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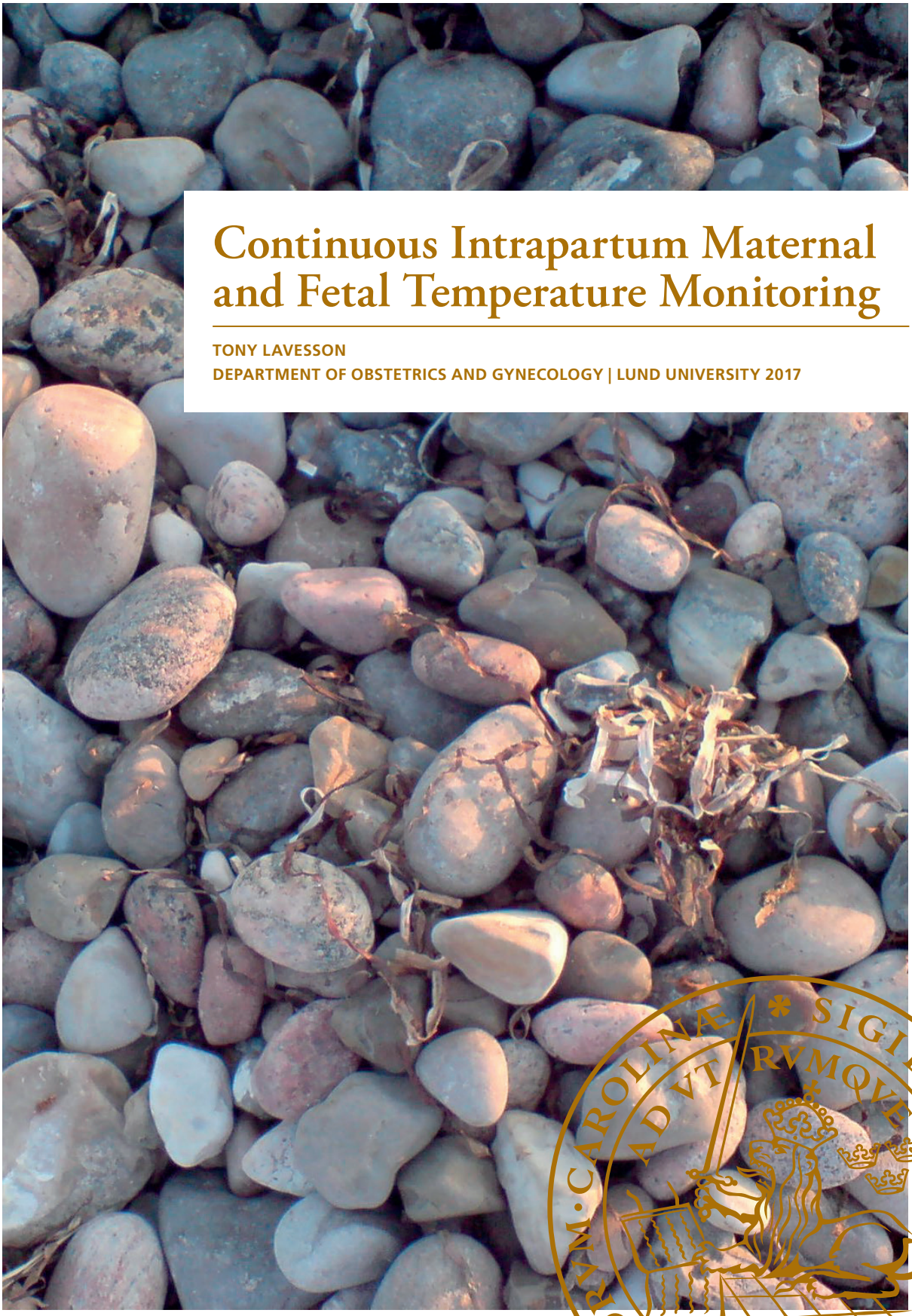

Continuous Intrapartum Maternal and Fetal Temperature Monitoring

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DEPARTMENT OF OBSTETRICS AND GYNECOLOGY | LUND UNIVERSITY 2017

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Tony Lavesson

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DOCTORAL DISSERTATION

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Abstract

The maternal temperature is normally increasing during delivery. Maternal fever in labor is a common problem. Such fever could represent a chorioamnionitis (CAM), leading to an increased risk of neonatal encephalopathy and subsequent cerebral palsy, as well as other complications. There are also noninfectious reasons for elevated temperature during delivery. There is no fetal heart rate that is specific for incipient or manifest CAM. Maternal fever in labor increases the risk of cesarean section and assisted vaginal delivery.

The fetal intrapartum temperature has been studied sparsely before. Fetal head heat flux has been found to be related to the metabolic condition of the fetus. Fetal skin temperature has been found to correlate with changing temperature and baseline fetal heart rate.

The aim of the present thesis was to investigate the fetal scalp temperature (FST) and maternal axillary temperature (MAT) during vaginal delivery relative to progression of labor, uterine contractions, epidural analgesia (EDA), and to construct normal temperature reference ranges related to stage of labor. The purpose was also to study FST and MAT and the relation to inflammatory response in the placenta. Furthermore, the present thesis attempted to establish whether paracetamol (acetaminophen) has effect on fetal and maternal temperatures in labor.

An equipment to continuously record fetal scalp temperature during labor was developed by placing a temperature sensor in the fetal scalp electrode aimed for fetal heart rate (FHR) monitoring. In the first study the equipment was validated in a fetal lamb model, where the intracranial and subcutaneous temperatures were measured. The subcutaneous temperature mirrored the intracranial temperature closely, even in a situation of increasing fetal hypoxia, with the intracranial temperature being higher.

In the following three studies the equipment was used in a total of 307 deliveries at Helsingborg hospital. The maternal temperature was measured axillary. The development of FST and MAT was examined during normal labor. The temperatures increased significantly by progression of labor, and significantly more in the presence of EDA. Reference intervals for maternal temperature were created. Changes of the FST were not seen during uterine contractions.

The relation between temperature and histological inflammatory changes was studied. There was a significant relation between inflammatory changes in the placenta, umbilical cord and amniotic membranes, and maximum FST and MAT. Women with EDA had significantly more often inflammatory changes.

Paracetamol is the only safe pharmacological choice to try to lower body temperature during delivery. The aim of the last study was to investigate the effect of paracetamol on maternal and fetal temperatures when given to febrile parturients. Neither maternal nor fetal temperatures decreased after paracetamol. However, paracetamol halted an increasing trend and stabilized the fetal temperature, i.e. it has an anti-pyretic effect.

Maternal, fetal, temperature, fever, pyrexia, labor, uterine contractions, delivery, chorioamnionitis, epidural analgesia, placenta, paracetamol, acetaminophen

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Keep your face to the sun and you will never see the shadows
Helen Keller

To Annika, Fredrik, Emmy and Filippa

Contents

Abbreviations

BIPDA	Before - increasing phase - peak - descent - after uterine contraction
BMI	Body mass index
°C	Degrees Celsius
CAM	Chorioamnionitis
CI	Confidence interval
CP	Cerebral palsy
CRF	Case report form
CRP	C-reactive protein
CS	Cesarean section
CTG	Cardiotocography
ECG	Electrocardiography, ST-analysis
EDA	Epidural analgesia
FHR	Fetal heart rate
FST	Fetal Scalp Temperature
GA	Gestational age
Hb	Haemoglobin
HIE	Hypoxic-ischemic encephalopathy
ICT	Intracranial temperature
IV	Intra venous
MAT	Maternal Axillary Temperature
NICU	Neonatal Intensive Care Unit
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
P	Probability
pH	power of hydrogen
RR	Relative risk
SCT	Subcutaneous temperature
SD	Standard deviation
STAN	ST-analysis, electrocardiography
UC	Uterine contraction

Explanation of key terms

Apgar	The Apgar score is a way to quickly assess the health of newborn children immediately after birth. Invented by Dr Virginia Apgar in 1953.
BMI	Body Mass Index was defined according to the standard definition, i.e. as weight in kilograms divided by the squared height in meters.
°C	Degrees Celsius. The Celsius scale is a centigrade temperature scale where there are one hundred steps or degrees between the freezing and boiling points of water.
°F	Degrees Fahrenheit
Caput succedaneum	is a fetal and neonatal condition of serosanguinous oedemal swelling caused by the pressure of the presenting part of the scalp against the dilating cervix.
CTG	Cardiotocography. Measurement of the fetal heartbeat pattern and the existence or frequency of contractions.
STAN	continuous ST-analysis of the fetal electrocardiogram, i.e. a continuous analysis of the ST-wave. The purpose is to detect if the fetus´ condition is deteriorating.
Paracetamol	is the same drug as acetaminophen.

List of original papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. T. Lavesson, I. Amer-Wåhlin, S. Hansson, D. Ley, K. Marsâl, P. Olofsson.
Continuous monitoring of fetal scalp temperature in labor: a new technology validated in a fetal lamb model.
Acta Obst Gynecol 2010;89:807-12.

II. T. Lavesson, K. Källén, P. Olofsson.
Fetal and maternal temperatures during labor and delivery: a prospective descriptive study.
Submitted, Accepted author version posted online: 16 Apr 2017.
J Matern Fetal Neonatal Med.

III. T. Lavesson, T. Sveberg Røste, I-M. Fyhr, P. Olofsson.
Relations between intrapartum maternal and fetal temperatures and placental inflammation.
Manuscript, submitted.

IV. T. Lavesson, F. Åkerman, K. Källén, P. Olofsson.
Effects on fetal and maternal temperatures of paracetamol administration during labour: a case–control study
Eur J Obstet Gynecol Reprod Biol. 2013;168(2):138-44.

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Populärvetenskaplig sammanfattning

Den födande kvinnan har en stigande temperatur under förlossningen. Bidragande faktorer till detta är muskelarbetet hon utför, epiduralbedövning, långvarigt värkarbete med mera. Det kan även ligga en infektion bakom temperaturförhöjningen. Man har observerat att det finns en ökad risk för barnet att utveckla hjärnskada och cerebral pares (CP) om mamman haft feber och infektion (uppåtstigande till fosterhinnor, moderkaka, navelsträng) under förlossningen. Det är svårt att avgöra om det föreligger en dylik infektion eller om det är annan anledning till febern. Infektionstecken utöver feber är diffusa, och det finns inget mönster hos fosterhjärtljuden som är specifikt för infektion. Följaktligen finns risk för både under- och överbehandling med antibiotika. Risken för instrumentell förlossning och akut kejsarsnitt är också högre om mamman har feber.

Fostrets temperatur under normal och komplicerad förlossning är relativt okänd, då den är ringa undersökt tidigare. Det som gjorts är att man på 1980 talet undersökte värmeavgivning från barnets skalp under förlossningen med en s.k. termistor som lades mot barnets huvud. Man kunde då se att det finns ett samband mellan värmeavgivningen och syra-bas balans hos barnet. På 1990 talet gjordes en undersökning där man mätte fostertemperatur med hjälp av en sond som placerades vid fostrets kind. En likadan sond placerades vid livmoderns inre vägg, och man kunde observera att fostertemperaturen är cirka 0,2 ºC högre än mammans temperatur. Ingen tillgänglig metod har funnits för att direkt studera fostrets temperatur.

Syftet med studierna i den här avhandlingen var att utvärdera en ny teknik för att mäta fostrets och mammans temperaturer kontinuerligt under förlossningen, både under normala och komplicerade förhållanden. En del av frågorna som behövde svar var: speglar temperaturen i fostrets skalp temperaturen inne i dess hjärna? Följs fostrets och mammans temperaturer åt under förlossningen och ökar de successivt? Finns det samband mellan temperaturerna underförlossningen och inflammation i moderkakan? Hur hög är fostrets temperatur då mamman har feber under förlossningen, och kan paracetamol sänka temperaturen då?

Den nya tekniken består i att traditionella skalpelektroder för mätning av fosterhjärtljuden (CTG och STAN) under förlossningen, modifierats så att de även kan mäta temperaturen precist. Ett litet hål har borrats i toppen på elektroden och i hålet har en spetsig temperatursensor placerats. Spetsen sticker ut 2-3 mm. När elektroden fästs på barnets huvud mäts temperaturen i eller strax på ytan av skalpvävnaden. Mammans temperatur har mätts i armhålan med en likadan ”naken” sensor, det vill säga utan skalpelektrod. Temperaturerna har mätts kontinuerligt under förlossningen och sparats i en hårddisk tillsammans med

information om bland annat värkar och fosterhjärtljud. Analyser av materialet har sedan skett i efterhand.

I den första studien gjordes 10 djurförsök i en ”lamm modell”. Temperaturen mättes inuti huvudet (intrakraniellt) och i underhuden (subkutant) samtidigt och kontinuerligt i en situation av tilltagande syrebrist. Återkommande navelsträngstillklämningar gav syrebristen och verifierades av upprepade mätningar av syra-bas status. Den subkutana temperaturen speglade den intrakraniella väl, även vid tilltagande syrebrist. Den nya tekniken fungerade väl och kunde anses validerad.

Samma teknik användes sedan i studie 2 till 4, som inkluderar mätningar på 307 födande kvinnor på Förlossningsavdelningen på Helsingborgs lasarett mellan augusti 2005 och februari 2008. Kvinnorna inkluderades då förlossningen startat, efter muntlig och skriftlig information, samt samtycke.

