatal outcomes: A large international prospective observational study. BJOG (Accepted manuscript). 2021;
84. Olofsson P. Determination of base excess in umbilical cord blood at birth: accessory or excess? Vol. 213, American journal of obstetrics and gynecology. United States; 2015. p. 259–61.
85. NICE. Overview | Intrapartum care for healthy women and babies | Guidance | NICE [Internet]. [cited 2020 May 23]. Available from: https://www.nice.org.uk/guidance/cg190
86. Thorp JA, Sampson JE, Parisi VM, Creasy RK. Routine umbilical cord blood gas determinations? Am J Obstet Gynecol. 1989 Sep;161(3):600–5.
87. White CRH, Mok T, Doherty DA, Henderson JJ, Newnham JP, Pennell CE. The effect of time, temperature and storage device on umbilical cord blood gas and lactate measurement: A randomized controlled trial. J Matern Neonatal Med. 2012;25(6):587–94.
88. Mokarami P, Wiberg N, Olofsson P. Hidden acidosis: An explanation of acid-base and lactate changes occurring in umbilical cord blood after delayed sampling. BJOG An Int J Obstet Gynaecol. 2013;120(8):996–1002.
89. Wiberg N, Källén K, Olofsson P. Delayed umbilical cord clamping at birth has effects on arterial and venous blood gases and lactate concentrations. BJOG. 2008 May;115(6):697–703.
90. Armstrong L, Stenson B. The effect of delayed sampling on umbilical cord arterial and venous lactate , and blood gases in clamped and unclamped vessels. 2006;(May).
91. Mokarami P, Wiberg N, Olofsson P. Hidden acidosis: An explanation of acid-base and lactate changes occurring in umbilical cord blood after delayed sampling. BJOG An Int J Obstet Gynaecol. 2013;120(8).

92. Goldaber KG, Gilstrap LC 3rd, Leveno KJ, Dax JS, McIntire DD. Pathologic fetal acidemia. Obstet Gynecol. 1991 Dec;78(6):1103–7.
93. ACOG Committee Opinion No. 348, November 2006: Umbilical cord blood gas and acid-base analysis. Obstet Gynecol. 2006 Nov;108(5):1319–22.
94. Herbst A, Wölner-Hanssen P, Ingemarsson I. Maternal fever in term labour in relation to fetal tachycardia, cord artery acidaemia and neonatal infection. Br J Obstet Gynaecol. 1997 Mar;104(3):363–6.
95. Wiberg N, Ka K. Physiological development of a mixed metabolic and respiratory umbilical cord blood acidemia with advancing gestational age. 2006;
96. Wiberg N, Källén K, Olofsson P. Base deficit estimation in umbilical cord blood is influenced by gestational age, choice of fetal fluid compartment, and algorithm for calculation. Am J Obstet Gynecol. 2006;195(6):1651–6.
97. Wiberg N, Källén K, Herbst A, Åberg A, Olofsson P. Lactate concentration in umbilical cord blood is gestational age-dependent: A population-based study of 17 867 newborns. BJOG An Int J Obstet Gynaecol. 2008;115(6):704–9.
98. Wiberg N, Kllén K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. Acta Obstet Gynecol Scand. 2010;89(10):1263–9.
99. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: Analysis of 51 519 consecutive validated samples. BJOG An Int J Obstet Gynaecol. 2012;119(7):824–31.
100. Knutzen L, Svirko E, Impey L. The significance of base deficit in acidemic term neonates. Am J Obstet Gynecol. 2015;213(3):373.e1-373.e7.
101. Lowe J. Intrapartum fetal asphyxia : Definition , diagnosis , and classification. Am J Obstet Gynecol. 1997;176:957–9.
102. Siggaard-Andersen O. The van Slyke equation. Scand J Clin Lab Invest Suppl. 1977;146:15–20.
103. Mokarami P, Wiberg N, Olofsson P. An overlooked aspect on metabolic acidosis at birth: blood gas analyzers calculate base deficit differently. Acta Obstet Gynecol Scand. 2012 May;91(5):574–9.
104. Amer-Wåhlin I, Hellsten C, Norén H, Hagberg H, Herbst A, Kjellmer I, et al. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: A Swedish randomised controlled trial. Lancet. 2001 Aug 18;358(9281):534–8.
105. Wiberg-Itzel E, Lipponer C, Norman M, Herbst A, Prebensen D, Hansson A, et al. Determination of pH or lactate in fetal scalp blood in management of intrapartum fetal distress: randomised controlled multicentre trial. BMJ. 2008 Jun;336(7656):1284–7.
106. Gjerris AC, Stær-Jensen J, Jørgensen JS, Bergholt T, Nickelsen C. Umbilical cord blood lactate: A valuable tool in the assessment of fetal metabolic acidosis. Eur J Obstet Gynecol Reprod Biol. 2008;139(1):16–20.
