QUALITY AND SAFETY IN CHILDBIRTH

THE ROLE OF ADVANCED GESTATIONAL AGE AND FETAL ACIDOSIS

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BY
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PhD Thesis 2024

AALBORG UNIVERSITY
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PREFACE AND ACKNOWLEDGEMENT

This thesis has been conducted over the past 6 years while I have been a PhD student at Danish Centre for Health Services Research at Aalborg University and employed as a consultant at Department of Gynaecology and Obstetrics at Aalborg University Hospital in Thisted.

The inspiration to this PhD came from my clinical work and my work with quality improvement and clinical guidelines in obstetrics.

I would like to thank my supervisors; Søren Paaske Johnsen for inspiring and encouraging me to do this PhD. Thank you for letting me be a part of "the DACS family" and letting me join you from the first day at the small office in "Søster Kathinkas hus" to a big and upcoming organization with great impact on research in Denmark. Thank you for your supervision, support - it has been a pleasure; Jesper Padkaer Petersen for your dedicated supervision and for introducing me to neonatology, Ulrik Schiøler Kesmodel for obstetrical supervision and always giving prompt answers to all my questions. Thank you Line Thellesen for being a very wise obstetrician, it has been a great support. We have been a great team and I am so grateful for your supervision and your dedicated work with designing and interpreting the studies and our work with the manuscripts. Thank you, Martin Jensen for helping me with the data management and Jan Valentin, for good company in the office and for statistical help and supervision and to Claus Klingenberg for your dedicated participation in the study on acidosis from birth.

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Thank you to the Elsaas Foundation, the Dagmar Marshalls Foundation at to Carsten Lenstrups foundation for funding.

Finally, I wish to thank my family, especially Torben, for always believing in me and for encouraging me to seek new challenges.

Charlotte Brix Andersson, april 2024,

DANSK RESUME

I Danmark er sikkerheden omkring fødsler høj og der arbejdes hele tiden med at forbedre denne. Studierne i denne afhandling bidrager til den øvrige løbende forskning på området.
Andelen af nyfødte der fødes med svær iltmangel i Danmark, er lav, lige omkring 0,5%. Iltmangel vurderes ved måling af pH i navlesnorsblod (NS-pH) lige efter fødslen. I Danmark anbefales det, at NS-pH måles ved alle fødsler og værdien registreres i Landspatientregisteret. Det er vigtigt at vide, om der har været iltmangel under fødslen, da iltmangel kan føre til alvorlige komplikationer hos børnene både umiddelbart efter fødslen og på lang sigt.
Vi ved, at risikoen for komplikationer for barnet og moderen stiger, hvis graviditeten går over terminen og at der er en stejl stigning efter graviditetsuge 42+0. Derfor anbefales det i Danmark, at alle gravide har født inden uge 42+0. Tidspunktet for igangsættelse i uge 41 er omdiskuteret og flere steder i verden er tidspunktet for anbefalet igangsættelse blevet ændret til uge 41+0.

I det første studie i denne ph.d. evaluerede vi implementeringen af rutinemæssig måling af NS-pH ved alle fødsler. Vores resultat viste, at det tog 3-4 år at implementere rutinemæssig NS-pH måling i Danmark og at der efter implementeringen blev målt to pH-er (som anbefalet, en fra venen og en fra arterien) i 77-83% af fødsler og mindst en NS-pH i 95-96% af alle fødsler. De situationer hvor der ikke blev målt pH, var overvejende helt ukomplicerede fødsler og i meget sjældne situationer, hvor barnet var svært påvirket ved fødslen.

I det andet studie undersøgte vi sammenhængen mellem lav NS-pH og neonatale komplikationer. De primære udkomme var et kompositmål bestående af neonatal død, respiratorbehandling, kølebehandling, behandling med inhaleret Nitrogen Oxid eller kramper. Som ventet viste studiet, at risikoen var højest hvis pH var under 7.0, men vi fandt også en øget risiko ved pH under 7.10 og en let øget risiko ved pH under 7.20. Studiet er vigtigt, når man skal fastsætte en tærskel for øget observation og behandling ved lav NS-pH.

I det tredje studie undersøgte vi risikoen for komplikationer for mor og barn ved fødsler i de første dage sammenlignet med de sidste dage i graviditetsuge 41. Da igangsættelse af fødslen påvirker denne risiko justerede vi for igangsættelse. Vi fandt, at risikoen for alvorlige komplikationer hos børnene var sjældne, men øget i de sidste dage at uge 41. Der var desuden en øget risiko for fødselskomplikationer (feber, tegn til påvirket barn ved fosterovervågningen, skulder dystoci, instrumentel

forløsning eller kejsersnit) samt en øget risiko maternelle komplikationer (svær blødning og svære bristninger) ved fødsler i de sidste dage af uge 41.

I studie IV undersøgte vi reproducerbarheden af resultater fra et randomiseret studie (The Swedish Post-term Induction Study (SWEPIS)) ud fra en stikprøve dannet ved sampling fra observationelle data (Rejection sampling). Det randomiserede studie sammenligner igangsættelse uge 41+0 med afventende holdning.
Vi fandt, at det var muligt at reproducere stort set alle resultater fra det randomiserede studie bortset fra resultaterne for perinatal død, der var højere end forventet i det randomiserede studie. Vi sammenlignede metoden med analyser baseret på propensity score og konstaterede, at resultaterne var sammenlignelige.

ENGLISH SUMMERY

The level of safety in childbirth in Denmark is high. There is an ongoing work to improve safety and this thesis is a supplement to this work.
Severe fetal hypoxia is seldom in Denmark (0.5%). It is important to know if the newborn infant has suffered from hypoxia during birth, as hypoxia may cause severe complications in the neonatal period and later in childhood. Umbilical pH (UC-pH), reveals if hypoxia is present. Since 2011 it has been recommended that UC-pH is measured in all births in Denmark.
It is known from previous studies that the risk of birth-related complications for infant and mother increases when the pregnancy continues beyond term, with a steep increase after gestational age (GA) 42+0 weeks. Because of this increased risk, induction of labour is recommended before GA 42+0 in most settings. The exact time of induction of labour in gestational week (GW) 41 is a matter of controversy, but lately the recommendation has changed in many settings to induction of labour in GA 41+0 weeks.

In Study 1 we evaluated the implementation of universal measurement of UC-pH in Denmark. The study showed that the implementation of universal UC-pH lasted 3 to 4 years before a plateau was reached at 77-83% for the recommended measurement of both umbilical cord artery and vein, and 95-96% for at least one pH measurement. Cases with missing UC-pH were primarily uncomplicated births and cases where the child was severely ill.