I den andra studien undersöktes fostrets skalp temperatur (FST) och mammans armhåls temperatur (MAT) i förhållande till förlossningens framskridande, värkar och epiduralbedövning (EDA). Under värk förändrades inte FST. Både FST och MAT ökade signifikant under förlossningens gång, och mer hos de kvinnor som fått en EDA. Referensområden skapades för normal temperatur under förlossning hos först- och omföderskor utan EDA, för olika delar av förlossningen.

Syftet med den tredje studien var att undersöka sambandet mellan FST och MAT och inflammation i moderkaka, navelsträng och fosterhinnor. Prover från dessa ställen togs efter förlossningarna, lades i formalin, och blev sedan undersökta med mikroskopering på Patologavdelningen, Helsingborgs lasarett. Slutsatsen blev att förekomst av inflammation var förknippad med högre FST och MAT, EDA och längre förlossningar.

Den fjärde studien syftade till att se om paracetamol har effekt på FST och MAT om det ges mot feber under förlossningen. En del av de kvinnor som inkluderades i studien och hade normal temperatur från början, utvecklade feber under förlossningen och fick 1 gram paracetamol i febernedsättande syfte. Paracetamol sänkte inte temperaturerna, men stoppade den stigande trenden och stabiliserade FST. De statistiska resultaten för MAT var inte enhälliga. Ett så kallat Typ 2 fel kan inte uteslutas, och frågan finns kvar huruvida paracetamol kan ha en anti-pyretisk effekt på fostret utan att samtidigt påverka på den maternella temperaturen.

Introduction

Temperature measurement

Temperature is a physical quantity. A variety of thermometers with different scales have existed to describe temperature through the years, at first most in meteorology. The scale of Fahrenheit already existed when Anders Celsius wrote about temperature measurement in 1742. The freezing and boiling points of water were used, and he range between them divided in one-hundred degrees, °C (Beckman, 2001). In the International System of Units kelvin is the SI unit for temperature, but Celsius and Fahrenheit is more often used. The relationship between temperature expressed in degrees Celsius (°C) and kelvin is:

$t = T - 273{,}15$ where t is the temperature in °C and T is the temperature in kelvin.

Fahrenheit is still is still the dominant unit in USA. The relationship between °C and degrees Fahrenheit is:

$T°C = (5/9) \times (T°F - 32)$

"Liquid-in-glass thermometers", in particular mercury thermometers, have existed for almost 300 years. This kind of thermometer relies on the expansion of a liquid with temperature, and requires visual reading. It is a simple way to measure temperature, but is currently not used so much because the concern for toxicity of mercury. In present time compact electrical thermometers, using an electrical sensor, are broadly used. Infra-red eardrum thermometers is also a method that is routinely used at hospital wards. The management is important to avoid errors. Phase-change (dot matrix) thermometers are non-electrical alternatives that uses inert chemicals on a thin plastic spatula, intended for oral use (National Physical Laboratory). Temporal artery thermometer, or forehead thermometers, uses the infra-red principle to measure temperature. The advantage is the non-invasive route, but the diagnostic accuracy is low (Penning et al., 2011; Geijer et al., 2016).

A method to measure gastrointestinal temperature using an ingestible temperature sensor has been developed. Studies described the use of such ingestible telemetric temperature pill as a reliable and valid method to assess gastrointestinal temperature, which can represent body core temperature (Bongers et al., 2015).

In the studies in this thesis electrical thermocouples are used. A thermocouple is an electrical device consisting of two dissimilar conductors forming electrical junctions at differing temperatures. There are a variety of thermocouples, with different accuracy. The thermocouples in the current studies measure the temperature with two decimals.

There are various sites used for measurement, including tympanic, rectal, oral, axillary skin, esophagus, intestinal, vaginal, in the bladder, intravasal and temporal/forehead. Different measuring sites offer different accuracy, advantages and disadvantages.

Oral temperature and tympanic temperature measurement is viable in the clinical setting. Rectal and esophagus temperatures are closer to the body core temperature than the oral and tympanic temperatures, but may cause discomfort. Gastrointestinal temperature measurement using the ingestible temperature sensor is close to the core temperature is not causing discomfort to the user (Lim et al., 2008).

When oral, skin and external auditory canal temperatures were compared with intrauterine temperature by Banejee et al (2004), the oral temperature had acceptable correlation with intrauterine temperature, but skin and external auditory canal temperature measurements did not correlate well. Oral temperature is feasible for intermittent measurement, but would not provide continuous data for offline parallel comparisons with fetal temperature.

In comparisons of body core temperature assessed as rectal and aural thermometry in hyperthermic exercising individuals, the aural temperature appeared to underestimate core temperature as determined by rectal temperature (Huggins et al., 2012).

Neither fetal scalp temperature nor maternal skin temperature represents the fetal respectively maternal body core temperatures. Temperature differs between axillary, mouth, tympanum, rectal and esophageal recordings in the same individual (Eyelade et al., 2011; Mazerolle et al., 2011; Teunissen et al., 2011).

Lefrant et al (2003) made simultaneous measurements of urinary bladder, esophageal, rectal, axillary, and inguinal temperatures versus pulmonary artery temperature in critically ill patients. They found that urinary bladder and esophageal electronic thermometers are more reliable than the electronic rectal thermometer which is better than inguinal and axillary gallium-in-glass thermometers to measure core temperature. The pulmonary artery temperature was in mean 0.27 ºC higher than the axillary temperature, but with a wide variation.

Definitions

Normal human body temperature, also known as normothermia or euthermia, is the typical temperature range found in humans and is essential to healthy cell functioning. There is not a single agreed-upon limit for normal temperature, and different limits are presented in the literature. Often 36 or 36.5 - 37.5 °C is mentioned as normal body temperature.

Homeothermy is thermoregulation that maintains a stable internal body temperature regardless of external influence. It involves mechanisms to control heat loss and gain so as to maintain a normal value for temperature (Imrie et al., 1990).

Fever, or pyrexia, is a body temperature of 38 °C and more. The range 37.5 – 37.9 °C is sometimes referred to as subfebrility.

Hyperthermia is a condition of increased body temperature because of non-functioning thermoregulation, e.g. stay in surrounding with high temperature or side effect of medication.

Thermoregulation

Body temperature is regulated in the hypothalamus, which functions as a ”thermocentrum”. In changes of body temperature, mechanisms to maintain normal temperature are started reflexively. Hypothalamus is informed about temperature changes through the temperature of the blood and nerve impulses about skin and core temperature.

The hypothalamus controls body temperature via the nerve system and hormonally. To change the temperature, heat production or heat loss can be regulated, e.g. by muscle activity (shivering) or vasodilatation/constriction.

The fetus has its own heat production, and is warmer than its mother (Randall et al. 1991). The thermal regulation mechanisms are through convective and conductive heat transfer (Rudelstorfer et al., 1991). The convective heat transfer, which represents about 85% of the heat loss, is the dominating way for the fetus to export the excessive heat, and it is done via the blood flowing in the umbilical cord to the placental circulation where the warmer fetal blood meets the colder maternal blood (Rudelstorfer et al., 1986; Macaulay et al., 1992). The conductive heat transfer represents heat transfer through the fetal skin and amniotic fluid to the uterine wall and to the birth channel.

The maternal body temperature increases during labor and the increase is greater in primiparae than in multiparae (Marx et al., 1975; Schouten et al. 2008). Due to uterine and skeletal muscle strain, long labor, infection after early amniorrhexis, and epidural analgesia, maternal pyrexia in labor is not uncommon.

Dangers of fever during parturition

Fever constitutes a threat to fetal health as it may be a symptom of intrauterine infection and fetal inflammatory reaction. It is well known, that the risk of cerebral palsy increases in children born by mothers with clinical signs of chorioamnionitis and fever (Anders et al., 2017; Bear et al., 2016; Yoon et al., 2003; Wu et al., 2003; Grether et al., 1997; Adamson et al., 1995). In such neonates, the inflammatory response with increased levels of cytokines correlates with development of cerebral white matter injury and cerebral palsy (Smulian et al., 2003). The etiology of white matter injury is not known but clinical data suggest that ischemia-reperfusion and/or infection-inflammation are important factors for the white matter injury (Hagberg et al., 2002).

Moreover, pyrexia itself might aggravate an existing hypoxia due to increased tissue oxygen consumption and a shift of the oxygen dissociation curve to the right (figure 1).

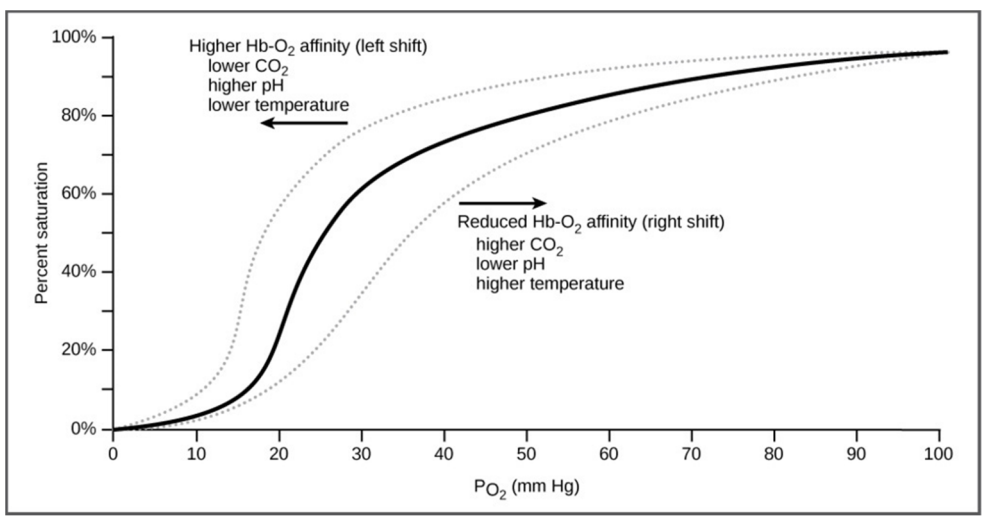

Figure 1
The oxygen-dissociation curve.

O2 is released in the tissues where the pO2 is low. In this situation Hb has a low affinity for oxygen. Other factors may cause a further reduction in Hb affinity for oxygen – i.e. a lower oxygen saturation for a given pO2.

Factors which result in shifting of the oxygen-dissociation curve to the right include increased concentration of pCO2, acidosis, raised temperature and high concentrations of 2,3 diphosphoglycerate (2,3 DPG). This causes the Hb to give up oxygen easier.

Maternal fever in labor increases the risk of cesarean section and assisted vaginal delivery (Lieberman et al., 1999).

In epidural analgesia-induced fever, the rate of early-onset seizures, low Apgar scores, neonatal hypotonia and assisted ventilation increases with the degree of maternal temperature elevation (Greenwell et al., 2012).

Earlier research

Fetal temperature have been studied sparsely earlier, even though it is a basic variable. In the 1980s, Rudelstorfer and colleagues (1983) studied heat flux from the fetal scalp during labor, which reflects the temperature gradient between the warmer fetus and the mother. They used a transducer with the size of 2.5 cm diameter and 1 mm thickness. The new variable heat flux was measured with the transducer attached to the fetal scalp after rupture of the membranes. They found a statistically significant correlation between heat flux from the fetal head and pH of umbilical artery blood.

Rudelstorfer and colleagues (1987) have also done a study on association between heat flux from the fetal scalp and the pH of fetal scalp blood, and found a significant correlation between heat flux measured immediately before the scalp blood sampling and the pH of fetal scalp blood. They therefore could conclude that fetal scalp heat flux is related to the metabolic condition of the fetus, but the method has not been further developed. Rudelstorfer and colleagues (1991) showed that heat flux in postmature and growth-retarded fetuses during delivery was higher than appropriately grown fetuses of the same length head size and gestational age. During the second stage there was also differences between groups, and the research group concludes that scalp heat flux measurements may indicate disturbances of placental exchange before acute hypoxia occurs.

Fusi et al. (1989) recorded maternal vaginal temperature via a small and flexible radiometer thermistor attached to the fetal scalp electrode, in a study of effects of pain relief on maternal temperature during labor.

The first equipment to measure fetal temperature in labor was developed by Randall and colleagues (1991), whom placed a fetal skin temperature sensor in a probe sandwiched between the fetal head and the lower uterine segment or the cervical canal.

Macaulay et al. (1992) used a similar technique, and measured the fetal skin and maternal uterine wall temperatures, from which they derived the temperature difference of 0.24 °C. There was a correlation between changing temperature and baseline fetal heart rate.

Aims of the investigations

The overall aim of the studies in this thesis was to study temperature changes during normal and complicated delivery.

The specific aims of the individual studies presented in this thesis are given below.

I. Continuous monitoring of fetal scalp temperature in labor: a new technology validated in a fetal lamb model.
   - to evaluate a new technical equipment for continuous recording of human fetal scalp temperature in labor.
   - to examine associations between fetal forehead subcutaneous temperature and intracranial temperature.

II. Fetal and maternal temperatures during labor and delivery: a prospective descriptive study.
   - to study the fetal scalp temperature and maternal axillary temperature during vaginal delivery relative to progression of labor, uterine contractions and epidural analgesia.
   - to construct normal temperature reference ranges related to stage of labor.

III. Relations between intrapartum maternal and fetal temperatures and placental inflammation.
   - to study the fetal scalp temperature and maternal axillary temperature during delivery relative to placental inflammation.

IV. Effects on fetal and maternal temperatures of paracetamol administration during labour: a case–control study
   - to study the effect of paracetamol (acetaminophen) on maternal and fetal temperatures in labor.