107. Tuuli MG, Stout MJ, Shanks A, Odibo AO, Macones GA, Cahill AG. Umbilical cord arterial lactate compared with pH for predicting neonatal morbidity at term. Obstet Gynecol. 2014 Oct;124(4):756–61.

108. Westgren M, Divon M, Horal M, Ingemarsson I, Kublickas M, Shimojo N, et al. Routine measurements of umbilical artery lactate levels in the prediction of perinatal outcome. Am J Obstet Gynecol. 1995;173(5):1416–22.
109. Wayenberg J-L. Threshold of metabolic acidosis associated with neonatal encephalopathy in the term newborn. J Matern neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2005 Dec;18(6):381–5.
110. Engidawork E, Chen Y, Dell'anna E, Goiny M, Lubec G, Ungerstedt U, et al. Effect of perinatal asphyxia on systemic and intracerebral pH and glycolysis metabolism in the rat. Exp Neurol. 1997;145(2 I):390–6.
111. Jonsson M, Nordén-Lindeberg S, Ostlund I, Hanson U. Metabolic acidosis at birth and suboptimal care--illustration of the gap between knowledge and clinical practice. BJOG. 2009 Oct;116(11):1453–60.
112. Hafström M, Ehnberg S, Blad S, Norén H, Renman C, Rosén KG, et al. Developmental outcome at 6.5 years after acidosis in term newborns: A population-based study. Pediatrics. 2012;129(6).
113. Victory R, Penava D, Da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. Am J Obstet Gynecol. 2004 Dec;191(6):2021–8.
114. Hanson U, Jonsson M, Norde S. Metabolic acidosis at birth and suboptimal care – illustration of the gap between knowledge and clinical practice. 2009;1–8.
115. Sadler LC, Farquhar CM, Masson VL, Battin MR. Contributory factors and potentially avoidable neonatal encephalopathy associated with perinatal asphyxia. Am J Obstet Gynecol [Internet]. 2016;214(6):747.e1-747.e8. Available from: http://dx.doi.org/10.1016/j.ajog.2015.12.037
116. Mrelashvili A, Russ JB, Ferriero DM, Wusthoff CJ. The Sarnat score for neonatal encephalopathy: looking back and moving forward. Pediatr Res [Internet]. 2020;88(6):824–5. Available from: http://dx.doi.org/10.1038/s41390-020-01143-5
117. Sarnat HB, Sarnat MS. Neonatal Encephalopathy Following Fetal Distress: A Clinical and Electroencephalographic Study. Arch Neurol [Internet]. 1976 Oct 1;33(10):696–705. Available from: https://doi.org/10.1001/archneur.1976.00500100030012
118. Rei M, Bernardes J. Best Practice & Research Clinical Obstetrics and Gynaecology Neurological damage arising from intrapartum hypoxia / acidosis. Best Pract Res Clin Obstet Gynaecol [Internet]. 2016;30:79–86. Available from: http://dx.doi.org/10.1016/j.bpobgyn.2015.04.011
119. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010 Jun;86(6):329–38.
120. van Handel M, Swaab H, de Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. Eur J Pediatr. 2007 Jul;166(7):645–54.

121. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;2013(1).
122. Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991–94. Acta Paediatr [Internet]. 2001 Mar 1;90(3):271–7. Available from: https://doi.org/10.1111/j.1651-2227.2001.tb00303.x
123. Thornton C, Hagberg H. Role of mitochondria in apoptotic and necroptotic cell death in the developing brain. Clin Chim Acta. 2015 Dec;451(Pt A):35–8.
124. Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. Best Pract Res Clin Obstet Gynaecol [Internet]. 2004;18(3):425–36. Available from: http://www.sciencedirect.com/science/article/pii/S1521693404000379
125. Kennedy RG. Electronic fetal heart rate monitoring: retrospective reflections on a twentieth-century technology. J R Soc Med. 1998;91:244–50.
126. Hon EH, Petrie RH. Clinical value of fetal heart rate monitoring. Clin Obstet Gynecol [Internet]. 1975 Dec [cited 2019 Nov 5];18(4):1–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/765031
127. Hon EH, Quilligan EJ. The classification of fetal heart rate. II. A revised working classification. Conn Med. 1967 Nov;31(11):779–84.
128. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961-1988. Obstet Gynecol. 1992 Jan;79(1):35–9.
129. Alfirevic Z, Devane D, Gyte GML, Cuthbert A. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev. 2017;2017(2).
130. Ingemarsson I. Svensk kvinnosjukvård under ett sekel 1904-2004 Chapter 12:Förlossningsövervakning. 2004.
131. Nelson KB, Dambrosia JM, Ting TY, Grether JK. Uncertain Value of Electronic Fetal Monitoring in Predicting Cerebral Palsy. N Engl J Med. 1996 Mar 7;334(10):613–9.