In Study II we investigated the association between UC-pH and neonatal complications. The primary outcome was a composite measure including neonatal death, therapeutic hypothermia, mechanical ventilation, treatment with inhaled Nitric Oxide or seizures. The results showed that compared to a UC-pH >7.20, the risk was highest in cases with UC-pH <7.00. We also found an increased risk among infants with UC-pH between 7.00 and 7.09 and, to a lesser extent, in the group with UC-pH between 7.10 and 7.20. The study is important when trying to decide on a threshold for observation and treatment in cases with low UC-pH.

In Study III we investigated the risk of complications in the first days of GW 41 compared to the last days of GW 41. Because induction of labour influences the occurrence of complications, we adjusted for induction of labour in the multivariate analysis. The results showed that neonatal complications were seldom but increased in the last days compared to the first days of GW 41. Concerning birth-related and maternal complications, we saw an increased risk of complications during birth (fever, operative vaginal birth, emergency Caesarean Section, signs of fetal distress and shoulder dystocia) and risk of post-partum haemorrhage and severe perineal

lacerations. Results from the study support previous knowledge and contributes to decide when to induce labour in late term pregnancies.

In Study IV we evaluated the reproducibility of results from a randomized trial using rejection sampling (RS) from observational data. The randomized trial was The Swedish Post-term Induction Study (SWEPIS) in which induction of labour in GA 41+0 week was compared to expectant management. The current study showed comparable results for most outcomes except perinatal death, which was unexpectedly high in the expectant management group. We compared the RS method to analysis based on propensity score and found similar results.

LIST OF STUDIES

Study I

Implementation of universal umbilical cord pH analysis in Denmark. A national register-based study
Charlotte Brix Andersson, Line Thellesen, Ulrik Schiøler Kesmodel, Jesper Padkaer Petersen, Søren Paaske Johnsen.

Published in Acta Obstetricia et Gynecologica Scandinavica Juli 2023

Study II

Association between umbilical cord pH levels and neonatal morbidity and mortality: A nationwide cohort study of infants born in Denmark 2012-2018.
Charlotte Brix Andersson, Claus Klingenberg, Line Thellesen, Søren Paaske Johnsen, Ulrik Schiøler Kesmodel, Jesper Padkaer Petersen.

Submitted to JAMA Network open, March 2024

Study III

Risk of complications in the late versus early days of the 42nd week of pregnancy: A nationwide cohort study
Charlotte Brix Andersson, Jesper Padkaer Petersen, Søren Paaske Johnsen, Martin Jensen, Ulrik Schiøler Kesmodel.

Published in Acta Obstetricia et Gynecologica Scandinavica, February 2022

Study IV

Reproducibility of a Labor Induction Strategy Comparison: A Nationwide Observational Study using Rejection Sampling
Charlotte Brix Andersson, Søren Paaske Johnsen, Line Thellesen, Jesper Padkaer Petersen, Ulrik Schiøler Kesmodel, Jan Brink Valentin

In progress

ABBREVIATIONS

CPAP	Continuous positive airway pressure
CPR	Personal identification number (Central Person Register)
CS	Cesarean section
CVC	Central venous catheter
DCRS	The Danish Civil Registration System
DNPR	The Danish National Patient Registry
GA	Gestational age
GDM	Gestational diabetes mellitus
GW	Gestational week
HR	Hazard ratio
IDDM	Insulin dependent diabetes mellitus
iNO	Inhaled Nitric oxide.
IQR	Interquartile range
LGA	Large for gestational age
NICU	Neonatal Intensive Care Unit
PS	Propensity score
RSA	Rejection sampling
SBE	Standard base excess
SGA	Small for gestational age
UCBA	Umbilical cord blood gas analysis
UC-pH	Umbilical cord pH

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CHAPTER 1. INTRODUCTION

According to World Health Organization (WHO), quality in health care must be effective, timely, based on evidence, safe (minimize risk and harm, including avoiding preventable injuries and reducing medical errors), people-centred, equitable, integrated, and cost-effective.[1]
This thesis focuses on the safety element, recognizing and preventing adverse outcomes in the newborn infant and the labouring woman.

The subjects of the thesis are presented in detail in studies comprising an evaluation of the validity of universal measuring of umbilical cord PH (UC-pH) as a test for compromised oxygen support to the fetus (hypoxia) during birth, an estimation on the risk of adverse fetal outcomes from hypoxia and the risk of adverse infant and maternal outcomes in late term births (gestational age (GA) 41+0–41+6), and an evaluation of the reproducibility of results from a randomized trial using rejection sampling (RS) from observational data.
Umbilical cord pH is an objective measure of hypoxia during birth. Hypoxia leads to an accumulation of acid in the fetal tissue (acidosis) and blood (acidemia) and can be detected in a blood sample from the umbilical cord (umbilical cord blood gas analysis (UCBA)). A UCBA reveals if acidemia is present as well as the source of the acidemia.
It is important to know if acidemia is present in non-vigorous infants to evaluate whether hypoxia is a contributing factor, and in vigorous infants as these infants might develop symptoms within the first hours of life.[2] Cases with low umbilical cord PH (UC-pH) undergo local perinatal audits supporting the interpretation of fetal surveillance and the risk of complications associated with labour and birth.
In 2009, the recommendation on UC-pH measuring in Denmark changed from selective measuring according to local recommendations, to a national recommendation to measure UC-pH in all cases.[3] Before 2009, the proportion of births where UC-pH was measured differed between delivery wards from no measured UC-pH to UC-pH measured in 77-83% of births. In some departments, UC-pH was measured in cases with non-reassuring fetal monitoring and/or in cases with a suspected increased risk of hypoxia.
Universal measuring of umbilical cord blood gas (UCBA) offers a unique opportunity to investigate the association between levels of acidemia and adverse fetal outcomes in the neonatal period and in the long run. Knowing the risk of adverse outcomes associated with acidemia makes it possible to evaluate the threshold for intensive observation or treatment.
Nationally and internationally obstetricians and midwives have focused on the risk of adverse maternal and infant outcomes in late term and post term pregnancies. Evidence of an increasing risk of infant mortality and morbidity with increasing GA

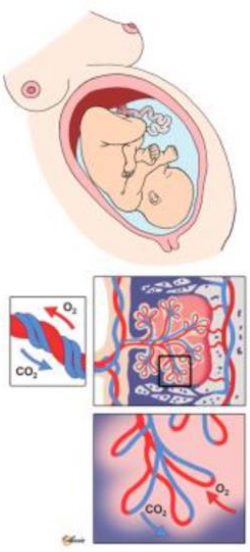
from gestational week (GW) 39/40 and a steep increase after GA 42+0 weeks paved the way for a change in recommendations in Denmark in 2011. This meant a change from induction of labor at GA 42+0 weeks to induction in GA 41+3–41+5 weeks with the intension that births should not take place after GA 42+0 weeks.[3-5] During the last few years, recommendations in many countries have changed towards offering induction of labour at GA 41+0 weeks and this has been the recommendation from WHO since 2018.[6-9]