Subjects and setting

I. Animal model

Study I was conducted at Clinical Research Center (CRC) in Lund, Sweden, in 2005. The experiments were performed on 10 fetal lambs in six pregnant date-mated ewes of mixed breed (four twin pregnancies) at a gestational age ranging 115-135 days. The Animal Research Ethics Committee, Lund University, approved the study (approval no. M18704).

II-IV. Human measurements

Study II-IV were conducted at the Delivery ward of Helsingborg hospital, Sweden, which was chosen for convenience. Data were collected between August 2005 and February 2008 and during this period the average annual birth rate at Helsingborg hospital was approximately 3200 births.

Three-hundred and seven women in the first stage of labor were continuously monitored with maternal axillar and fetal scalp temperatures in addition to regular monitoring with cardiotocography (CTG) and fetal ECG ST segment analysis (STAN^{TM}) (Neoventa Medical AB, Mölndal, Sweden). All women received verbal and written information about the study at the Delivery ward. They had to give their oral and written consent to participate. The study was consecutive in the sense that when the author of this thesis, or one of the specially trained midwifes, were present eligible women were asked to participate. All studies were approved by the Ethics Committee of the Medical Faculty of Lund University, Sweden.

Methods

Temperature monitoring system

The technological system used in all of the four studies in this thesis is named Milou™ Temperature Monitoring System (Figure 2), and was developed by Medexa Diagnostisk Service AB, Limhamn, Sweden.

The system enables measurement of two temperatures simultaneously. The temperatures are measured by the Fetal Care Temperature monitor (Figure 3), a high precision instrument for fetal and maternal temperature measurement. This monitor is connected to a medical grade panel computer which is approved for medical use, i.e. there is no risk of leakage of electricity and it is spill and dust resistant. The Fetal Care Temperature monitor is equipped with an optical isolation module on the serial output, which isolates it from the connected computer.

The temperatures are displayed online on the computer screen and stored in the computer hard disc together with CTG, STAN and tocometry data (Figure 4). The data can be analyzed offline later. With a digital movable "Vertical Ruler", any point of time during the recordings can be chosen to display the maternal and fetal temperatures in °C with two decimals.

To obtain the CTG and STAN information the temperature system has to be connected to a STAN™ apparatus for CTG and ECG ST interval analysis (Neoventa Medical AB, Mölndal, Sweden). The information is transmitted by cable from the STAN™ machine to the Milou™ System, where it is displayed together with the thermal information. The equipment has a measurement precision of ± 0.0 grades ˚C.

Handling of the equipment in the current studies was only done by trained and especially instructed personnel, i.e. myself or some of the midwifes on the delivery ward of Helsingborg Hospital.

Temperature electrode

Traditional and commercially available fetal scalp CTG electrodes (GoldtraceTM, Neoventa Medical AB, Mölndal, Sweden) were modified to also record the fetal scalp temperature. In the center of the plastic case of the electrode, a small hole was drilled and a pointed bi-metal thermocouple temperature sensor (Medexxa GmbH, Hasloh, Germany) glued into the hole (Figure 5, 6 and 7). The pointed pin sensor is sharp and projects approximately 2 mm above the plastic surface to penetrate the fetal scalp when the spiral electrode is screwed into the fetal scalp skin, to measure the temperature in the scalp tissue. The fixation of the traditional electrode to the skin through the metal helix keeps the pin of the temperature sensor in place. Since the pointed pin sensor is placed in the middle of the electrode it is only in contact with the fetal scalp skin and there is no risk of measuring the maternal temperature with the fetal electrode. Figure 8 shows the mark after the temperature electrode. The fetal head skin was not inspected in every case.

The cable that connects the temperature sensor to the Fetal Care Temperature monitor is a bi-metal coaxial cable.

The maternal temperature was recorded simultaneously and non-invasively by taping a ‘naked’ bi-metal temperature sensor of the same kind, i.e. a sensor without the CTG spiral electrode, in the axilla. A thermal isolator pad with a heat-reflecting surface facing towards the skin was used to fix the maternal electrode to the skin. The maternal sensor was connected to the Fetal Care Temperature monitor via the same type of coaxial cable as the fetal temperature sensor.

The Milou™ Temperature Monitoring System was equipped with a software tool called “Vertical Ruler”. With the “Vertical Ruler” any point of time of the recordings could be chosen to display the different parameters, i.e. fetal and maternal temperatures in ˚C with two decimals, fetal heart rate, ST-segment analysis and tocometry. This was done off-line.

Paper I

Procedure

Before start of the human temperature studies the new method and technical equipment had to be evaluated. This was done in a fetal lamb model. The model was already established and had been used in other experiments at Biomedicinskt Centrum (BMC) in Lund, Sweden.

The ewes were intubated after i.v. ketamine-thiopental induction of anesthesia and received an arterial cannula. The subsequent anesthesia was maintained with inhalation of isoflurane, i.v. infusion of the short-acting opioid remifentanil, and intermittent i.v. injections of the likewise short-acting anesthetic propofol.

A laparotomy was done on the ewe under sterile conditions via a midline incision of the maternal abdomen. The uterus was visualized and a hysterotomy was done followed by a small amniotomy. The fetus was gently exteriorized by cesarean section.

After exteriorization of the fetal head and neck, a sterile rubber glove was immediately placed over the fetal head to prevent breathing. Throughout the experiment the fetus was oxygenated via the umbilical cord circulation. A catheter placed in the fetal jugular vein was used for blood sampling, but only pH values were reported in study I since the aim of the study was not to compare temperature with blood status or fetal responses to hypoxia. The skin on the forehead was opened with a small incision and a 3 mm hole drilled very carefully through the skull bone in the midline, without affecting the brain membranes. A bi-metal thermocouple temperature sensor was inserted and placed between the skull bone and the *dura mater*. This sensor is the same kind of ´naked´ bi-metal thermocouple temperature sensor as was used in the human experiments in study II-IV, i.e. without the cardiotocography electrode. The sensor was fixed in this position by putting bone wax in the hole in the skull.

A second temperature sensor of the same kind was placed subcutaneously via the same incision on the forehead skin. Then the skin was closed with superglue and a continuous suture with the two sensors in place; intracranial and subcutaneous. To avoid cooling of the fetal head a sterile plastic bag was put over the exteriorized parts of the lamb. Bi-metal coaxial cables connected the two temperature sensors with the Milou™ Temperature Monitoring System instrument. The bi-metal cables were of the same kind as the ones used in study II-IV. The intracranial temperature (ICT) and subcutaneous temperature (SCT) were then simultaneously and continuously recorded throughout the experiment.

The part of the umbilical cord was gently exteriorized. Fetal hypoxia was induced by intermittent umbilical cord compressions. The experiment continued until fetal asystole occurred, after which the fetus was delivered for resuscitation as part of another study. In the four twin gestations, the second fetus was left untouched *in utero* while the experiment was performed on the first fetus; subsequently, after delivery of the first fetus the experiment continued with the second fetus. The hysterotomy and laparotomy were closed at the end of the experiments and the ewes survived the procedure.

The temperature data were stored in the Milou™ system computer for *post hoc* analyses. The movable "Vertical Ruler" was used to read the ICT and SCT. In this way, the stored temperature data were off-line extracted at every 5 min throughout the experiment.

Nota bene that the fetal and maternal input gates on the Fetal Care™ monitor in the Milou™ Temperature Monitoring system were used for the ICT and SCT sensors. The maternal temperature was not investigated in study I.

Statistical analyses

Statistical analyses were performed with simple and polynomial linear regression analyses. A two-sided P value < 0.05 was regarded as statistically significant. Statistical analyses were performed with aid of StatView® (SAS Institute Inc., Cary, NC, U.S.A.) computer software.

Commonalities paper II-IV

Procedure

The equipment Milou™ Monitoring System that was validated in study I was then used in study II-IV to measure fetal scalp temperature (FST) and maternal axillary temperature (MAT). The studies are prospective observational studies. In total three-hundred and seven experiments were done at the maternity unit, Helsingborg Hospital, Sweden. All women gave their oral and written informed consent to participate. The study was consecutive in the sense that when I (T.L.) or one of the specially instructed and trained midwifes were in service, eligible women were asked to participate. The participants and the personnel were informed that the temperature measurements must not have any influence on the clinical management. Conventional fetal surveillance was done by the midwife using the

STAN™ apparatus, where CTG, ST analysis, and tocodynamometry were displayed.

The specially produced fetal scalp electrode with the mounted temperature probe for measurement of FST, was applied after spontaneous or artificial rupture of the membranes. If the latter was done, this was performed to augment labor or to apply a scalp electrode for improved CTG signal quality.

Simultaneously, the MAT was recorded non-invasively by the 'naked' bi-metal temperature sensor attached to the armpit of the woman. The recordings continued until delivery.

The room temperature was routinely set to 23.0-24.0 ˚C and regularly checked with a mercury thermometer, and noted in the STAN™ log.

At any time during an experiment, the recording could be paused if the woman wanted to, for example, go to the bathroom. The cables connecting her to the STAN™ and Milou™ machines were then pulled out of the machines, twisted together and taped to the leg of the woman. After the interruption, the cables were applied to the machines again, and the recording started again. Other from such interruptions, FST and MAT were continuously monitored together with CTG and ST-analysis.

Clinical information about cervical dilatation, parity etc. was retrieved from partograms and medical records.

The CTG traces were retrospectively classified according to the Swedish National Guidelines for CTG interpretation during the window from 10 min before to 10 min after each time point of temperature readings.

Technical problems

The first recordings were done without technical problems. As the number of saved recordings increased, the hard drive memory in the computer where the recordings were saved was diminishing. After one-hundred and eighty-five recordings the computer had to be changed to a new computer. In the new computer the "Vertical Ruler"-tool was not included. The last one-hundred and twenty-two recordings were done without any technical problems, but the off-line readings of the temperatures had to be done visually.

Statistical analyses

All statistical analyses were performed with aid of StatView® (SAS Institute Inc., Cary, NC, U.S.A.) computer software, except for the analyses with mixed-effect models statistics (GaussTM, Aptech Systems Inc., Maple Valley, WA, USA) that were performed by my co supervisor Karin Källén, Lund. A two-tailed *P* value <0.05 was regarded statistically significant. If not otherwise stated, in the text and tables the test with the lowest *P* value (i.e., highest significance) is reported.

Paper II

Procedure

Inclusion criteria were cephalic presentation, no risk of transmission of maternal infectious disease to the fetus, no suspicion of fetal coagulopathy, and gestational age 36 weeks or more. Exclusion criteria were ongoing acetaminophen treatment for pyrexia, eardrum temperature ≥38.0 ˚C at the start of registration, non-cephalic lie, fetal face or forehead presentation, pregnancy shorter than 36 weeks, maternal hepatitis or HIV infection, suspicion of fetal coagulopathy, or other contraindications for applying a fetal scalp electrode.

The maternal eardrum temperature was measured at the start of labor and then on clinical indications, and fever was defined as a temperature ≥38.0 ˚C. If the woman developed fever and received treatment with acetaminophen after inclusion, it was regarded as a dropout from the study.

The temperatures recorded at cervical dilatations of 2-3 cm, 5 cm, 7-8 cm, 10 cm were noted, and when the cervix was fully dilated and retracted. A 20-min sequence of good signal quality of all recorded parameters was chosen to represent each stage of cervical dilatation. During the 20-min window a legible UC was selected for measurements of the temperatures immediately before the start of contraction (denoted B), during the increasing phase of contraction (I), at the peak (P), during the descent (D), and immediately after (A).

The use and time of oxytocin for augmentation of labor, EDA, operative delivery (cesarean section, forceps, or ventouse), and Apgar score <7 at 5 min were noted for each case. Immediately after birth, arterial and venous umbilical cord blood were sampled for blood gas analyses, and an arterial pH <7.10 was classified as acidemia.

Statistical analyses

Comparisons of continuous variables between groups were performed with the Mann-Whitney *U* test. Linear and polynomial mixed-effect models statistics up to the fifth degree for repeated measurements were used to detect significant differences between longitudinal measurement points. All FST B-I-P-D-A measurements were included in a mixed-effect models analysis. Simple linear regression analysis and Spearman's rank correlation test (rho) were used to estimate relations between continuous variables.

Paper III

Procedure

Inclusion criteria were informed consent from the woman, ability to understand oral and written Swedish, cephalic presentation, no contraindication to apply a fetal scalp electrode, no suspicion of fetal coagulopathy, and gestational age 35 weeks or more. Exclusion criteria were inability to understand Swedish, non-cephalic lie, fetal face or forehead presentation, pregnancy shorter than 35 weeks, maternal hepatitis or HIV infection, suspicion of fetal coagulopathy, or other contraindications for applying a fetal scalp electrode.

Immediately after birth, arterial and venous umbilical cord blood were sampled for blood gas analyses, and an arterial pH <7.10 was classified as acidemia.

After birth tissue specimens from the placenta, umbilical cord and chorioamniotic membranes were taken for later microscopic histological analysis. The membranes were cut off the placenta and turned to a roll. The umbilical cord was cut 3 cm from the placenta. The following 5 cm was cut off and discarded, and the consequent 5 cm was saved. A 2 x 2 cm piece of the placenta including the cord insertion was saved, as well as 4 more peripheral 2 x 2 cm pieces of the placenta. The pieces included the full placental thickness. All seven specimens were put in Formaldehyde 4% and stored until preparation for microscopy. The Formaldehyde was exchanged once during storage.