132. Clark SL, Hamilton EF, Garite TJ, Timmins A, Warrick PA, Smith S. The limits of electronic fetal heart rate monitoring in the prevention of neonatal metabolic acidemia. Am J Obstet Gynecol. 2017 Feb;216(2):163.e1-163.e6.
133. Ayres-de-Campos D, Bernardes J. Twenty-five years after the FIGO guidelines for the use of fetal monitoring: Time for a simplified approach? Int J Gynecol Obstet [Internet]. 2010;110(1):1–6. Available from: https://www.sciencedirect.com/science/article/pii/S0020729210001505
134. Tommaso M Di, Pinzauti S, Bandinelli S, Poli C, Ragusa A. Continuous electronic fetal heart monitoring versus intermittent auscultation during labor: Would the literature outcomes have the same results if they were interpreted following the NICHHD guidelines? Adv Clin Exp Med Off organ Wroclaw Med Univ. 2019 Sep;28(9):1193–8.
135. Chen H-Y, Chauhan SP, Ananth C V, Vintzileos AM, Abuhamad AZ. Electronic fetal heart rate monitoring and its relationship to neonatal and infant mortality in the United States. Am J Obstet Gynecol. 2011 Jun;204(6):491.e1-10.

136. Parer JT. Fetal heart-rate monitoring. Vol. 2, Lancet (London, England). England; 1979. p. 632–3.
137. Dore SR, Ehman W. No. 396-Fetal Health Surveillance: Intrapartum Consensus Guideline. 2020 [cited 2020 May 23]; Available from: https://doi.org/10.1016/j.jogc.2019.05.007
138. Vintzileos AM, Antsaklis A, Varvarigos I, Papas C, Sofatzis I, Montgomery JT. A randomized trial of intrapartum electronic fetal heart rate monitoring versus intermittent auscultation. Obstet Gynecol. 1993 Jun;81(6):899–907.
139. Rhöse S, Heinis AMF, Vandenbussche F, Van Drongelen J, Van Dillen J. Inter- and intra-observer agreement of non-reassuring cardiotocography analysis and subsequent clinical management. Acta Obstet Gynecol Scand. 2014;93(6).
140. Caughey AB, Cahill AG, Guise J-M, Rouse DJ. Safe prevention of the primary cesarean delivery. Am J Obstet Gynecol. 2014 Mar;210(3):179–93.
141. Blackwell SC, Grobman WA, Antoniewicz L, Hutchinson M, Gyamfi Bannerman C. Interobserver and intraobserver reliability of the NICHD 3-Tier Fetal Heart Rate Interpretation System. Am J Obstet Gynecol. 2011 Oct;205(4):378.e1-5.
142. Vintzileos AM, Nochimson DJ, Antsaklis A, Varvarigos I, Guzman ER, Knuppel RA. Comparison of intrapartum electronic fetal heart rate monitoring versus intermittent auscultation in detecting fetal acidemia at birth. Am J Obstet Gynecol. 1995 Oct;173(4):1021–4.
143. Ingemarsson E, Ingemarsson I, Solum T, Westgren M. A one-year study of routine fetal heart rate monitoring during the first stage of labor. Obstet Gynecol Surv. 1981;36(8):419–20.
144. Ghi T, Morganelli G, Bellussi F, Rucci P, Giorgetta F, Rizzo N, et al. Cardiotocographic findings in the second stage of labor among fetuses delivered with acidemia: a comparison of two classification systems. Eur J Obstet Gynecol Reprod Biol [Internet]. 2016;203:297–302. Available from: http://dx.doi.org/10.1016/j.ejogrb.2016.06.028
145. Tranquilli AL. Fetal heart rate in the second stage of labor: Recording, reading, interpreting and acting. J Matern Neonatal Med. 2012;25(12):2551–4.
146. Ingemarsson, Ingemar Ingemarsson E. Fosterövervakning med CTG. Studentlittteratur; 2012.
147. Herbst A, Ingemarsson I. Intermittent versus continuous electronic monitoring in labour: a randomised study. Br J Obstet Gynaecol. 1994 Aug;101(8):663–8.
148. Ayres-De-Campos D, Spong CY, Chandraharan E. FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography. Int J Gynecol Obstet. 2015;131(1):13–24.
149. Ekengård F, Cardell M, Herbst A. Impaired validity of the new FIGO and Swedish CTG classification templates to identify fetal acidosis in the first stage of labor Impaired validity of the new FIGO and Swedish CTG classification templates to identify fetal acidosis in the first stage of l. J Matern Neonatal Med [Internet]. 2021;0(0):1–8. Available from: https://doi.org/10.1080/14767058.2020.1869931

150. Ekengård F, Cardell M, Herbst A. Low sensitivity of the new FIGO classification system for electronic fetal monitoring to identify fetal acidosis in the second stage of labor. Eur J Obstet Gynecol Reprod Biol X. 2021;9:0–4.