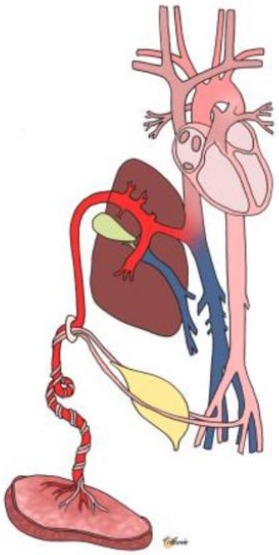
Time of induction of labor in uncomplicated late term pregnancies has been a matter of debate in Denmark. To qualify this debate, it is necessary to know the change in the risk of adverse outcomes for the mother and the infant during GW 41, and to know the advantages and risks of adverse outcomes from induction of labour in uncomplicated pregnancies at GA 41+0. The latter has been investigated in several randomized trials and observational studies. Limitations in the randomized trials primarily concern the lack of statistical strength to estimate the risk of rare complications. The risk of confounding from the indication for induction of labour is challenging in observational studies.[5, 10-12]

1.1 FETAL HYPOXIA

In the fetal circulation, vital organs in need of the most oxygenated blood (heart, brain, liver, and adrenal glands) are prioritized and the lungs are bypassed since the gas exchange takes place in the placenta. Oxygenated blood from the placenta reaches the fetus via the umbilical cord vein, and deoxygenated blood returns to the placenta via the umbilical cord arteries.

Figure 1: Fetal and placental circulation. Oxygenated blood from the placenta reaches the fetus via the umbilical cord vein, and deoxygenated blood returns to the placenta via the umbilical cord arteries. Shunts secure that oxygenated blood reaches vital organs and that the lungs are bypassed. With permission from Lotte Clevin (Copyright)





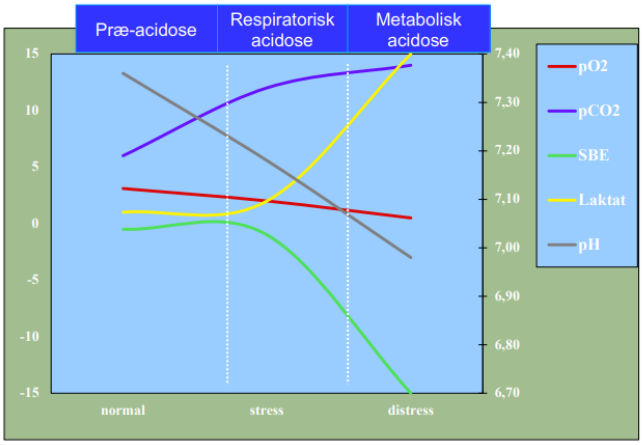
Compromised oxygen supply to the fetus, or hypoxia, is seen in different clinical situations such as uterine tachysystole, acute obstetric situations with compromised circulation in the umbilical cord, or with compromised or abrupted oxygen diffusion across the placental membranes as seen in fetal vascular malperfusion.[13-15]
A fetus with good resources has a battery of well-developed defence mechanisms against hypoxia; the high fetal haemoglobin concentration has a high affinity to oxygen and the fetus is able to optimize the shunting of oxygenated blood to vital organs.[16] If oxygen supply to the fetus is already compromised during pregnancy, as in placental insufficiency, the superimposed stress from hypoxia during birth is more likely to result in severe hypoxia, leading to tissue damage.[17]
If the oxygen supply is compromised, the metabolism in the fetal tissue shifts from aerobic to anaerobic, which results in an accumulation of lactic acid (lactate) in the fetal tissue leading to metabolic acidosis. Moreover, a compromised circulation between the placenta and the fetus, as in tachysystole, leads to an accumulation of carbon dioxide in the blood, which adds to the acidemia (respiratory acidosis). Hence, a decrease in pH in the fetal blood can be of metabolic or respiratory origin, or often a mixture of the two. Respiratory acidemia resolves when the child starts breathing or after ventilation if breathing is not spontaneous. Metabolic acidosis takes longer to develop, recovery is longer, and it may potentially cause permanent harm to vital organs.[16]
Lack of oxygen supply and accumulation of lactate in the brain may cause serious damage leading to hypoxic-ischemic encephalopathy with possible severe neurological impairment (cerebral palsy) or death.[18,19] The initial phase of brain

injury occurs during and immediately after birth. Resuscitation of the neonate then leads to apparent stabilization during the first few hours of life; however, a second wave of injury, which occurs 6-15 hours after birth and is triggered by a cascade of events, may lead to delayed neuronal loss.[2,18,20]
Besides resuscitation and respiratory support, the only effective treatment to reduce adverse neurological outcomes following hypoxia is therapeutic hypothermia initiated within 6 hours after birth. This is to reduce or prevent the second wave of injury to the brain.[21-23]
The most significant clinical effect of acidosis is probably related to cardiac function. Severe acidemia causes decreased myocardial contractility and diminished cardiac output, which may contribute to lack of oxygen supply to the fetal brain.[24,25]

1.2 UMBILICAL CORD BLOOD ANALYSIS

Umbilical cord blood analysis (UCBA) consists of pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), bicarbonate (HCO^-_3), lactate and standard base excess (SBE) in the umbilical artery and vein.
UC-PH reveals if, or at which level, acidemia is present. PCO_2, HCO^-_3, lactate and SBE indicate whether the acidosis is respiratory or metabolic. (Figure 2)

Figure 2: The association between individual components from UCBA are used to determine whether acidemia is of respiratory or metabolic origin.
With Permission from Thomas Bergholt and Jan Stener Jørgensen.



Cord blood is relatively easy to sample but there are pitfalls in sampling and interpretation of the results; there is a risk of falsely abnormal values if the blood

sampling or analysis are delayed; SBE is calculated by an algorithm and results depend on the fetal compartment of assessment and lactate changes with GA.[16,26,27] Also, PH is not an ideal parameter for estimating the cumulative exposure to lack of oxygen since pH is a logarithmic term and does not give a linear measure of the accumulation of acid in the blood. A change in hydrogen ion concentration associated with a fall in pH from 7.0 to 6.9 is almost twice the change associated with a fall in pH from 7.3 to 7.2.[15]
UC-pH and lactate are both shown to be good predictors of neonatal adverse outcome.[28,29]