The tissue specimens were handled at the Pathology ward at Helsingborg Hospital. Specimens were gradually dehydrated and embedded in paraffin blocks, sectioned by microtomy into slices of 3-4 µ thickness, and then placed on glass slides and stained with Hematoxylin and Eosin. The histology examinations were done by Dr Sveberg Røste, who was blinded to clinical and temperature data. The inflammation was graded according to Kraus et al. (2004).

The maximum FST recorded in each woman was identified and visually read with one decimal. The MAT corresponding to the time of the maximum FST was also read. The CTG was classified without knowledge of the histological findings.

Statistical analyses

Statistical comparisons of continuous parameters were performed with the Mann-Whitney *U* test. The Chi-square test or Fisher's exact test were used for categorical variables. Multiple logistic regression analysis was used to reveal effects of independent parameters on the occurrence of placental inflammation.

Paper IV

Procedure

Inclusion criteria were informed consent from the woman, ability to understand oral and written Swedish, cephalic presentation, no contraindication to apply a fetal scalp electrode, no suspicion of fetal coagulopathy, and gestational age 36 weeks or more. Exclusion criteria were inability to understand oral and written information, non-cephalic lie, fetal face or forehead presentation, maternal hepatitis or HIV infection, suspicion of fetal coagulopathy, or other contraindications for applying a scalp electrode.

The cohort of the one-hundred and eighty-five women with continuous FST and MAT recordings in labor and "Vertical Ruler" available, was used in study IV. 18 women whom received paracetamol were retrospectively identified from data in medical charts and partograms. According to the maternity unit's written instructions, all 18 women received 1000 mg paracetamol (acetaminophen, Panodil®, GlaxoSmithKline AB, Solna, Sweden) orally. The indication for paracetamol administration was an ear temperature ≥38.0 ˚C. Paracetamol could be repeated every 6 h if needed.

For each paracetamol case, two control cases without paracetamol were chosen, matched for parity, use of epidural analgesia, and opening of the cervix ± 1 cm. Maternal age, gestational age and oxytocin administration were not matched for. For each paracetamol case and control, the dual temperature recordings were noted 60 min before paracetamol administration (called time T-60), 30 min before paracetamol (T-30), time of paracetamol administration (time T0), and then every 30 min until delivery. T0 in controls corresponds to cervical dilatation ± 1 cm at

T0 in the respective paracetamol case. The researcher who read the temperatures was blinded to case and control allocation.

The baseline fetal heart rate (FHR) was visually assessed for 20-min windows, starting 10 min before and ending 10 min after each time T. The FHR assessment was also blinded from allocation.

Statistical analyses

Dichotomous category data were compared with Fisher´s exact test. Continuous data were compared between groups with Mann-Whitney *U* test, and longitudinal data with Wilcoxon matched-pairs signed-ranks test. The difference between the shapes of the temperature curves among the paracetamol and control groups was evaluated using third order mixed-effect models for repeated measurement data. Since the data included repeated measurements, the mixed-effect models (considering both fixed and random effects) were used in order to address the issue of covariation between measures on the same patient.

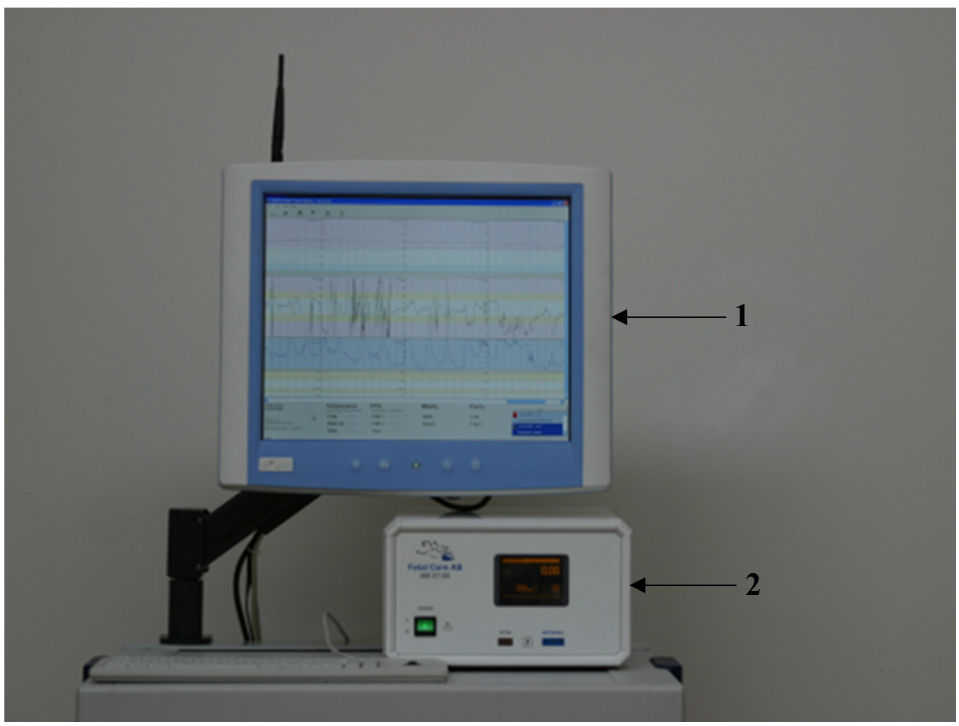

Figure 2
The Milou™ Temperature Monitoring System. 1) Temperature data is displayed on the computer screen online together with CTG and ST-analysis, but is also stored in the system hard disc for post hoc offline analyses. 2) The Fetal Care Temperature monitor (see Figure 3 for close-up).

Figure 3
The Fetal Care Temperature monitor. Fetal and maternal temperatures are shown with two decimals. The delta temperature is also displayed (fetal minus maternal temperature).

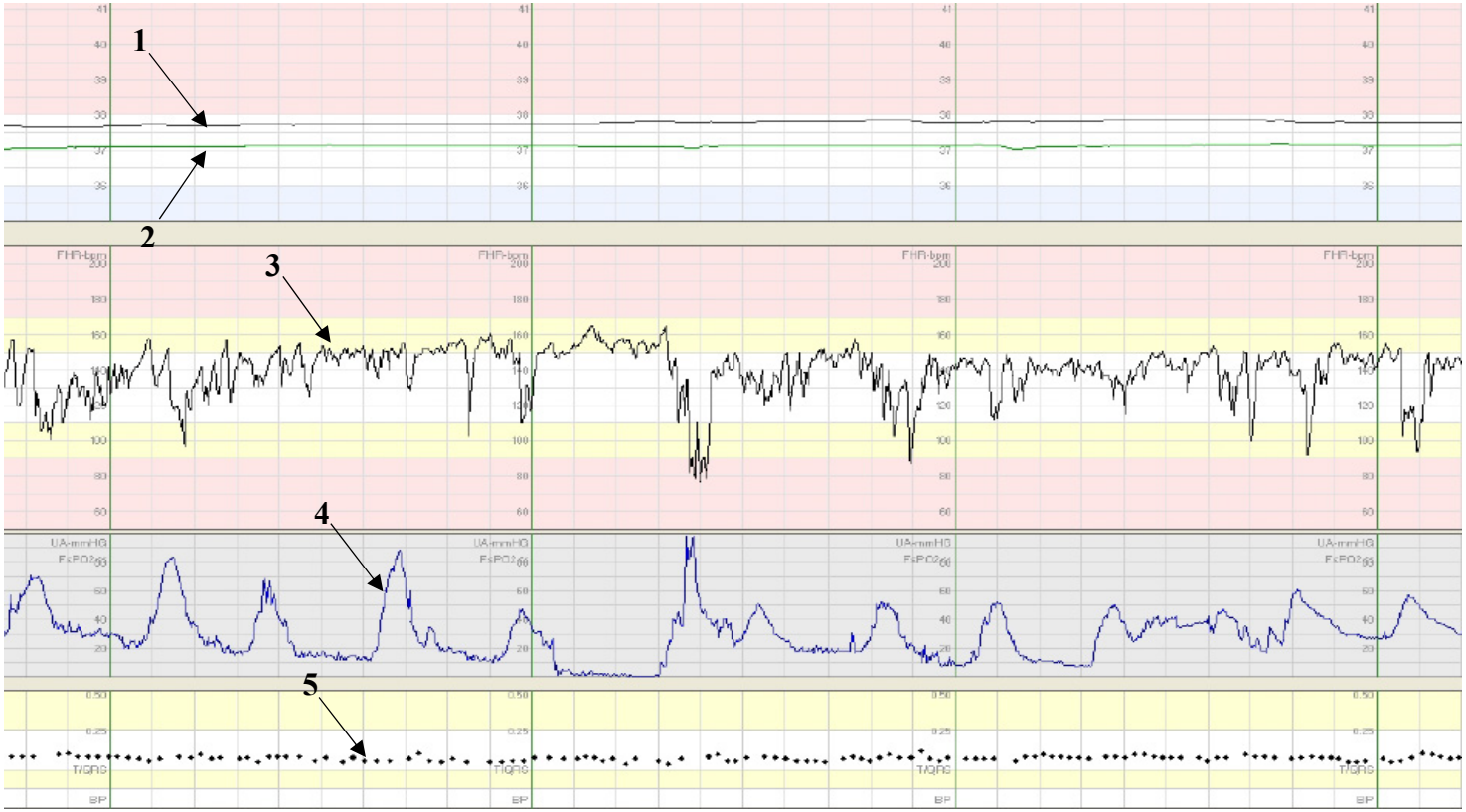

Figure 4
Example of registration from the Milou™ Temperature Monitoring System. Graphs from above indicated by numbered arrows: 1) fetal temperature, 2) maternal temperature, 3) fetal heart rate, 4) tocogram and 5) fetal ECG ST segment analysis (T/QRS ratio).

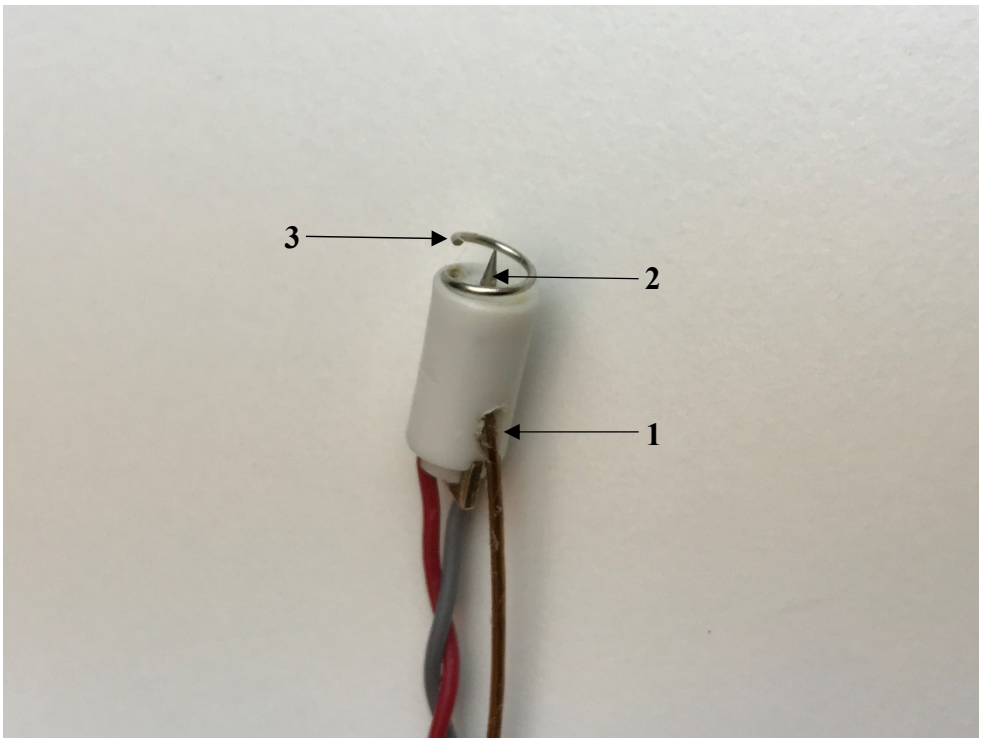

Figure 5
Close-up on the electrode used for measurement of CTG, STAN and fetal scalp temperature. 1) A small hole was drilled in the plastic case of the electrode, and a bi-metal thermocouple temperature sensor glued into the hole. 2) The pointed pin sensor projects approximately 2 mm above the plastic surface to penetrate the fetal scalp when the spiral electrode is screwed into the fetal scalp skin. 3) The traditional single-stranded metal helix that is screwed into the fetal scalp for for registration of CTG and ST-analysis (STAN).