151. Huch A, Huch R, Rooth G. Guidelines for blood sampling and measurement of pH and blood gas values in obstetrics. Based upon a workshop held in Zurich, Switzerland, March 19, 1993 by an Ad Hoc Committee. Eur J Obstet Gynecol Reprod Biol. 1994 May;54(3):165–75.
152. Ryding EL, Wijma B, Wijma K. Posttraumatic stress reactions after emergency cesarean section. Acta Obstet Gynecol Scand. 1997 Oct;76(9):856–61.
153. Ayers S, Bond R, Bertullies S, Wijma K. The aetiology of post-traumatic stress following childbirth: A meta-analysis and theoretical framework. Psychol Med. 2016;46(6):1121–34.
154. Ramm O, Woo VG, Hung YY, Chen HC, Ritterman Weintraub ML. Risk factors for the development of obstetric anal sphincter injuries in modern obstetric practice. Obstet Gynecol. 2018;131(2):290–6.
155. Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015. November 2018. Available www.europeristat.com.
156. Sandall J, Tribe RM, Avery L, Mola G, Visser GH, Homer CS, et al. Short-term and long-term effects of caesarean section on the health of women and children. Lancet (London, England). 2018 Oct;392(10155):1349–57.
157. Betrán AP, Ye J, Moller A, Zhang J, Gülmezoglu AM. The Increasing Trend in Caesarean Section Rates : Global , Regional and National Estimates : 1990-2014. 2016;1–12.
158. Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L, et al. Global epidemiology of use of and disparities in caesarean sections. Lancet (London, England). 2018 Oct;392(10155):1341–8.
159. Wang M, Chua SC, Bouhadir L, Treadwell EL, Gibbs E, McGee TM. Point-of-care measurement of fetal blood lactate - Time to trust a new device. Aust New Zeal J Obstet Gynaecol [Internet]. 2018 Feb 1 [cited 2018 Feb 12];58(1):72–8. Available from: http://doi.wiley.com/10.1111/ajo.12671
160. Holzmann M, Nordström L. Follow-up national survey (Sweden) of routines for intrapartum fetal surveillance. Acta Obstet Gynecol Scand. 2010 May;89(5):712–4.
161. van den Berg P, Schmidt S, Gesche J, Saling E. Fetal distress and the condition of the newborn using cardiotocography and fetal blood analysis during labour. Br J Obstet Gynaecol. 1987 Jan;94(1):72–5.
162. Stein W, Hellmeyer L, Misselwitz B, Schmidt S. Impact of fetal blood sampling on vaginal delivery and neonatal outcome in deliveries complicated by pathologic fetal heart rate: a population based cohort study. J Perinat Med [Internet]. 2006 Jan 1 [cited 2020 Mar 2];34(6):479–83. Available from: https://www.degruyter.com/view/j/jpme.2006.34.issue-6/jpm.2006.093/jpm.2006.093.xml

163. Jørgensen JS, Weber T. Fetal scalp blood sampling in labor – a review. Acta Obstet Gynecol Scand [Internet]. 2014;93(6):548–55. Available from: http:https://doi.org/10.1111/aogs.12421
164. Hilal Z, Mrkvicka J, Rezniczek GA, Dogan A, Tempfer CB. Accuracy of intrapartum fetal blood gas analysis by scalp sampling. Medicine (Baltimore). 2017;96(49):e8839.
165. Alfirevic Z, Devane D, Gyte GML. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Vol. 2013, Cochrane Database of Systematic Reviews. 2013. p. CD006066.
166. Den Berg P Van, Schmidt S, Gesche J, Saling E. Fetal distress and the condition of the newborn using cardiotocography and fetal blood analysis during labour. Obstet Gynecol Surv. 1987;42(8):499–500.
167. Haverkamp AD et al. A controlled trial of the differential effects of intrapartum fetal monitoring. Am J Obs Gynecol. 1979;134(4):399–408.
168. Zalar RWJ, Quilligan EJ. The influence of scalp sampling on the cesarean section rate for fetal distress. Am J Obstet Gynecol. 1979 Sep;135(2):239–46.
169. Young DC, Gray JH, Luther ER, Peddle LJ. Fetal scalp blood pH sampling: its value in an active obstetric unit. Am J Obstet Gynecol. 1980 Feb;136(3):276–81.
170. Reif P, Haas J, Schöll W, Lang U. [Foetal scalp blood sampling: impact on the incidence of Caesarean section and assisted vaginal deliveries for non-reassuring foetal heart rate and its use according to gestational age]. Z Geburtshilfe Neonatol. 2011 Oct;215(5):194–8.