1.3 VALIDATING PAIRED UMBILICAL CORD BLOOD GAS SAMPLES

Reference values and thresholds used for acidemia are almost always based on UCBA from the umbilical artery. Reference values for umbilical cord venous blood have been investigated, but venous blood comes from the placenta after clearance of a surplus carbon dioxide, which overestimates the metabolic component of fetal acidosis.[16]
To ensure a sample from the umbilical artery, blood is sampled from both the umbilical artery and vein. Different criteria have been used to define if the two samples are from two different vessels. Most criteria are based on differences in pH and pCO2.The original criterion from Westgate et al. (1994) was based on a difference in pH $\geq$ 0.02 and a difference in pCO2 $\geq$ 3.8 mmHg. More recent criteria from Kro (Kro Criteria 2010) included a GA-adjusted criterion for difference in pH and a criterion for pCO2 based on a difference of $\geq$5.25 mmHg and a venous pCO2 >21.75 mmHg.[30,31] Others have argued that a less tight criterion (pH $\geq$ 0.01 and pCO2 $\geq$3.4 mmHg) does not increase the rate of a false-positive diagnosis of acidemia and provides more “valid” data to clinicians in neonates with clinical signs of hypoxia.[32]
A study by White et al. found that using a “minimal” criterion (pH, pCO2, and an indicator of acidemia (lactate or BE) available from one vessel) diagnosed more non-vigorous neonates with abnormal UCBA. They concluded that if paired cord blood samples are not available in non-vigorous neonates, use of UCBA from a single vessel is sufficient since it does not increase the number of false positives.[32]
In the Danish recommendations, the criterion for valid pH is pH measured from two different vessels with a difference in pH $\geq$0.02. [33]

1.4 UNIVERSAL OR SELECTIVE UMBILICAL CORD BLOOD GAS ANALYSIS

There is an ongoing debate whether UCBA should be measured selectively or universally. In settings with a selective approach, UCBA is often restricted to cases with suspected hypoxia during birth or to high-risk pregnancies.
On the individual level, the benefits from UCBA are to know if metabolic or respiratory acidemia is present and to which extent. This may guide the clinicians in the observation and treatment of the infant. Knowing UCBA may also be beneficial if the child shows signs of neurological impairment later in life. In combination with other clinical information, UCBA can usually provide a robust defence in infants with a suspected intrapartum hypoxic event.[15]
On an organisational level, universal UCBA has more than one advantage; UCBA is an important measure of quality in maternity care and data can be compared over time and between maternity wards at regional and national level; introducing universal UCBA is shown to increase the sampling experience among delivery staff and hereby increase the chance of successful sampling in infants in high-risk births and in acute obstetric situations; knowing UCBA in non-vigorous and in vigorous cases and evaluation of all cases with acidemia are important for educational reasons and is shown to reduce the incidence of acidemia over time.[34-37]
Cost-effectiveness analyses have shown that changing the recommendation from selective to universal UCBA reduces costs due to fewer admissions to special care units.[38]
Arguments against universal UC-pH measurement are that the test is not clinically relevant and has a low sensitivity in low-risk pregnancies and vigorous infants. Moreover, that it is important to avoid medical procedures with no clear clinical indication.[39-41]
Since 2009, the recommendation in Denmark has been universal UCBA.[33] UC-pH, but not the other components in the UCBA, is registered centrally in the Danish National Patient Registry (DNPR).

1.5 TRESHOLD FOR PATOLOGICAL ACIDEMIA

There is no global consensus on definitions of normal pH, cord blood gases or lactate, and different threshold values for abnormality have been used.
It is not relevant to define severe acidemia statistically using deviation from the normal population values since acidosis is generally tolerated by the fetus without sequelae until acidosis becomes very severe. It is more clinically relevant to define the threshold for severe or pathological acidemia, as the threshold at which the incidence of adverse clinical outcomes starts to correlate strongly.
Based on previous studies, the most common cut-off for severe or pathological acidemia is pH <7.00.[15, 20, 42-46] This threshold is based on older studies on the risk of

adverse outcomes at different levels of acidemia. However, these studies are small and based on a selected proportion of a total cohort.
More recent studies have shown that the risk of adverse outcomes increase significantly at 7.10 to 7.12 and have suggested that the threshold should be reconsidered.[19,47] It has also been suggested that the threshold should be individualized using known risk factors, similar to the screening for Down's syndrome.[19] This was supported by the risk of encephalopathy being markedly increased if acidosis was combined with other risk factors. This is exemplified by the marked increase in risk of encephalopathy if acidosis and chorioamnionitis are present at the same time.[48,49]

1.6 THE ACIDOTIC PARADOX

When trying to estimate the association between hypoxia and the risk of adverse outcome we assume that hypoxia leads to tissue acidosis leading to acidemia and that acidemia correlates with the risk of adverse outcome. A prerequisite for this is that acidemia reflects the level of acidosis in the tissue, and that acidemia is harmful for the fetus. These two assumptions might not be correct.
First, not all fetuses with tissue acidosis have acidemia. Some fetuses may produce acid in the tissues without developing circulating acidemia. This is seen in mild acidosis and in complete circulatory arrest where acid may accumulate in the tissues and not enter the blood stream until after resuscitation and restoring of the circulation.[25]
Second, mild or moderate acidemia might not be harmful or might even be beneficial for the fetus. A fetus with hypoxia may establish a mild or moderate acidemia that facilitates certain beneficial processes. Failure to establish this 'beneficial acidemia' might cause the fetus to be at increased risk of adverse outcomes.[25] There are many possible mechanisms in 'beneficial acidemia'. Previous human and animal studies have suggested that metabolic acidemia causes an increase in cerebral blood flow, reduces brain hypoxia and that acidemia lowers the need of oxygen in the brain by reducing non-essential activity. Moreover, the infant has an ability to use lactic acid as an alternative fuel for brain metabolism.[50-53]
The acidotic paradox describes the situation with hypoxic brain injury without coincident acidemia. The paradox explains why infants with encephalopathy often has a UC-pH >7.00 and the theory is that these infants might still have been hypoxic but were unable to develop acidemia as a response.[19,25]