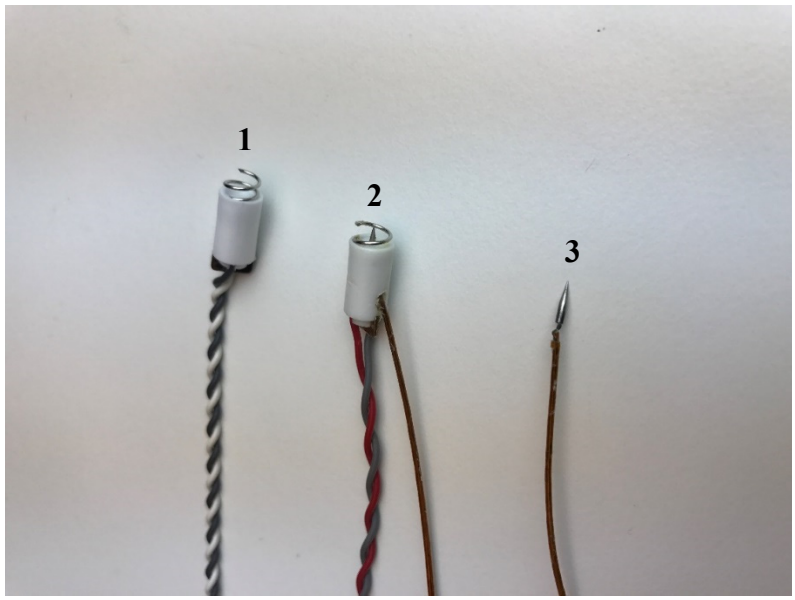

Figure 6
1) Traditional scalp electrode for registration of CTG and ST-analysis (STAN). 2) Modified scalp electrode for measurement of CTG and STAN, in addition with fetal scalp temperature (FST). 3) A ”naked” temperature probe used for the modification of the traditional scalp electrode. This is also used to measure the maternal axillary temperature.

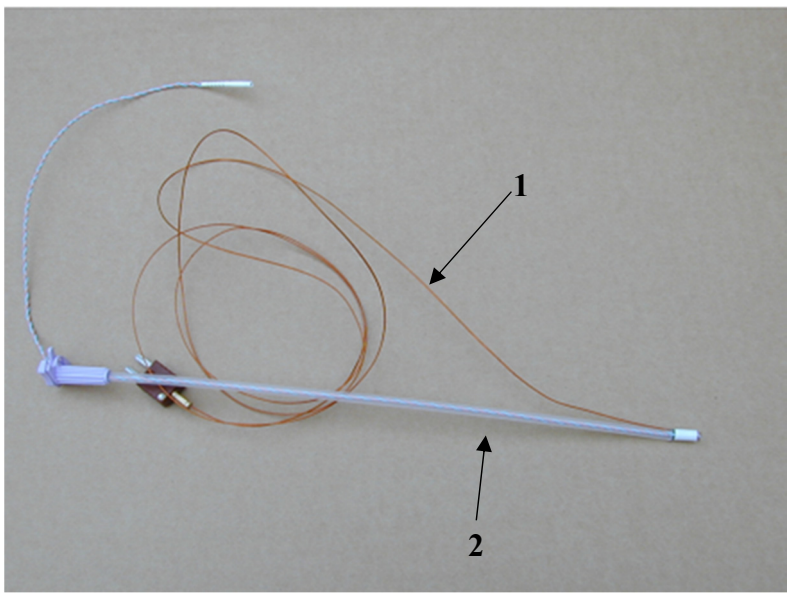

Figure 7
The electrode used for measurement of CTG, STAN and fetal scalp temperature; appearance before application. 1) The temperature sensor, to be connected to the Fetal Care Temperature monitor. 2) The CTG/STAN electrode, to be connected to the STAN machine.

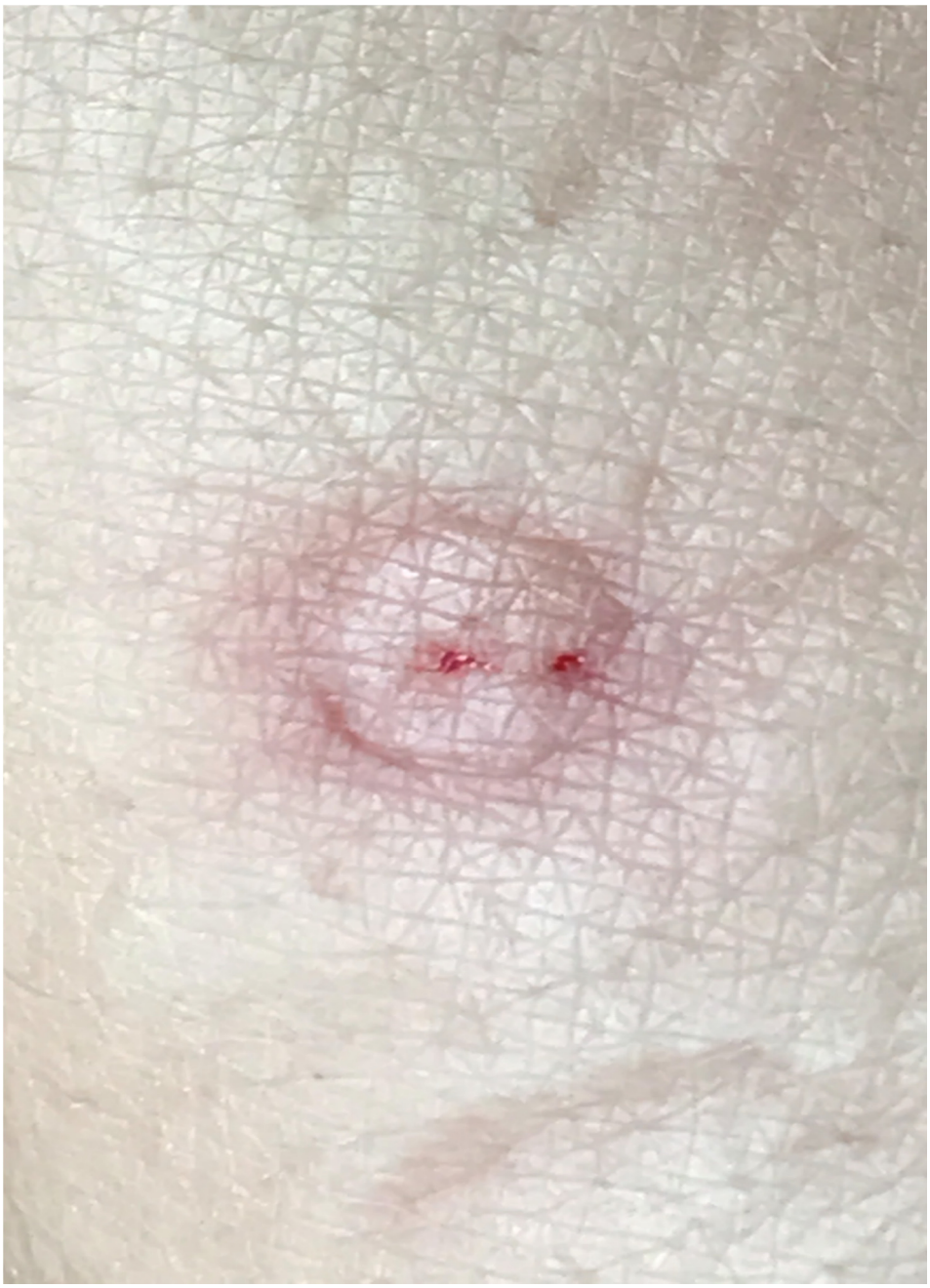

Figure 8
Mark in the skin after the temperature electrode.

Results

Paper I. Continuous monitoring of fetal scalp temperature in labor: a new technology validated in a fetal lamb model

Both intracranial and subcutaneous temperatures (ICT and SCT) were successfully recorded and saved in the hard drive in all 10 cases, and could be reviewed and examined with the "Vertical Ruler" tool.

With increasing acidosis, the temperatures decreased. Figure 9 shows the progressive changes of pH in venous jugular blood for each fetus during induced hypoxia, indicating increasing acidosis.

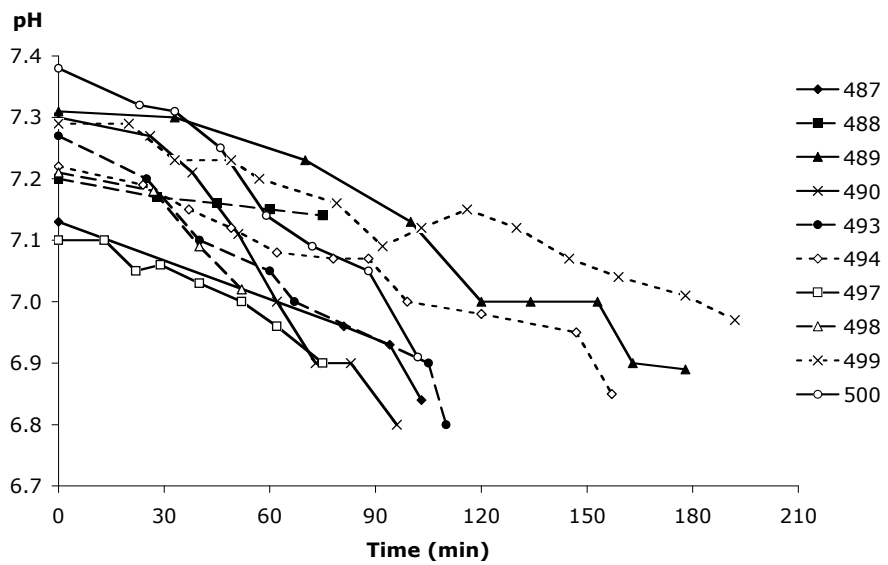

Figure 9
Jugular vein blood pH during experimental hypoxia in 10 fetal lambs. Numbers indicate the individual fetuses.

In all cases, a strong correlation between the ICT and SCT was found (P=0.001); the correlation coefficients by simple linear regression ranged between 0.76 and 0.97 (median 0.88) and by second grade polynomial regression 0.80–0.99 (median 0.89). Calculated for only the last 30 minutes of the experiments, i.e. when the fetal condition deteriorated, the correlation coefficients ranged between 0.84 and 1 (median 0.98) for both simple and second grade polynomial calculations.

Figure 10 illustrates the scattergram of all paired ICT–SCT measurements. The ICT exceeded the SCT in a large majority of recordings. The maximum difference between SCT and ICT in individual fetuses ranged from 0.31 to 3.64 °C and the mean difference ranged from -0.12 to 1.98 °C. After an initial system stabilization period of 10 min, the delta temperature values (ICT minus SCT) were less than 1.5 °C throughout the experiment in all but one case.

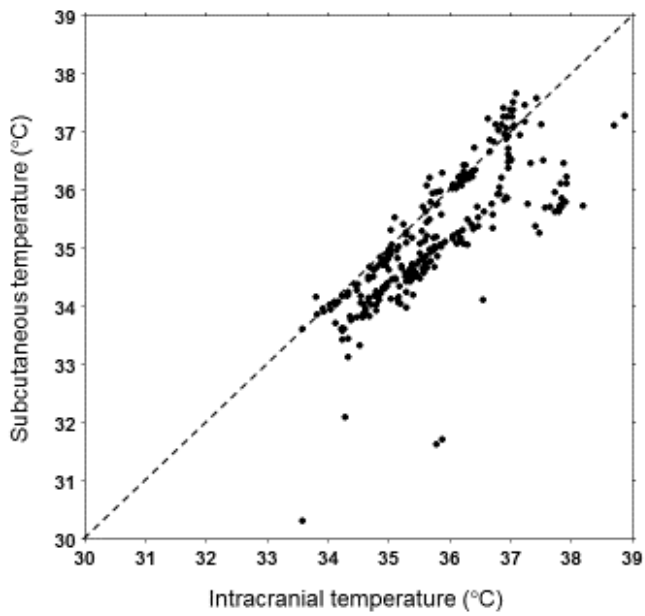

Figure 10
Paired intracranial and subcutaneous temperature recordings in 10 fetal lambs exposed to severe hypoxia (n = 255). The scattergram shows recordings after exclusion of the first 10 minutes of the experiments and after exclusion of four outliers (temperatures 23.61–26.07 °C). The interrupted diagonal line denotes the line of identity.

There were four pairs of twins but we found no adverse effect on the second twin after the experiment on the first twin; the initial jugular vein pH was equal in one twin pair and in the other three pairs higher in the second twin.

In all but one fetus the experiment lasted for at least 90 minutes. Figure 11 shows an example of an individual temperature recording.

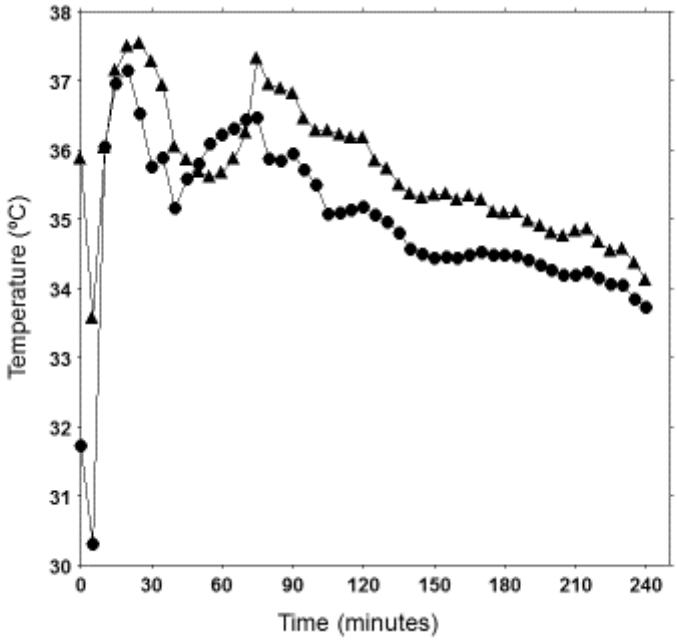

Figure 11
ICT and SCT scalp temperature in one of the fetuses (no. 499) during the experiment. The line with black triangles denotes ICT and the line with black circles denotes SCT.

Paper II. Fetal and maternal temperatures during labor and delivery: a prospective descriptive study

Of 160 women asked to participate, one woman declined and 18 dropped out due to fever and acetaminophen treatment. Nine women had suboptimal temperature recordings due to computer software problems, leaving 132 women for statistical analyses.