171. Mozurkewich E, Wolf FM. Near-infrared spectroscopy for fetal assessment during labour. Cochrane database Syst Rev. 2000;(3):CD002254.
172. East CE, Begg L, Colditz PB, Lau R. Fetal pulse oximetry for fetal assessment in labour. Cochrane database Syst Rev. 2014;10.
173. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane database Syst Rev. 2015 Dec;2015(12):CD000116.
174. Saling E. A new method for examination of the fetus during labor:introduction,technic and basics. Arch Gynak. 1962;197:108–22.
175. Bowe ET, Beard RW, Finster M, Poppers PJ, Adamsons K, James LS. Reliability of fetal blood sampling. Maternal-fetal relationships. Am J Obstet Gynecol. 1970;107(2):279–87.
176. Ingemarsson I, Ph D, Arulkumaran S. Copyright protected material. Am J Obs Gynecol. 1986;155:66–9.
177. Bretscher J SE. pH values in human fetus during labor. Am J Obs. 1967;97(7):906–11.
178. Sontag L. W. and Wallace R.F. Changes in the rate of the human fetal heart in response to vibratory stimuli. Am J Dis Childhood. 1936;51:583–9.
179. Skupski DW, Rosenberg CR, Eglinton GS. Intrapartum fetal stimulation tests: A meta-analysis [Internet]. Vol. 99, Obstetrics and Gynecology. 2002 [cited 2019 Jun 7]. p. 129–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11777523
180. Goodwin TM, Milner-Masterson L, Paul RH. Elimination of fetal scalp blood sampling on a large clinical service. Obstet Gynecol. 1994 Jun;83(6):971–4.

181. Perkins RP. Requiem for a heavyweight: the demise of scalp blood pH sampling. J Matern Fetal Med. 1997;6(5):298–300.
182. Clark SL, Gimovsky ML, Miller FC. The scalp stimulation test: a clinical alternative to fetal scalp blood sampling. Am J Obstet Gynecol [Internet]. 1984 Feb 1 [cited 2020 Jan 16];148(3):274–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6695974
183. Hughes O, Murphy DJ. Comparing second-line tests to assess fetal wellbeing in Labor: a feasibility study and pilot randomized controlled trial. J Matern Neonatal Med [Internet]. 2020 Jan 12 [cited 2020 Jan 22];1–9. Available from: https://www.tandfonline.com/doi/full/10.1080/14767058.2020.1712704
184. SMITH NC, SOUTTER WP, SHARP F, McCOLL J, FORD I. Fetal scalp blood lactate as an indicator of intrapartum hypoxia. BJOG An Int J Obstet Gynaecol. 1983;90(9):821–31.
185. Shimojo N, Naka K, Nakajima C, Yoshikawa C, Okuda K, Okada K. Test-strip method for measuring lactate in whole blood. Clin Chem [Internet]. 1989 Sep 1;35(9):1992–4. Available from: https://doi.org/10.1093/clinchem/35.9.1992
186. Westgren M, Kruger K, Ek S, Grunevald C, Kublickas M, Naka K, et al. Lactate compared with pH analysis at fetal scalp blood sampling: a prospective randomised study. Br J Obstet Gynaecol. 1998 Jan;105(1):29–33.
187. Westgren M, Kublickas M, Kruger K. Role of lactate measurements during labor. Obstet Gynecol Surv. 1999 Jan;54(1):43–8.
188. Stål I, Wennerholm UB, Nordstrom L, Ladfors L, Wiberg-Itzel E. Fetal scalp blood sampling during second stage of labor–analyzing lactate or pH? A secondary analysis of a randomized controlled trial. J Matern Neonatal Med. 2020;
189. Pascual Mancho J, Marti Gamboa S, Redrado Gimenez O, Crespo Esteras R, Rodriguez Solanilla B, Castan Mateo S. Diagnostic accuracy of fetal scalp lactate for intrapartum acidosis compared with scalp pH. J Perinat Med. 2017 Apr;45(3):315–20.
190. Rørbye C, Perslev A, Nickelsen C. Lactate versus pH levels in fetal scalp blood during labor-using the Lactate Scout System. J Matern Neonatal Med. 2016;29(8).
191. O'Brien YM, Murphy DJ. The reliability of foetal blood sampling as a test of foetal acidosis in labour. Eur J Obstet Gynecol Reprod Biol. 2013;167(2):142–5.