1.7 SHORT- AND LONG-TERM OUTCOME ASSOCIATED WITH ACIDEMIA

1.7.1 Short-time adverse outcome associated with acidemia

The risk of neonatal complications associated with acidemia in term infants have been investigated in several studies. An overview of studies within the last 30 years is included in the appendix of the thesis. (Table S1)
The studies are all prospective observational studies based on cases with acidemia, either as a simple exposure or with acidemia as part of a combined exposure. The studies vary according to definition of acidemia, stratifications, comparisons, and outcomes. All studies in Table S1 included term births but some also included preterm births and some studies excluded births with GA >40+6 weeks. [54-75]
The most common exposure was UC-pH <7.00 but exposure ranged between 6.90 and 7.20. Outcomes differed but most studies reported on Apgar score, admission to NICU, encephalopathy/seizures and neonatal death.
The association between acidemia and adverse neonatal outcomes is complex. The risk of adverse neonatal outcome is increased if the fetus is more fragile e.g., in connection with placental insufficiency, maternal medical diseases such as diabetes or in case of intrapartum fever. [54,76-78] The risk of adverse neonatal outcome is also increased in cases with acute obstetric situations such as uterine rupture or shoulder dystocia. In these situations, the risk of hypoxia is also increased.[54]
Different approaches have been used to overcome the risk of bias in the association between acidemia and adverse neonatal outcome. Some study populations only included those with a low risk of acidosis and neonatal adverse outcomes (non-anomalous infants born by planned Caesarean section (CS), without general anaesthesia), others excluded infants born to women with an increased risk (preeclampsia, GA >41+0 weeks), infants born from complicated births (meconium stained or bloody amniotic fluid, chorioamnionitis, uterine rupture) or infants who are small for gestational age (SGA). In other studies, the populations were restricted to infants with a 5-minute Apgar score <7 or admission to a NICU. [40,41,63-68, 70,71]
In most studies, only the crude results were reported but in one study they reported results from multivariate analyses with adjustment for parity, maternal age, maternal race/ethnicity, insurance type, chronic hypertension, GDM, and preeclampsia. In another study, results were adjusted for maternal obesity and time from anaesthesia to birth. [66,68]
The primary limitation in these studies is lack of strength. This is mainly because of the low incidence of severe acidemia and the low incidence of adverse neonatal outcomes but also the selective approach to UCBA measuring in most settings. The proportion of births with measured UC-pH in existing studies ranged from 40% to 90%.[72,73]
In settings with a low proportion of measured UCBA, the policy was selective measuring of UCBA, which means that UCBA is measured in cases with high risk

of acidemia and high risk of adverse neonatal outcomes. This might have overestimated the occurrence of acidosis and adverse outcomes.
Acidemia is a proxy for acidosis but acidemia is not always present in cases with tissue acidosis. (See section on the acidotic paradox). This means that the studies did not capture all cases with tissue acidosis. Unfortunately, it is not possible to measure tissue acidosis, and the best alternative is to measure the UCBA. Measurement of the pH, lactate, and blood gasses in fetal blood in the first hours after births might be a better alternative for predicting adverse outcome, but this is not an acceptable alternative in non-vigorous infants with normal UCBA.[15,65]
In studies which only included the pH in the exposure it was not possible to distinguish between respiratory and metabolic acidosis. Hence, a part of the included infants with acidemia would not be at increased risk of an adverse neonatal outcome since the respiratory acidosis will resolve after the first breath.[16]

Results from selected studies are shown in Table 1. Selection was based on the population size, publishing year and relevance to the results in the study on acidemia included in this thesis.
Results from the studies are difficult to interpret since they are reported as absolute risks (with or without p values), OR, or RR, and either as below versus above a UC-pH level or in UC-pH intervals.
From results in Table 1 it seems that the risk of a 5-minute Apgar score <7 and admission to a NICU was increased if UC-pH was below 7.20 and the risk of seizures and respiratory distress was increased if UC-pH was below 7.10.
Bligard et al found that the risk of the composite measure including neonatal death, encephalopathy, therapeutic hypothermia, seizures, intubation, and respiratory distress was doubled if UC-pH was below 7.20 compared to UC-pH ≥7.20.[68] Gonen et al (2023) found that among low-risk births, the risk of the composite outcome consisting of neonatal sepsis, necrotizing enterocolitis, phototherapy, blood transfusion, neurological morbidity, or respiratory morbidity was increased at UC-pH <7.10 compared to UC-pH >7.15 (7.1% vs. 1.2%).[40]

Table 1 Association between UC-pH and adverse neonatal outcomes.

Author Year	n	Respiratory distress	5-minute Apgar score <7	Admission to NICU	Seizures	Neonatal death
<7.00						
Sabol et al. 2016[66]	133	7.6% vs.1.1% (p<0.001)		28.9% vs.4.4 % (p<0.001)		
Morgan et al. 2015[54]	1265	14% vs. 0.4% (p<0.001) RR 38 (33–44)			6.0% vs. 0.1% (p<0.001) RR 60 (47–77)	2.0% vs. 0.01% (p<0.001) RR 127 (80–243)
Yeh et al. 2012[19]	1112		RR 49.1 (34.0–70.8)	RR 6.4 (5.7–7.1)	RR 16.9 (8.5–32.5)	
Lavrijsen et al. 2005[74]	95		OR 0.9 (0.7–1.2)		12% vs. 1% OR 2.9 (0.6–15.1)	2 % vs. 0%
<7.05						
Yeh et al. 2012[19]	1364		7.01-7.05 RR 11.7 (7.5–18.3)	7.01-7.05: RR 1.6 (1.4–1.9)	7.01-7.05: RR 5.2 (2.2–12.3)	
<7.10						
Gonen et al.2023[40]	14		14.3% vs. 0.1% (p=0.95)		0 vs. 0.05	
Gonen et al. 2019[41]	17	2.8% vs. 4.9%	8.3% vs. 0.4% (p<0.001)		2.8% vs. 0.3% (p=0.1)	
Sabol et al. 2016[66]	906	4.7% vs. 1.0% (p<0.05)			11.4% vs 4.3% (p<0.05)	
Yeh et al. 2012[19]	3070		7.06-7.10: RR 7.0 (4.6–10.6)	7.06-7.10 RR 1.70 (1.5–1.9)	7.06-7.10 RR 2.6 (1.1–6.0)	
<7.15						
Gonen et al. 2023[40]	39		7.7% vs.0.06% (p<0.001)		0.05% vs.0% (p=0.89)	None
Gonen et al. 2019 [41]	70	1.3% vs. 5.0%	8.3% vs. 0.4% (p<0.001)		1.3% vs. 0.3% (p=0.89)	
Yeh et al. 2012[19]	5625		7.11-7.15: RR 3.9 (2.6–5.9)	7.11-7.15: RR 1.4 (1.3–1.6)	7.11-7.15: RR 1.9 (0.9–4.1)	
<7.20						
Bligard et al. 2022[68]	252	4.4% vs.7.4% RR 2.0 (1.4–2.8)	5.2% vs. 1.2% (p<0.01)	1.6% vs. 0.8% (p=0.19)	0.4% vs. 0.1% RR 3.63 (0.33–38.6)	None
Yeh et al. 2012[19]	10 107		7.16-7.20: RR 2.6 (1.7–3.9)	7.16-7.20: RR 1.2 (1.1–1.3)	7.16-7.20: RR 1.4 (0.7–3.0)	

Data are in %, OR/RR (95%CI) and p-value are indicated when available.

Bligard et al. Comparison: UC-pH ≥7.20.