Ninety-nine women (75%) had a spontaneous onset of labor and 33 (25%) were induced by common reasons.

The numbers of ongoing registrations were 30 at 2-3 cm of cervical dilatation, 69 at 5 cm, 107 at 7-8 cm, 108 at 10 cm, and 85 at fully dilated and retracted cervix.

The CTG was classified as normal, intermediary or abnormal at 2-3 cm in 86.7%, 10.0% and 3.3% of cases, respectively, at 5 cm in 91.3%, 4.3% and 4.3%, at 7-8 cm in 78.5%, 10.3% and 11.2%, at 10 cm in 73.1%, 13.9% and 13.0%, and at fully dilated and retracted cervix in 44.7%, 30.6% and 24.7% of cases. No CTG trace

was classified as preterminal (variability <2 bpm with no accelerations, with or without tachycardia or decelerations).

Nine women had oxytocin augmentation only in the first stage of labor, 24 women only in the second stage, and 44 women in both the first and second stages of labor.

In total 1598 temperature recordings were included in the statistical analyses of FST during uterine contractions. When the fetal B-I-P-D-A temperatures were systematically tested in different polynomial models, the fifth degree equation featured the lowest *P* value (*P*=0.2), i.e., there were no statistically significant changes in temperature curve shapes during uterine contractions.

In calculations on temperature changes during the course of labor, the five B-I-P-D-A measurements at each cervical dilatation time point was used for description of FST. Calculated backwards from the time of delivery (time 0), the temperature increased significantly and linearly with progression of labor (mixed-effect models, linear model and fifth degree polynomial model *P*<0.0001, respectively). Figure 12 shows the individual and mean fetal temperature changes.

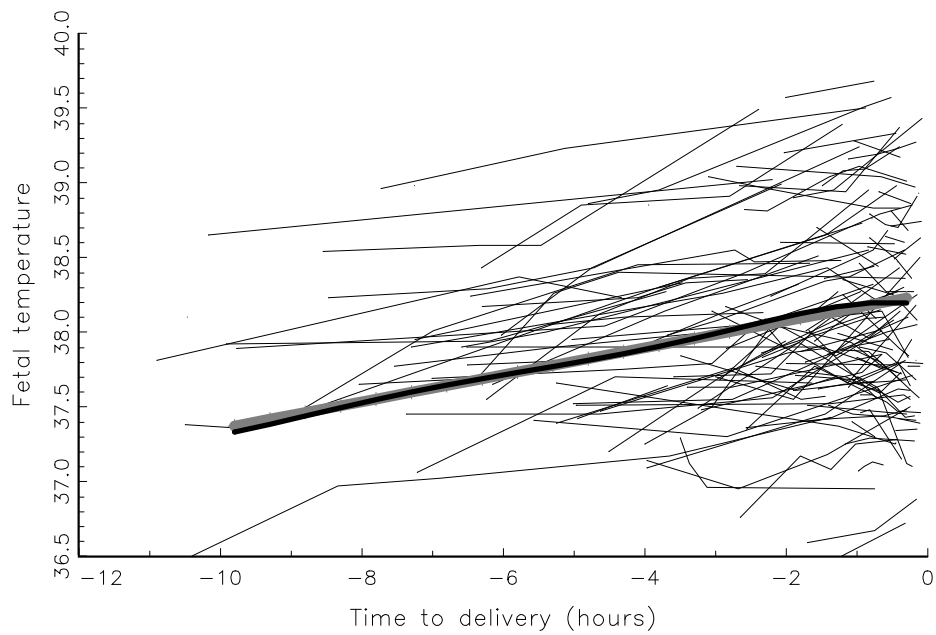

Figure 12
Fetal scalp temperature increasing linearly and significantly by remaining time to birth in 132 laboring women. Thin lines represent individual fetuses, the bold grey line represents the weighted mean from a mixed-effect analyses using a linear model (*P*<0.0001), and the black bold line represents the corresponding results using a fifth degree polynomial model (*P*<0.0001).

Calculation of MAT was done in the same way, and showed that the maternal temperature also increased significantly and linearly by progression of labor (mixed-effect models, linear model and fifth degree polynomial model $P<0.0001$, respectively).

The delta-temperature (FST minus MAT) decreased significantly during the 10 hours preceding delivery (fifth degree polynomial model, $P=0.0046$; simple linear regression, $P=0.0064$), i.e., the MAT increased more than the FST.

The overall highest readings were FST 39.93 ˚C and MAT 39.17 ˚C. In Figure 13 paired FST and MAT recordings from different stages of cervical dilatation (N=342) are plotted. There was a significant correlation between the parameters (simple linear regression analysis, R=0.78, $P<0.0001$). The fetal temperature was in all points higher than the maternal. The delta temperature ranged from 0.12 to 3.20 ˚C. Among maternal readings <38.0 ˚C (N=271), the fetal readings ranged from 36.39 to 39.57 ˚C, with 29/271 (10.7%) of the readings being ≥38.5 ˚C, 6/271 (2.2%) ≥39.0 ˚C, 1/271 (0.4%) ≥39.5 ˚C, and none ≥40.0 ˚C. Among maternal readings ≥38.0 ˚C (N=71), the fetal readings ranged 38.30 to 39.92 ˚C, with 31/71 (43.7%) of the readings being ≥39.0 ˚C, 8/71 (11.3%) ≥39.5 ˚C, and none ≥40.0 ˚C.

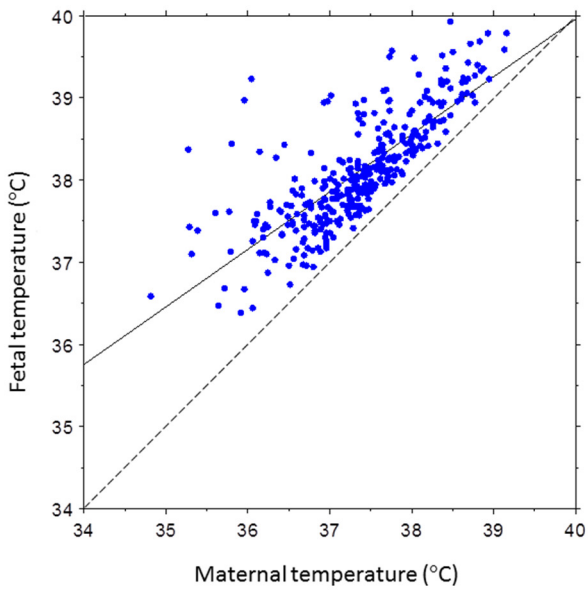

Figure 13
Correlation between maternal axillary temperature and fetal scalp temperature in 342 paired recordings (simple linear regression analysis; R=0.78, $P<0.0001$). The solid line represents the regression line and the interrupted line is the line of identity.

The fetal and maternal temperatures were calculated separately in the groups with (N=48) and without (N=84) EDA. Due to few cases, the polynomial calculations were not performed above the fourth degree mixed-effect model. Both the fetal and maternal temperatures increased significantly in both groups, but the temperatures were higher and the upward pointing slopes steeper in the EDA group (Figure 14). In the EDA as well as in the none-EDA group, the delta temperatures decreased significantly ($P \leq 0.02$).

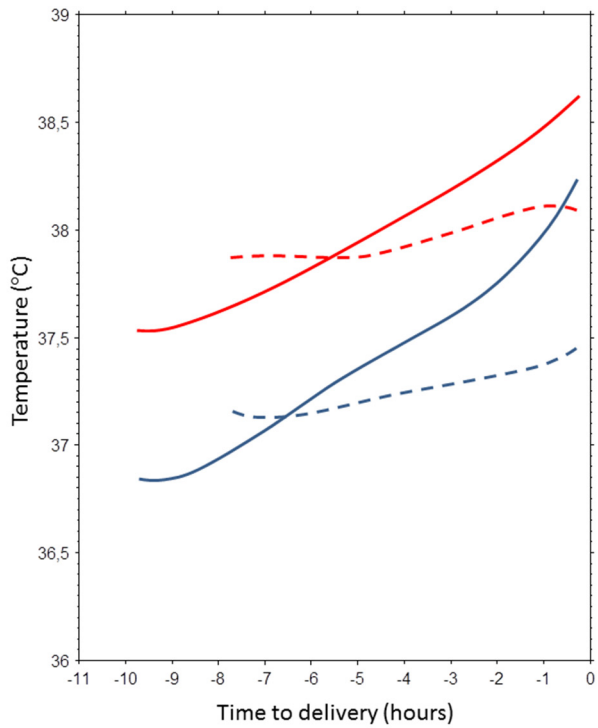

Figure 14
Maternal and fetal temperature in women with and without epidural analgesia relative to remaining time to delivery. Upper solid line: FST in women with EDA; upper denoted line: FST in women without EDA. Lower solid line: MAT in women with EDA; lower denoted line: women without EDA.

In the none-EDA group, we studied the MAT by parity. Nulliparae were warmer than multiparae. Using linear mixed-effect models statistics to calculate temperature changes per hour, reference intervals were constructed for nulli- and multiparae (Table 1). The mean increases in temperature per hour of labor were for both nulliparae and multiparae 0.1 ˚C.

Table 1.
Reference intervals* (mean ± 2 standard deviations, SD) for maternal temperature by stage of labor and absence of epidural analgesia.

	Nulliparous women				**Multiparous women**			
Cervical dilatation	Remaining time in labor (h), mean	Temperature (˚C) reference interval			Remaining time in labor (h), mean	Temperature (˚C) reference interval		
		Mean	-2SD	+2SD		Mean	-2SD	+2SD
2-3cm	8.37	37.08	35.66	38.50	4.10	36.94	35.62	38.26
5 cm	5.99	37.33	35.97	38.69	2.37	37.12	35.82	38.41
7-8 cm	3.94	37.55	36.23	38.86	1.32	37.23	35.95	38.50
10 cm	2.15	37.73	36.45	39.02	0.69	37.29	36.02	38.56
Retracted	0.97	37.86	36.58	39.13	0.31	37.33	36.06	38.60

*obtained from linear mixed effect model analyses.

The relations between FST and MAT, respectively, and oxytocin augmentation and umbilical cord arterial pH, respectively, were calculated for values recorded at a cervical dilatation of 10 cm. No significant differences in temperatures were found between women with and without oxytocin augmentation, though there was a tendency towards a higher MAT (Mann-Whitney *U* test, P=0.06, mean difference 0.2 ˚C) as well as a higher FST (P=0.07, mean difference 0.2 ˚C) in women with oxytocin augmentation. Considering the longer labor in women with oxytocin and then calculating the temperature increases per hour of labor, there were no differences in MAT or FST between the groups (P=0.9 and 0.07, respectively). No statistical associations were found between cord artery pH and the FST and MAT, respectively (simple linear regression analysis, Spearman's rho, both $P \geq 0.5$). The newborns having an umbilical cord artery pH <7.10 (N=7) did not show any differences in FST at 7-8 cm, 10 cm or retracted cervix compared to newborns with no acidemia (N=106) (Mann-Whitney *U* test, P=0.26).

Paper III. Relations between intrapartum maternal and fetal temperatures and placental inflammation

This study was performed on the registrations without the "Vertical Ruler"-tool. One-hundred-twenty-three women were asked to participate in the study and none declined. One placenta sample was discarded since the marking label was unreadable and one temperature recording was lost since it was not properly saved in the hard drive memory, leaving 121 women for statistical analysis. None of these women had substandard quality temperature recordings.

Ninety-six women (79%) had a spontaneous onset of labor and 25 (21%) were induced. Fifty-two women had oxytocin augmentation only in the first stage of labor, 67 women only in the second stage, and 43 women in both the first and second stages of labor.

Twenty-one women got acetaminophen treatment against fever. Antibiotics were given in 20 cases. The mean MAT in women with and without antibiotics was 37.9 ˚C and 37.6 ˚C, respectively and the mean FST was 38.3 ˚C and 38.1 ˚C, respectively (Mann-Whitney *U* test, P=0.080 and 0.19, respectively).

The maximum FST occurred at full cervical dilatation in 110 cases, in two cases at 9 cm and in one case at 8 cm dilatation. An emergency cesarean section was performed in seven women and the temperatures were then read just before the interruptions of the CTG and temperature recordings (in three cases at 8 cm, in two cases at 6 cm, in one case at 4 cm, and in one case at 3 cm cervical dilatation).

In one woman the temperature recordings ran to only 6 cm and the rest of the recording was lost.

The mean MAT was 37.6 °C (standard deviation [SD] 0.6 °C, median 37.6 °C, range 35.9-38.9 °C). The mean FST was 38.1 °C (SD 0.5 °C, median 38.1 °C, range 36.9-39.4 °C).

At the time of temperature readings, the CTG was classified as normal in 70.2%, intermediary in 21.5%, and abnormal in 8.3% of cases. No CTG trace was classified as preterminal (variability <2 bpm with no accelerations, with or without tachycardia or decelerations).

Overall, inflammation on the maternal side of the placenta (called 'maternal inflammation') was found in 18 cases: 16 in stage 1 and two in stage 2, but none in stage 3 (see grading of inflammation, Table 2). The corresponding numbers with inflammation on the fetal side (called 'fetal inflammation') were 12, three and none. Twenty-one cases showed maternal and/or fetal inflammation. To enable statistical calculation, stages 1 and 2 were merged together in the respective groups, i.e., 18 cases in the maternal inflammatory response group and 15 in the fetal inflammatory response group. Both the MAT and FST were significantly higher in the presence of inflammation (Mann-Whitney *U* test, P=0.003 and <0.001, respectively).