192. Iorizzo L, Klausen TW, Wiberg-Itzel E, Ovin F, Wiberg N. Use of Lactate ProTM2 for measurement of fetal scalp blood lactate during labor - proposing new cutoffs for normality, preacidemia and acidemia: a cross-sectional study. J Matern Fetal Neonatal Med [Internet]. 2019 Jun 3 [cited 2019 Mar 11];32(11):1762–8. Available from: https://www.tandfonline.com/doi/full/10.1080/14767058.2017.1416603
193. Ridenour R V., Gada RP, Brost BC, Karon BS. Comparison and validation of point of care lactate meters as a replacement for fetal pH measurement. Clin Biochem. 2008;
194. Mahendru AA, Lees CC. Is intrapartum fetal blood sampling a gold standard diagnostic tool for fetal distress? Eur J Obstet Gynecol Reprod Biol [Internet]. 2011 Jun [cited 2019 Mar 11];156(2):137–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21300427

195. Al Wattar BH, Lakhiani A, Sacco A, Siddharth A, Bain A, Calvia A, et al. Evaluating the value of intrapartum fetal scalp blood sampling to predict adverse neonatal outcomes: A UK multicentre observational study. Eur J Obstet Gynecol Reprod Biol. 2019;240:62–7.
196. Tuffnell D, Haw WL, Wilkinson K. How long does a fetal scalp blood sample take? BJOG [Internet]. 2006 Mar [cited 2019 Mar 11];113(3):332–4. Available from: http://doi.wiley.com/10.1111/j.1471-0528.2006.00859.x
197. Holzmann M, Cnattingius S, Nordstrom L. Outcome of severe intrapartum acidemia diagnosed with fetal scalp blood sampling. J Perinat Med. 2011;39(5):545–8.
198. Holzmann M, Wretler S, Cnattingius S, Nordström L. Cardiotocography patterns and risk of intrapartum fetal acidemia. J Perinat Med. 2015;43(4):473–9.
199. Holzmann M, Wretler S, Nordström L. Absence of accelerations during labor is of little value in interpreting fetal heart rate patterns. Acta Obstet Gynecol Scand. 2016;95(10):1097–103.
200. Holzmann M, Cnattingius S, Nordström L. Lactate production as a response to intrapartum hypoxia in the growth-restricted fetus. BJOG An Int J Obstet Gynaecol. 2012;
201. Åkerman F, Mokarami P, Källén K, Olofsson P. The small-for-gestational-age fetus has an intact ability to develop lacticemia when exposed to hypoxia: a retrospective comparative register study. J Matern neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2018 May;31(10):1290–7.
202. Zaigham M, Källén K, Olofsson P. Assessment of lactate production as a response to sustained intrapartum hypoxia in large-for-gestational-age newborns. Acta Obstet Gynecol Scand. 2018;
203. Chandraharan E. Should national guidelines continue to recommend fetal scalp blood sampling during labor? Vol. 29, Journal of Maternal-Fetal and Neonatal Medicine. 2016. p. 3682–5.
204. Mahmood UT, Gorman CO, Marchocki Z, Brien YO, Murphy DJ, Tahir U, et al. Fetal scalp stimulation (FSS) versus fetal blood sampling (FBS) for women with abnormal fetal heart rate monitoring in labor : a prospective cohort study cohort study. J Matern Neonatal Med [Internet]. 2018;0(0):1742–7. Available from: https://doi.org/10.1080/14767058.2017.1326900
205. Liljeström L, Wikström AK, Skalkidou A, Åkerud H, Jonsson M. Experience of fetal scalp blood sampling during labor. Acta Obstet Gynecol Scand. 2014;93(1):113–7.
206. Wretler S, Nordström L, Graner S, Holzmann M. Risk factors for intrapartum acidemia - a cohort study. J Matern neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2018 Dec;31(24):3232–7.
207. Birgisdottir BT, Holzmann M, Varli IH, Graner S, Saltvedt S, Nordström L. Reference values for Lactate Pro 2™ in fetal blood sampling during labor: A cross-sectional study. Vol. 45, Journal of Perinatal Medicine. 2017. p. 321–5.
208. Lowe B, Beckmann M. Involving the consultant before fetal blood sampling. Aust New Zeal J Obstet Gynaecol. 2016;56(4):387–90.
209. Bowler T, Beckmann M. Comparing fetal scalp lactate and umbilical cord arterial blood gas values. Aust New Zeal J Obstet Gynaecol. 2014;54(1):79–83.

210. Wiberg-Itzel E, Pettersson H, Cnattingius S, Nordström L. Association between lactate concentration in amniotic fluid and dysfunctional labor. Acta Obstet Gynecol Scand. 2008;87(9):924–8.
211. Toffaletti J, Hammes ME, Gray R, Lineberry B, Abrams B. Lactate measured in diluted and undiluted whole blood and plasma: Comparison of methods and effect of hematocrit. Clin Chem. 1992;38(12):2430–4.