Sabol et al: Neonates with 5-minute Apgar scores of 7. Comparison: UC-pH >7.00 and UC-pH >7.10

Morgan et al: Acidemia definition: UC-pH <7.00 and SBE >12 mmol/L. Comparison: UC-pH ≥7.00 and SBE <12 mmol/L

Yeh et al: Comparison: UC-pH 7.26-7.30. N calculated from cases admitted to NICU. Seizures: All encephalopathy with seizures.

Lavrijsen et al: Comparison: UC-pH >7.15.

Heller et al: Comparison: UC-pH >7.20

Gonen et al. (2023): Low risk births. Comparison: UC-pH >7.15.

Gonen et al. (2019): Only planned CS. Comparison: UC- >7.15.

1.7.2 Long-time adverse outcome associated with acidemia

The association between acidemia and long-term outcome has been investigated in several studies. These studies, like studies on short-term outcomes, are difficult to compare because of different definitions of exposure, stratification, comparison, and outcomes.

Acidemia and mortality after one year:
Myrhaug et al. (2023) did a systematic review on the association between UC-pH and mortality among children born at term.[79] The review included 10 studies investigating the association between acidemia and mortality, but only four studies reported mortality after one year follow-up. These four studies were included in a meta-analysis (357 cases with acidemia).[75,76,80,81] Results from the meta-analysis were uncertain and had a wide confidence interval (RR 5.72, 95% CI 0.90–36.27). The definition of acidemia was different in four studies ranging from a UC-pH <7.00 to <7.10.[79]

Acidemia and cerebral palsy (CP):
The systematic review by Myrhaug et al. included eight studies reporting the risk of CP and four studies (679 cases with acidemia) were included in the meta-analysis.[7576,82,83] The rest of the studies were not included because of different definitions of CP and acidemia. The RR for CP was 4.40 (95% CI 0.86–13.39) if UC-pH was <7.00.[79]

Acidemia and neurodevelopmental outcome:
Results from studies on neurodevelopmental outcomes are difficult to interpret. Results from the meta-analysis from Myrhaug et al. suggest that children born with mild acidosis performed better in the Bayley Scales of Infant and Toddler Development test at 36-42 months of age compared with children without acidemia. The Bayley Scales of Infant and Toddler Development test is used to evaluate the functional level concerning cognition, language, motor skills, social-emotional development, and adaptive behaviour.[84] The results were based on 2 studies (80 cases) comparing cases with mild/moderate acidemia to cases with no acidemia, both including children with minor signs of encephalopathy (very low level of evidence).[80] The results suggest that infants with mild/moderate acidosis but no clinical symptoms, might not have an increased risk of late adverse neurodevelopmental outcomes and that mild acidemia might have a neuroprotective effect on the fetus. (See section on the acidotic paradox).

Acidemia and attention deficit hyperactivity disorder (ADHD):

The risk of ADHD was investigated in a national cohort study from Finland including 295 687 infants with measured UC-pH. Of these, 9924 (3.4%) had UC-pH < 7.10. The occurrence og ADHD in this group was increased with 32 % (HR 1.32, 95% CI 1.10–1.58) compared to the group with UC-pH >7.20. The cohort was not restricted to term infants and adjusting for GA reduced the HR to 1.23 (95% CI1.02–1.48).[85]

1.8 LATE TERM PREGNANCIES

The average duration of human pregnancy is estimated to be 280 days (40 weeks of gestation) from the date of the last menstrual period. Methods for due date estimation include calculation from the date of the last menstrual period in spontaneously conceived pregnancies, date of embryo transfer in pregnancies conceived by assisted reproduction, and ultrasound measurement of the embryo in the first trimester. All methods are associated with uncertainty, but due date established by ultrasonography in the first trimester is considered the most reliable method.[86,87]

In the past, the period from GA 37+0 weeks to 41+6 weeks was considered "term,". However, research has shown that neonatal outcomes vary depending on the time of birth within this 5-week GA range. To address this, it has been recommended that the label "term" should be replaced with the designations *early term* (37+0 weeks through 38+6 weeks), *full term* (39+0 weeks through 40+6 weeks), *late term* (4+0 weeks through 41+6 weeks), and *post term* (42+0 weeks and beyond) to more accurately describe births occurring at or beyond GW 37.[88]
The mechanisms initiating spontaneous labour at term is not fully understood and the cause of prolonged pregnancy is largely unknown.[89,90] Observational studies have identified an association between post-term pregnancy and primigravity, advanced maternal age, maternal obesity, previous post-term pregnancy and male fetus.[91-95]

1.8.1 Risk of adverse infant outcome in late term pregnancy

One of the concerns related to late GA is the increase in stillbirths and neonatal death. A systematic review from Muglu et al (2019) showed that the risk of stillbirth at term varied from 1.1 to 3.2 per 1000 pregnancies. The overall GW-specific risk of stillbirth increased with GA from 0.11/1000 at GW 37 (95% CI 0.0–70.15) to 3.18/1000 at GW 42 (95% CI 1.84–4.35).[96]
The causes of perinatal death in late term and post term pregnancies were investigated in a recent study based on perinatal audit cases from the Netherlands (109 cases). The study showed that in pregnancies with GA ≥41+0 weeks compared

to pregnancies at GA 39+0–40+6 weeks, stillbirth occurred relatively less often antepartum and more often intrapartum. The most relevant condition of death was placental insufficiency (10.1%), intrapartum asphyxia (9.2%), umbilical cord complications (9.2%), antepartum fetal asphyxia (7.3%), acute infection (5.5%) and neonatal asphyxia (10.1%).[97]
The risk of neonatal adverse outcomes in late term, low risk, spontaneous births has been investigated in observational studies.[98-102] Comparison of the results from these studies is challenging because of heterogeneity according to the definition of low-risk pregnancies, stratification, comparison, and outcomes. Neonatal outcomes after term CS have been described but may not be generalised to vaginal births.[103,104] Results from the most recent and comprehensive studies are summarised in Table 2.

Results from the two largest studies by Cheng et al. and Murzakanova et al., and the study by Caughey et al. showed an increased occurrence of low Apgar score, meconium-stained amnion fluid, fetal macrosomia, admission to NICU, and respiratory complications in GW 41 compared to GW 39 or 39/40.[98,100,101] In a smaller study by Linder et al., no increase in risk of fetal complications was reported. They excluded fetal growth restriction (<10th percentile), intrapartum fever, umbilical artery pH<7.20 or 5-minute Apgar score< 7 from the cohort, which may explain the results.[99]

The pathophysiology behind the increased risk of stillbirth and adverse neonatal outcome with advancing GA is largely unknown. Some argue that the main reason is placental insufficiency. This is supported by the increasing occurrence of SGA cases with advancing GA, the high frequency (10.1 %) of placental insufficiency in the study of perinatal audit cases from the Netherlands and the increased occurrence of oligohydramnios in late GA.[97,98,105] The pathogenesis behind placental insufficiency in late term and post term pregnancies is thought to be reduced placental growth, reduced placental transport, and increased oxidative stress. Many of these changes are similar to the changes seen in pre-eclampsia.[106] Also, the gradual change from fetal haemoglobin to adult hemoglobin with less affinity to oxygen (20% in at term) reduces oxygen supply to the fetus.[16]

Studies on the long-term outcomes of late term and post term pregnancies are sparse. One study by Moster et al (2010) investigated the risk of CP among 1 682 441 singleton term infants born between 1967 and 2001 in Norway and found that 1938 were registered with CP. The risk of CP was slightly increased in GW 41 (1.08/1000 compared to 0.99/1000 in GW 40 (RR 1.1, 95% CI 1.0–1.2). In GW 42, the risk increased to 1.36/1000 (RR 1.4, 95% CI 1.2–1.6).[107]

Table 2: Studies comparing neonatal outcome in GW 41 to GW 39/39-40 among low-risk singleton births with spontaneous onset.