Table 2.

Grading of inflammation in placenta, chorioamniotic membranes and umbilical cord according to Kraus et al.

Maternal Inflammatory Response

Stage 1 (early), acute subchorionitis and/or acute chorionitis.

Maternal neutrophils are in the subchorionic fibrin and/or membranes at the junction between the decidua and chorioamnion.

Stage 2 (intermediate), acute chorioamnionitis.

Maternal neutrophils are in the connective tissues of the chorionic plate and membraneous chorioamnion.

Stage 3 (late), necrotizing chorioamnionitis.

Hypereosinophilia of the amnion basement membrane, karyorrhexis of neutrophils, necrosis, and sloughage of amnionic epithelial cells.

Fetal Inflammatory Response

Stage 1 (early), chorionic vasculitis and/or umbilical phlebitis.

Fetal neutrophils are seen in the wall of a chorionic vessel or the umbilical vein.

Stage 2 (intermediate), umbilical arteritis.

Fetal neutrophils are in the wall of one or both umbilical arteries. A few neutrophils may also be present in the Wharton's jelly.

Stage 3 (late), necrotizing funisitis or concentric umbilical perivasculitis.

Bands of degenerating neutrophils and eosinophilic debris are arranged in concentric arcs surrounding one or more umbilical vessels. Capillary neovascularisation may be present.

Sixty-two (51%) women received an EDA. Both the MAT and FST were significantly higher in women with EDA (Mann-Whitney *U* test, $P<0.001$ and <0.001, respectively).

Among the 21 women with maternal and/or fetal inflammation, the time of active labor was longer than among those without inflammation (Mann-Whitney *U* test, $P=0.039$), whereas there were no significant differences for other labor parameters (the time elapsing from amniorrhexis to partus, from fully cervical dilatation to partus, and from maximum FST recording to partus) (Mann-Whitney *U* test, $P\geq0.11$). Inflammation was not more common among women given antibiotics (Fisher's exact test, $P=0.75$).

The time from start of labor to partus was in mean 10.0 h ± 4.2 h (median 9.9, range 2.0-21.4) in women with EDA and 5.0 h ± 3.4 h (median 4.3, range 0.5-19.9) in women without EDA (Mann-Whitney *U* test, $P<0.0001$).

Inflammation was more common in women with EDA (16/62 vs. 5/59; Fisher's exact test, $P=0.016$). In a multiple logistic regression analysis with inflammation as the dependent parameter, the odds ratio (OR) for active labor was 1.12 (95% CI 1.01-1.24) per hour of active labor, and for EDA it was 3.76 (95% CI 1.28-11.04), but with both variables included in the analysis the significances disappeared (active labor OR 1.06 with 95% CI 0.94-1.20, and EDA OR 2.76 with 95% CI 0.81-9.41).

Paper IV. Effects on fetal and maternal temperatures of paracetamol administration during labour. A case-control study

Eighteen women received paracetamol. Consequently the number of controls was 36. In no woman was paracetamol given repeatedly. For one paracetamol case 3-para with epidural analgesia it was not possible to find a perfect match for parity in one of the controls, so a 2-parous woman with epidural analgesia was chosen instead. Women in the control group were significantly older but no significant differences were found for gestational age, time parameters, mode of delivery, Apgar score, umbilical cord artery pH, and neonatal morbidity.

Thirteen women in the paracetamol group received EDA, and consequently 26 in the control group. T0 occurred at different degree of dilatation of the cervix: 2 cm dilatation in one case, 4 cm in one case, 5 cm in two cases, 6 cm in two cases, 7 cm in two cases, 10 cm in nine cases and retracted in one case.

Recordings were done until delivery. Maximum length of a recording was 570 min. As the women delivered no statistical comparisons, except for the mixed-effect models for repeated-measurement data, were done when the number of paracetamol cases became fewer than 10. This happened beyond 150 min.

The overall percentage of missing or unreadable temperature values were in the maternal paracetamol group 18%, maternal control group 20%, fetal paracetamol group 15% and in the fetal control group 13%. The main reason for missing values was that the registration was paused when time T occurred (the woman visited the bathroom, took a walk, etc.). In some instances the temperature signal quality was poor and the offline temperature measurements thus disabled.

Maternal temperatures: From T-60 to T60 the temperature was higher in the paracetamol group ($P \leq 0.03$). In the paracetamol group there was a significant increase in temperature from T-60 to T-30 ($P=0.01$), whereupon no temporal changes occurred (T0 versus other T's: $P \geq 0.4$; step-by-step comparisons between T's: $P \geq 0.1$). In the control group the temperature increased gradually from T-30 to T90 after which no further increase occurred (T-60 to T-30: $P=0.7$; T90-T120: $P=0.1$; T120-T150: $P=0.4$) (Figure 15).

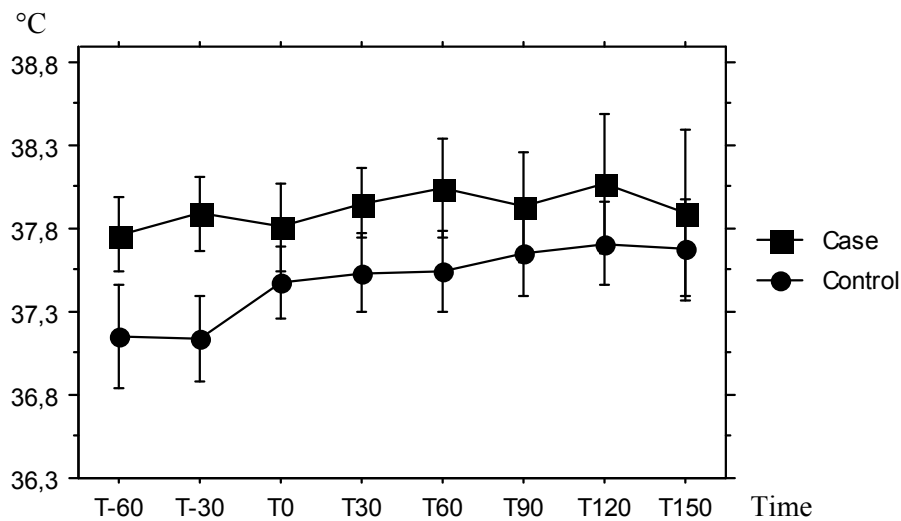

Figure 15
Maternal axillary temperature from 60 min before (T-60) administration of paracetamol (T0) to 150 min after (T150). The figure shows mean temperatures with 95% confidence intervals in the paracetamol group (filled squares) and the control group (filled circles).

Fetal temperatures: At all T-times from T-60 to T90 the temperature was higher in the paracetamol group ($P \leq 0.04$). In the paracetamol group, the temperature

increased significantly from T-60 to T-30 and from T-30 to T0 (and from T-60 to T0), after which no significant changes occurred (T0 versus T's after T0: $P \geq 0.1$; step-by-step comparisons between T's: $P \geq 0.7$). In the control group there was a gradual increase in temperature, except from T-60 to T-30 ($P=0.06$) (Figure 16).

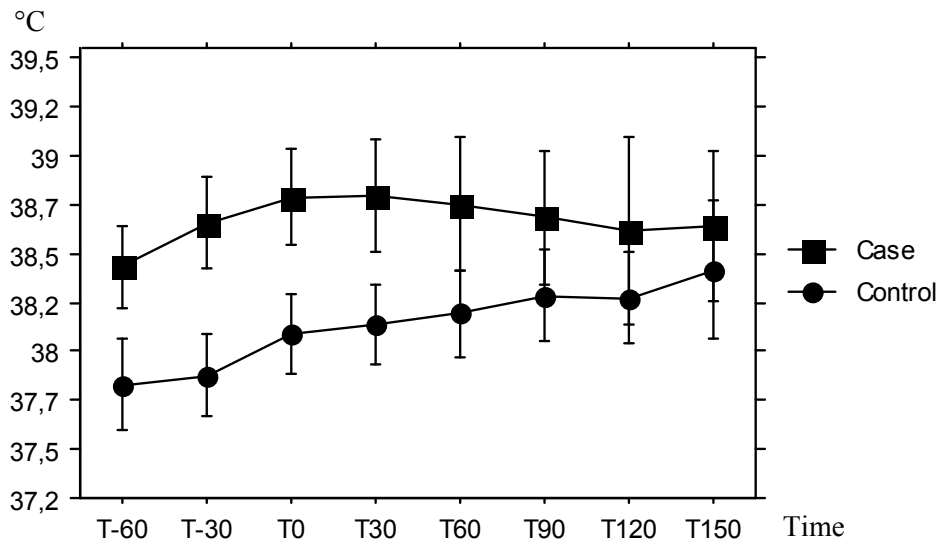

Figure 16
Fetal scalp temperature from 60 min before (T-60) administration of paracetamol (T0) to 150 min after (T150). The figure shows mean temperatures with 95% confidence intervals in the paracetamol group (filled squares) and the control group (filled circles).

The calculation with mixed-effect models for repeated-measurement data was done from T0 until delivery in all paracetamol cases and controls. There was no significant difference in curve shapes between the maternal paracetamol and control groups ($P=0.4$), but the curve shapes for fetal temperatures were significantly different ($P=0.01$).

Delta temperatures, i.e. FST minus MAT, were calculated for all paracetamol and control cases at each time T from T-60 to T300. There were neither in the paracetamol group (T0 versus other T's: $P \geq 0.2$, step-by-step comparisons between T's: $P \geq 0.07$) nor in the control group (T0 versus other T's: $P \geq 0.09$, step-by-step comparisons between T's $P \geq 0.06$) any significant changes in delta temperatures, except for T0 to T240 ($P=0.03$) in the control group. In the paracetamol group, the mean delta temperature varied from 0.47 ˚C to 0.79 ˚C. The mean delta temperature in the control group varied from 0.47 ˚C to 0.73 ˚C.

The basal FHR was at each measurement point positively correlated with FST when calculated in the total material ($P \leq 0.006$). In the paracetamol group the basal

FHR was significantly higher than the control group at all times ($P \leq 0.047$) (Figure 17). In the paracetamol group there were significant increases in the basal FHR from T-60 to T-30 ($P=0.02$), T-30 to T0 ($P=0.02$) and from T-60 to T0 ($P=0.008$). After T0 there were no significant changes in basal FHR in the paracetamol group, neither in comparisons between T0 and other T times ($P \geq 0.2$) nor in stepwise comparisons ($P \geq 0.2$). In the control group there was a significant increase in the basal FHR from T-60 to T-30 ($P=0.045$) and from T-60 to T0 ($P=0.049$). For other comparisons there were no significant changes in the basal FHR, neither in comparisons between T0 and other T times ($P \geq 0.2$) nor in stepwise comparisons ($P \geq 0.3$).

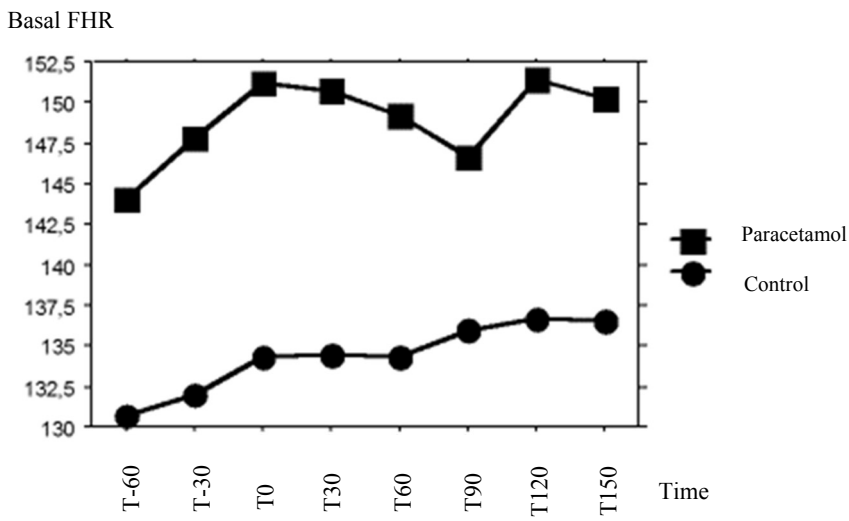

Figure 17
Basal fetal heart rate in case (paracetamol) and control groups.

Discussion

This research consists of four observational, prospective and experimental studies on fetal temperature in relation to maternal temperature in the human during labor and delivery, using a new technology.

In the first paper a fetal lamb model was used. None of the recordings failed, the technique was well functioning, and the method could be validated. Since the subcutaneous temperature mirrored the intracranial temperature well (with the intracranial temperature being higher), even in a situation of severe hypoxia, changes in subcutaneous temperature could be used to detect changes in fetal core temperature, although it is not possible to exactly judge on the fetal intracranial temperature from scalp temperature recordings.

In paper II-IV it was not the subcutaneous temperature but rather the intradermal temperature that was measured in fetuses, but it is reasonable to assume that the subcutaneous and intradermal temperatures are closely related. The pointed pin sensor is sharp and projects approximately 2 mm above the surface of the electrode. As I could observe, it actually penetrates the skin, but I have not inspected all of the subjects for appearance of the electrode-mark on the fetal head *post partum*, and there is a possibility that some of the fetal temperature recordings are actually a measurement from the surface of the skin. However it is unlikely to be a maternal or vaginal temperature, because the metal helix of the traditional electrode kept the pin of the temperature sensor in place, and if the electrode was not attached to the fetal head, the CTG and STAN registration did not work, and in that case a new electrode was applied.