212. Stewart L, Mackay L, Wijeratne NG, Wallace E, Carr B, East C, et al. Point of Care Measurement of Cord Blood and Fetal Scalp Lactate : Problems of Haematocrit Interference. In 2014. p. 2–3.
213. East CE, Davey M-A, Kamlin COF, Davis PG, Sheehan PM, Kane SC, et al. The addition of fetal scalp blood lactate measurement as an adjunct to cardiotocography to reduce caesarean sections during labour: The Flamingo randomised controlled trial. Aust N Z J Obstet Gynaecol. 2021 Mar;
214. Wiberg N, Klausen TW, Tyrberg T, Nordström L, Wiberg-Itzel E. Infant outcome at four years of age after intrapartum sampling of scalp blood lactate for fetal assessment. A cohort study. van Wouwe JP, editor. PLoS One [Internet]. 2018 Mar 23 [cited 2019 Mar 11];13(3):e0193887. Available from: https://dx.plos.org/10.1371/journal.pone.0193887
215. Allen RM, Bowling FG, Oats JJN. Determining the fetal scalp lactate level that indicates the need for intervention in labour. 2004;(July):549–52.
216. Reif P, Lakovschek I, Tappauf C, Haas J, Lang U, Sch??ll W. Validation of a point-of-care (POC) lactate testing device for fetal scalp blood sampling during labor: Clinical considerations, practicalities and realities. Clin Chem Lab Med. 2014;52(6).
217. van Horssen R, Schuurman TN, de Groot MJM, Jakobs BS. Lactate point-of-care testing for acidosis: Cross-comparison of two devices with routine laboratory results. Pract Lab Med [Internet]. 2016;4:41–9. Available from: http://dx.doi.org/10.1016/j.plabm.2015.12.005
218. Heinis A, van Dillen J, Oosting J, Rhose S, Vandenbussche F, Van Drongelen J. Clinical evaluation of Statstrip Lactate for use in fetal scalp blood sampling. Acta Obstet Gynecol Scand. 2017 Mar;96(3):334–41.
219. Orsonneau J-L, Fraissinet F, Sébille-Rivain V, Dudouet D, Bigot-Corbel E. Suitability of POC lactate methods for fetal and perinatal lactate testing: considerations for accuracy, specificity and decision making criteria. Clin Chem Lab Med [Internet]. 2013 Jan 1 [cited 2018 Feb 12];51(2):397–404. Available from: https://www.degruyter.com/view/j/cclm.2013.51.issue-2/cclm-2012-0201/cclm-2012-0201.xml
220. Heinis AMF, Spaanderman ME, Gunnewiek JMTK, Lotgering FK. Scalp blood lactate for intra-partum assessment of fetal metabolic acidosis. Acta Obstet Gynecol Scand. 2011 Oct;90(10):1107–14.
221. Heinis AMF, Dinnissen J, Spaanderman MEA, Lotgering FK, Gunnewiek JMTK. Comparison of two point-of-care testing (POCT) devices for fetal lactate during labor. Clin Chem Lab Med. 2012 Jan;50(1):89–93.

222. Luttkus AK, Fotopoulou C, Sehouli J, Stupin J, Dudenhausen JW. Technical performance of lactate biosensors and a test-strip device during labour. Z Geburtshilfe Neonatol. 2010 Apr;214(2):62–7.
223. ABL 800 user manual [Internet]. Available from: https://www.radiometer.com/en/products/blood-gas-testing/abl800-flex-blood-gas-analyzer#
224. Statstrip xpress user manual. https://www.kruuse.com/ecommerce/userfiles/kno/296200_NovaVet_usermanual_EN.pdf.
225. Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference Ranges for Hematocrit and Blood Hemoglobin Concentration During the Neonatal Period: Data From a Multihospital Health Care System. Pediatrics. 2009;123(2):e333-337.
226. PrimeStat User manual [Internet]. Available from: https://physiology.case.edu/media/eq_manuals/eq_manual_STAT_Profile_Prime_Instructions_for_Use_Manual.pdf
227. LactatePro2 user manual [Internet]. Available from: http://www.arkray.eu/english/upload/docs/B120312-01A LT-1730.pdf
228. Martin Bland J, Altman DG. STATISTICAL METHODS FOR ASSESSING AGREEMENT BETWEEN TWO METHODS OF CLINICAL MEASUREMENT. Lancet. 1986 Feb 8;327(8476):307–10.
229. Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: Clinical example of sepsis. Vol. 29, Intensive Care Medicine. 2003. p. 1043–51.
230. Carstensen B. Comparing methods of measurement : Extending the LoA by regression. 2009;(September).
231. Ingemarsson I, Ingemarsson E, Spencer JA. Fetal Heart Rate Monitoring. A Practical Guide. Oxford University Press; 1993.