Author, year	N	Intrauterine death	5-minute Apgar score<7.0	Meconium-stained amnion fluid	Macrosomia	NICU admission	Respiratory outcome
Cheng et al. 2008[101]	253 227		0.9% vs. 0,6% 1.37 (1.29–1.45)	10.3% vs. 5.2% 2.04 (2.00–2.07)	19.2% vs.7.9% 2.04 (2.00–2.07)		Hyaline membrane disease 0.2% vs. 0.1%, 1.17 (1.05–1.31) Mechanical ventilation 0.4% vs.0.3%, 1.28 (1.18–1.39) Meconium aspiration syndrome 0.3% vs.0.3%, 2.12 (1.91-2.35)
Murzakanova et al. 2020[98]	146 196	0% vs 0.7% -	1.1% vs 0.6% 1.55 (1.46–1.66)	24.5% vs. 18.7% 1.65 (1.63–1.67)		4.8% vs. 3.5% 1.31 (1.27–1.35)	CPAP or an endotracheal tube 0.6% vs. 0.4% 1.39 (1.28–1.51)
Caughey et al. 2004[100]	5685	0.9% vs.0.4% 2.69 (1.08–7.29)	- 2.00 (1.44–2.78)	17% vs 8.0% 2.19 (1.99–4.41)	3.0% vs. 1.0% 3.43 (2.72–4.33)	5.4% vs. 3.9% 1.12 (1.02–1.26)	
Linder et al. 2014[99]	5185	0.1% vs.0.1% 1.2 (0.4–3.3)	0.2% vs. 0.2% -	-	6.5% vs.2.7% -	3.3% vs.2,9% 1.1 (0.9–1.4)	Composite respiratory outcome* 1.2% vs.0.9%, 1.3 (0.9–1.8)
Heimstad et al. 2006[104]	4852		1.6% vs. 1.8%				

Numbers are in % and adjusted OR with 95% confidence intervals. N= numbers (GW 41)

Cheng et al: Low risk, excluded non cephalic presentation, prior CS preexisting maternal cardiac diseases, lung diseases, chronic hypertension, and diabetes. Multivariate analysis with adjustment for maternal age, parity, race/ethnicity, maternal education, number of prenatal care visits, and smoking

Murzakanova et al: Excluded congenital malformations, breech deliveries, and stillbirths. Multivariate analysis with adjustment for maternal age, parity, education, smoking, diabetes type 1, diabetes type 2, gestational diabetes, and preeclampsia.

Caughey et al: Multivariate analysis with adjustment for maternal demographics, length of labour induction, and birth weight.

Linder et al: Low risk, excluded hypertensive disorders, diabetes, cholestasis of pregnancy, placental abruption, fetal growth restriction (10th percentile), intrapartum fever, umbilical artery pH<7.20 or 5-minute Apgar score<7, and fetal major structural or chromosomal anomalies. Multivariate analysis with adjustment for maternal age, parity, mode of birth, birth weight and fetal sex assigned? at birth. Mortality not defined.

*Composite respiratory outcome including transient tachypnoea, respiratory distress syndrome, meconium aspiration syndrome pneumothorax, need for oxygen administration, CPAP or mechanical ventilation.

Heimstad et al: Term infants

1.8.2 Risk of adverse maternal outcome in late term pregnancy

The risk of adverse maternal outcome in late term, low risk, spontaneous births has been investigated in some of the studies mentioned above and in a study by Caughey et al. including 16 946 births in GW 41**.** The studies showed an increased risk of emergency CS, operative vaginal birth, and an increased risk infection during or after birth (Table 3) [98-102,108] The study by Caughey et al. investigated the risk of 3rd or 4th degree perineal laceration and post-partum haemorrhage >1000 ml; both complications were increased in GW 41 compared to GW 39. The cohort in the study by Caughey et al was not restricted to spontaneous births but in the multivariate analysis they had adjusted for induction of labour.[108]

1.8.3 Induction of labor in late term pregnancy.

The time of induction of labour in late term or post term pregnancies is a matter of controversy. Since evidence of adverse outcome in late term and post term pregnancies is growing, recommendations have changed towards earlier induction of labour often at 41+0, which has also been recommended by WHO since 2018.[6-9]
The evidence for induction in GA 41+0 weeks is based on randomised trials and observational studies. The randomised trials, comparing induction of labour in GA 41+0 to expectant management, is criticised for lack of strength and selection bias and the observational studies are criticized due to problems with confounding by indications for induction.
A recent Cochrane review included 34 RCTs (21 030 women and infants). The result from the meta-analysis comparing induction of labour at 41+0 to expectant management showed that the risk of perinatal death in the induction group was reduced by 69% (RR 0.31, 95% CI 0.15–0.64), the risk of a 5-minute Apgar score <7 was reduced by 27% (RR 0.73, 95% CI 0.56–0.96) and the risk of admission to a NICU was slightly reduced (RR 0.88 95% CI 0.80–0.96).[5]
In most of the observational studies the reduction in perinatal death in the induction group was comparable to results in randomized trials but results for the 5-minute Apgar score and admission to a NICU are different showing no difference or an increased risk in the induction group.[12,109-111]
Concerning maternal outcomes, the Cochrane review showed that induction of labour at GA 41+0 week had a slightly lowering effect on the risk of CS (RR 0.90, 95% CI 0.85–0.95) but there was no effect on the risk of operative vaginal birth, 3rd or 4th degree perineal lacerations or the risk of postpartum hemorrhage.[5] Almost all observational studies have shown an increased risk of emergency CS in the induction groups. Table 4 shows the unadjusted and adjusted risk from the most recent and comprehensive observational studies. The studies by Danilack et al., Pyykonen et al., and Ravelli et al. were based on propensity score (PS) matching.

Table 3. Studies comparing maternal outcomes in GW 41 to GW 39/39-40 among low-risk singleton births.