It took in general up to 10 min for the experimental system to stabilize in the animal lamb model, and the same applied for the human model. The 10 min of stabilization was only seen at start-up of a measurement, and not if the registration had been paused and started again. In case of a vaginal examination a temporary slight decline in fetal scalp temperature was seen, but after the examination it took in general maximum a half minute for the fetal temperature to stabilize. No sources of false too high fetal or maternal temperature were detected.

As described, there was a problem with the hard drive memory at first. That lead to some unexpected interruptions of recordings and storage, and extra work for the specially instructed midwifes and myself. After the Milou™ computer was

upgraded there were no such problems, and recordings were securely saved without extra work. The electrodes used in the studies in this thesis are expensive, especially the manually mounted fetal scalp electrode. That is a problem if large studies, or even clinical use, are considered. A disadvantage with the method, as it was set up during the studies, was that there had to be both the CTG and STAN™ machine, and the Milou™ Temperature Monitoring System machine in the delivery room, beside the woman. The temperature sensors from the scalp electrode (that parted into the CTG/STAN electrode and the temperature sensor) and the maternal axilla, connected to the Milou™ instrument, meant more "cabling" around the woman. Less machinery and cabling would be desirable to do larger studies. Apart from these disadvantages, it is easy to use the equipment and data can simultaneously be analyzed both on-line and off-line.

Regarding continuous maternal temperature measurement, the axillary site was the least inconvenient for the women, but it was vitiated with a higher degree of variation and poor signal quality as women were sweating and moving around during labor and delivery. A rectal probe would probably result in better recordings and better represent the body core temperature, but also implicate more discomfort. Oral temperature measurements would give adequate intermittent information but not continuous data for offline parallel comparisons with fetal temperature.

The current research shows that the temperatures of the fetus and its mother increases during delivery. No rapid changes were seen though, and an intermittent control of the fetal temperature would be viable to assess the thermal development during delivery.

In the second paper we hypothesized that the fetal temperature may vary, possibly increase, during uterine contractions. The hypothesis was grounded on the fact that a great part of the fetomaternal heat transfer goes through the placental circulation (Rudelstorfer et al., 1986; Andrianakis et al., 1994), and uterine contractions can mean intermittent obstruction of the maternal placental circulation. We investigated the fetal scalp temperature before, during and after contractions but found no significant changes. This indicates that there is no rapid variation in placental cooling effect; an alternative explanation is that the scalp capillary blood circulation stagnates during uterine contractions due to pressure on the fetal head and that small and rapid temperature changes are then not reflected by scalp temperature monitoring.

With progression of labor, the fetal and maternal temperatures increased significantly. The mean increase in FST was 0.4 ˚C (from cervical dilatation 2-3 cm to full dilatation and retraction) and the corresponding mean MAT increase was 0.6 ˚C, thus, with progression of labor the temperature difference slightly narrowed. The fetal temperature was in all cases higher than the maternal.

Women with EDA had higher temperatures. This is in analogy with previous studies (Arendt et al., 2013; Segal S 2010; Curtin et al., 2015). Both FST and MAT curves directed upwards were steeper than in women without an EDA, and the resulting temperatures were higher. At full dilatation and retraction the mean FST was approximately 0.5 ˚C higher and the mean MAT 0.7-0.8 ˚C higher in women with EDA.

Nulliparae showed higher MAT than multiparae. This is in congruence with previous studies (Herbst et al., 1995; Marx et al., 1975). We constructed reference curves for maternal axillary skin temperatures in nulli- and multiparae without EDA. Reference curves for fetal temperatures were not constructed.

We found no evidence that oxytocin augmentation *per se* is associated with higher temperatures.

Researchers (Rudelstorfer et al., 1983; Rudelstorfer et al,. 1987) have earlier found associations between heat flux and the metabolic condition of the fetus. In our study no statistical relations could be found between FST and MAT, respectively, and umbilical cord artery pH, but there were too few cases of fetal acidemia in the series to analyze the association between fever and acidemia.

Fetal fever has not previously been defined. In this study 2.2% of the FST recordings were above 39.0 ˚C, 0.4% above 39.5 ˚C, and none above 40.0 ˚C in afebrile women (MAT <38.0 ˚C). The overall highest FST was 39.93 ˚C. In paper I we observed up to 1.5 ˚C difference between the higher intracranial temperature and the subcutaneous temperature, suggesting that the intracranial temperature might be up to 41.4 ˚C. Above 41.0 ˚C, fever could be dangerous by inducing denaturation of proteins (Chemistry Explained, 2017). Based on this a FST of 39.5 ˚C might then approach the upper limit of 41.0 ˚C for a “safe” fetal intracranial temperature. The susceptibility to both is hyperthermia and hypoxia is though individual and a certain upper safe fetal temperature limit in hypoxic fetuses can probably not be settled.

In the third paper we could conclude that inflammatory changes in the placenta, umbilical cord and chorioamniotic membranes are associated with higher fetal scalp and maternal axillary temperatures. Cases of inflammation were not so many, and to enable statistical calculation, different stages of inflammation were merged together in the respective groups. We made no attempt to demonstrate a critical temperature level for occurrence of placental inflammation because the overlap in temperatures between those with and those without inflammation was considerable.

Inflammation was also associated with a longer time of active labor and EDA, but in combination in a multiple logistic regression analysis we found that neither active labor nor EDA were alone independent determinants for development of

inflammation. The explanation is that women with EDA had a significantly longer time of active labor, i.e., it is not the EDA *per se* that increases the risk of placental inflammation but the time of active labor. This is in accordance with findings in other studies (Kim et al., 2015).

Chorioamnionitis is most often an ascending local inflammatory process, where the neutrophils first invade the maternal side and later the fetal side (Kim et al., 2015). This is in congruence with our findings, whereas there were a few more cases with inflammation on the maternal side (acute subchorionitis, chorionitis or chorioamnionitis).

Continuous temperature measurements were done, but we chose to use the temperature at 10 cm cervical dilatation to study the correlation inflammation-temperature because it takes a few hours for the neutrophil migration.

In the fourth paper we showed that the ongoing increases in fetal temperatures in febrile women in labor were halted by 1000 mg paracetamol (acetaminophen) orally. As a result of paracetamol medication the fetal temperatures stabilized, i.e. showed no further increases, but the temperatures did not drop. In the fetal control group the temperatures continued to increase, and therefore we concluded that paracetamol has an antipyretic effect on fetal temperature. Different statistical tests showed the same result.

We were surprised that the same statistical evaluations of maternal temperatures showed no unanimous results. Wilcoxon matched-pairs signed-ranks test showed patterns similar to the fetal temperatures, but trend analysis with the mixed-effects models, showed that in the paracetamol group there was no significant difference in the shapes of individual temperature curves in comparisons with temperature curves in the control group. This latter finding indicates that paracetamol had no effect on maternal temperatures in the paracetamol group.

Since it is biologically not feasible that paracetamol had an effect on fetal temperatures without affecting maternal temperatures, and the fetal-maternal delta temperatures did not change significantly over time in any group, the difference in statistical outcomes might be a consequence of the differences in observation time between the statistical tests and the fairly small number of paracetamol cases and controls. The possibility of a type II statistical error cannot be excluded and it remains an open question whether paracetamol can have an anti-pyretic effect in the fetus without affecting maternal temperature.

A prospective randomized placebo-controlled trial would more unambiguously than the present case-control study show the effectiveness of paracetamol in febrile parturients. However, randomizing febrile women to treatment with placebo is ethically questionable.

In the fourth paper we noted that the maternal ear temperature in general was higher than the axilla temperature. This explains why some women getting paracetamol had a fairly normal axilla temperature at the time they received paracetamol. Again, skin temperature is the least reliable compared to other measurement sites (Eyelade et al., 2011).

In summary the Milou^{TM} temperature measurement system functioned well and provided a reliable and fairly simple way to assess the fetal and maternal temperatures during labor. Precision of the system is enough to assess the temperatures. Fetal temperatures showed minimal oscillations until the bearing down phase of the second stage of labor and descent of the fetal head, when many recordings became unstable due to exposure of the scalp electrode to room air. Maternal recordings showed more fluctuations due to the measuring site we chose, with, not unexpectedly, the sweating and movements among women in labor.

Conclusions

I. In animal experiments using the new equipment to continuously measure temperature described in this thesis, the fetal forehead subcutaneous temperature mirrored the intracranial temperature closely, even during severe hypoxia. With increasing acidosis, the temperatures decreased.

The intracranial temperature was higher than the subcutaneous.

None of the 10 recordings failed.

II. During uterine contractions there was no significant variation in fetal scalp temperature.

Both fetal scalp temperature and maternal axillary temperature increased significantly during the progression of labor. The fetal temperature was in all cases higher than the corresponding maternal temperature.

The increases in fetal and maternal temperatures during labor were significantly greater in the presence of epidural analgesia.

Nulliparity was associated with higher temperatures. Reference values for maternal axillary temperature at different stages of cervical dilatation were created for nulli- and multiparae.

III. Inflammatory changes in the placenta, umbilical cord and chorioamniotic membranes were associated with higher fetal and maternal temperatures.

These inflammatory changes were also associated with a longer time of active labor and EDA, but neither active labor nor EDA were alone independent determinants for development of inflammation.

IV. The ongoing increases in fetal temperatures in febrile women in labor were halted by 1000 mg paracetamol (acetaminophen) orally, but the fetal temperatures did not decrease after paracetamol. Paracetamol stabilized the fetal temperatures, i.e. they did not increase further. Since in the control group the fetal temperatures increased with advancing time of labor, the findings indicate an antipyretic effect of paracetamol even though the temperatures did not fall.

The effect of paracetamol on maternal temperature was inconclusive.

Reflections for future work

The maternal continuous temperature recordings in this thesis were done axillary, in the armpit, because it was the most convenient site. However, due to sweating and movements the recordings showed a relatively high degree of poor signal quality. In future research other sites for maternal measurement should be considered for better recordings and better representation of the body core temperature. Intermittent maternal temperature measurements, e.g. oral or rectal, could be considered. That would give adequate intermittent information, but not continuous data for offline parallel comparisons with fetal temperature.

For continuous fetal measurements the specially produced scalp electrode was used, as described above. The technique is fairly simple and of no additional inconvenience for the delivering woman. Nonetheless it meant another machine in the room, i.e. the Milou™ Temperature Monitoring System instrument, which had to be placed beside and linked to the STAN™ apparatus. The high cost of the manually mounted scalp electrode thermosensor is a limitation for clinical use. Less expensive "temperature/CTG-electrodes" and a development of a machine that could register all of the information would enable much bigger studies of temperature.

All women included in this thesis were monitored with ECG ST interval analysis, together with CTG and temperatures. A study of this material to see if the ECG ST interval analysis "signals" differently in different temperature levels and fever could give a better understanding of the ECG ST interval analysis method.

Further research on the effects of paracetamol (acetaminophen) on fetal and maternal temperatures would be of importance to further survey the relationship. In study IV we observed that paracetamol halted an increasing trend among fetuses to 18 mothers with fever during labor. That is a fairly small series, and the statistics were not unanimous regarding the maternal axillary temperatures. A bigger case-control study could provide further knowledge on the effects of paracetamol on fetal and maternal temperatures. Furthermore, a prospective randomized placebo-controlled trial would more unambiguously show the effectiveness of paracetamol in febrile parturients. However, randomizing febrile women to treatment with placebo is ethically doubtful, but might be feasible in cases of slight maternal temperature elevations and for a short time of withholding active treatment, and in absence of fetal distress.

Statistical calculations on the hole material in this thesis concerning associations between fetal temperature in the end of delivery and acid-base status in the umbilical cord showed a significant association, but no association between maternal temperature and acid-base status was found. Another maternal measuring site with less artifacts than the axilla, could possibly show associations between umbilical acid-base status and maternal intrapartum temperature. Further research on fetal temperature and associations to umbilical blood pH could lead to a development of a new way to assess the metabolic condition of the fetus intrapartum.

Intrauterine infection/inflammation is a risk factor for neonatal complications including periventricular leukomalacia which is associated with the subsequent development of impaired neurological outcomes of variable severity and cerebral palsy. An activation of the cytokine network is involved. Blood samples from vena umbilicalis have been taken after delivery in the women included in the current studies. The blood samples, intended for cytokine analysis, are frozen and storaged at Clinical Research Center in Malmö, Sweden. Future studies could be done on this material to examine the relations between fetal and maternal intrapartum temperature and concentrations of the most important cytokines.

During the temperature studies we identified women with fever and women with relatively low temperature in labor, and collected a specimen from the placenta and a blood sample from vena umbilicalis in those women. Both placenta sample and blood sample were rapidly frozen to minus 80 ˚C. The material is still frozen to date and enables future study on gene expression.

The room temperature was measured regularly and noted in the temperature studies. Even modest differences may have impact on the maternal and fetal temperatures. Future studies, on the current material or new studies, could provide further knowledge on this.

We did not examine the roll of C-reactive protein (CRP) or bacterial cultures in the studies in this thesis. Research on associations between fetal temperature, and CRP and bacterial cultures could allow us to gain further valuable knowledge.

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Continuous Intrapartum Maternal and Fetal Temperature Monitoring

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III. Relations between intrapartum maternal and fetal temperatures and placental inflammation
IV. Effects on fetal and maternal temperatures of paracetamol administration during labour: a case–control study

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