232. Fosteroverv̊agning under fodslen [Internet]. DSOG Guidelines. Available from: thttps://static1.squarespace.com/static/5467abcce4b056d72594db79/t/5c84e7be8165f5cb5fb3e309/1552213956671/Fosteroverv̊agningunderfødsel.pdf#page=1itle
233. Mokarami P, Wiberg N, Källén K, Olofsson P. Arterio-venous blood gas Δvalues for validation of umbilical cord blood samples at birth are not only biased by sample mix ups but also affected by clinical factors. Acta Obstet Gynecol Scand. 2019 Feb 1;98(2):167–75.
234. Glasser L, Sutton N, Schmeling M, Machan JT. A comprehensive study of umbilical cord blood cell developmental changes and reference ranges by gestation, gender and mode of delivery. J Perinatol [Internet]. 2015;35(7):469–75. Available from: http://www.nature.com/doifinder/10.1038/jp.2014.241
235. Trochez RD, Sibanda T, Sharma R, Draycott T. Fetal monitoring in labor: are accelerations good enough? J Matern Fetal Neonatal Med [Internet]. 2005 Nov 7 [cited 2019 Mar 11];18(5):349–52. Available from: http://www.tandfonline.com/doi/full/10.1080/14767050500261770

236. Nurani R, Chandraharan E, Lowe V, Ugwumadu A, Arulkumaran S. Misidentification of maternal heart rate as fetal on cardiotocography during the second stage of labor: The role of the fetal electrocardiograph. Acta Obstet Gynecol Scand. 2012;91(12):1428–32.
237. Washio H, Takeshita D, Sakata S. Parasympathetic nervous activity is associated with oxytocin in multiparous, but not primiparous, women during the perinatal period. Clin Exp Pharmacol Physiol. 2020 Jan;00:1–11.
238. Clark SL, Gimovsky ML, Miller FC. Fetal heart rate response to scalp blood sampling. Am J Obstet Gynecol. 1982 Nov 15;144(6):706–8.
239. Goodman DM, Mlay P, Thielman N, Small MJ, Schmitt JW. Using fetal scalp stimulation with Doppler ultrasonography to enhance intermittent auscultation in low-resource settings: A diagnostic trial from Tanzania. BMC Pregnancy Childbirth. 2019 Feb 13;19(1).
240. Weber T. Continuous Fetal Scalp Tissue pH Monitoring During Labor: An Analysis of 152 Consecutive Cases. Acta Obstet Gynecol Scand. 1980;59(3):217–23.
241. Lorne M. Mendell. Constructing and Deconstructing the Gate Theory of Pain. Pain [Internet]. 2014;155(22):210–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf
242. Léguillier T, Jouffroy R, Boisson M, Boussaroque A, Chenevier-Gobeaux C, Chaabouni T, et al. Lactate POCT in mobile intensive care units for septic patients? A comparison of capillary blood method versus venous blood and plasma-based reference methods. 2018;
243. Chilinda GK, Gadama LA, Stones W. Point-of-care umbilical arterial lactate and newborn outcomes in a low resource setting: Cohort study. BMC Res Notes. 2018;11(477).
244. Su TY, Reece M, Chua SC. Lactate study using umbilical cord blood: Agreement between Lactate Pro hand-held devices with blood gas analyser and evaluation of lactate stability over time. Aust New Zeal J Obstet Gynaecol [Internet]. 2013 Aug [cited 2021 Mar 20];53(4):375–80. Available from: https://pubmed.ncbi.nlm.nih.gov/23550587/
245. Knutzen L, Anderson-Knight H, Svirko E, Impey L. Umbilical cord arterial base deficit and arterial pH as predictors of adverse outcomes among term neonates. Int J Gynecol Obstet. 2018;142(1):66–70.
246. Cahill A, Macones G, Smyser C, López J, Inder T, Mathur A. Umbilical Artery Lactate Correlates with Brain Lactate in Term Infants. Am J Perinatol. 2016 Oct;34(06):535–40.
247. Wiberg N, Källén K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. Acta Obstet Gynecol Scand. 2010 Oct;89(10):1263–9.
248. Thayyil S, Chandrasekaran M, Taylor A, Bainbridge A, Cady EB, Chong WKK, et al. Cerebral Magnetic Resonance Biomarkers in Neonatal Encephalopathy: A Meta-analysis. Pediatrics. 2010;125(2):e382 LP-e395.

249. Wiberg N, Källén K. Fetal scalp blood lactate during second stage of labor: determination of reference values and impact of obstetrical interventions. J Matern Neonatal Med. 2017;30(5):612–7.
250. Cummins G, Kremer J, Bernassau A, Brown A, Bridle HL, Schulze H, et al. Sensors for fetal hypoxia and metabolic acidosis: A review. Vol. 18, Sensors (Switzerland). MDPI AG; 2018. p. 1–22.