Author Year	N	Emergency CS	Operative vaginal birth	Chorioamnionitis	Endometritis/ myometritis	3rd or 4th degree perineal lacerations	Post partum haemorrhage
Cheng et al. 2008[101]	253 227	19.8% vs.12.8% 1.46 (1.44-1.48)	9.6% vs. 7.6% 1.14 (1.11-1.16)	2.7% vs. 1.6% 1.49 (1.45-1.54)			
Murzakanova et al. 2020[99]	146 196	7.0% vs. 3.6% -	12.0% vs. 7.5% -				
Caughey et al. 2007[108]	16 946	5.1% vs. 4.4% 1.28 (1.20- 1.36)	13.3% vs 9.4% 1.29 (1.20-1.37)	5.1% vs. 2.7% 1.60 (1.45-1.77)	2.0% vs. 1,3% 1.46 (1.14-1.87)	6.7% vs. 4.0% 1.58 (1.44-1.73	>1000 ml 4.1% vs. 2.5% 1.21 (1.10-1.32)
Caughey et al. 2004[100]	5685	21.2% vs.14.0% 1.32 (1.17-1.53)	18.5% vs. 15.5% 1.14 (1.05, 1.23)	2.7% vs. 1.7% 1.21 (1.04-1.41)	15.3% vs. 7.7% 1.46 (1.14-1.87)		
Heimstad et al. 2006[102]	4852	5.8% vs.3.8%	12.0% vs.8.9%				>500 ml 8.0% vs. 6.5%

Numbers are in % and adjusted odds ratios with 95% confidence intervals.

In the multivariate analysis GW 41 was compared to GW 39.

Cheng et al: Low risk, excluded non-cephalic presentation, prior CS preexisting maternal cardiac diseases, lung diseases, chronic hypertension, and diabetes. Multivariate analysis adjusted for maternal age, parity, race/ethnicity, maternal education, number of prenatal care visits, and smoking. Maternal febrile morbidity was not defined.

Murzakanova et al: Excluded congenital malformations, breech deliveries, and stillbirths. Multivariate analysis adjusted for maternal age, parity, education, smoking, diabetes type 1, diabetes type 2, gestational diabetes, and preeclampsia.

Caughey et al. (2004): Multivariate analysis adjusted for maternal demographics, length of labour induction, and birth weight.

Caughey et al. (2007): Low risk singleton births. Excluded pregnancies with diabetes mellitus, gestational diabetes, chronic hypertension, preeclampsia, placenta previa, breech presentation, and congenital anomalies. Multivariate analysis adjusted for maternal demographics, length of labour, induction, use of epidural, birthweight, and mode of birth (except for CS and operative vaginal birth).

Heimstad et al.: Singleton term attending an ultrasound scan before GW 22.

Stock et al. reported on the risk of post-partum haemorrhage and 3rd or 4th degree lacerations. They showed a decreased risk of post-partum haemorrhage in the induction group (adjusted RR 0.75, 95% CI 0.71–0.79) and no change in the risk of 3rd or 4th degree lacerations (adjusted RR 0.93, 95% CI 0.81–1.07).[12]

Table 4 Risk of CS after induction of labour compared to expectant management in GW 41. The exact time of induction differs between studies.

Author Year	N	Crude RR (95% CI)	Adjusted RR (95%CI)
Stock 2012 [12]	1 271 549	1.14 (1.10 -1.18)	1.06 (1.02 -1.11)
Danilack 2015 [110]	166 559	1.43 (1.34–1.53)	1.39 (1.28–1.51)
Pyykonen 2017 [109]	212 716	-	1.17 (1.06–1.28)
Ravelli 2023 [108]	239 971	1.54 (1.44–1.65)	1.52 (1.42–1.63)

Stock et al: Results were adjusted for maternal age, parity, period, deprivation category, and birth weight.
Danilack et al: PS included maternal age, race, parity, insurance, hospital, and year of hospital discharge and the 100 most common ICD–9 diagnoses. Results were adjusted for hypertensive disorder, diabetic disorder, intrauterine growth restriction, parity, and maternal age.
Pyykonen et al: PS included parity; maternal age, BMI, smoking, previous CS, infertility treatment, labour unit, year, month, and weekday of birth, and the 450 most typical diagnostic codes for pregnant women.
Ravelli et al: PS included late start of antenatal care, parity, ethnicity, infertility treatment, maternal age, socioeconomic status quintiles, induction characteristics of the delivery units, year of birth, birthweight percentile, and male sex assigned at birth. Results were adjusted for parity, ethnicity, infertility treatment, and maternal age.

CHAPTER 2. AIMS AND HYPOTHESIS

The aim of this PhD thesis was to evaluate the risk of adverse outcomes associated with hypoxia during birth and late GA.

The hypothesis was that the UC-pH threshold for increased risk of adverse neonatal outcome used in most settings (UC-pH <7.00) does not capture all infants at risk and that the risk of adverse maternal and fetal outcomes increases with increasing GA in late term pregnancies. The hypothesis in study IV was that the RS method can be used in the attempt to evaluate the consequences associated with induction of labour in GA 41+0 weeks based on observational data.

Study I The aim of this study was to evaluate the national implementation of universal measurement of UC-pH in Denmark.

Study II The aim was to investigate the association between low UC-pH and the risk of adverse neonatal outcomes within the first 28 days after birth.

Study III The aim was to compare the risk of neonatal morbidity and pregnancy- and birth-related complications between GA 41+4–42+0 and GA 41+0–41+3.

Study IV The aim was to investigate the reproducibility of results from a randomised trial using RS from observational data.

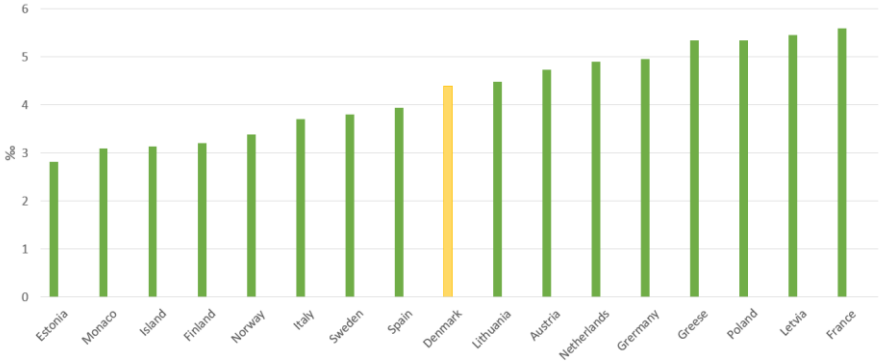
CHAPTER 3. METHODS

3.1 DESIGN AND SETTING

All four studies in this thesis were conducted as observational population-based studies based on data from Danish national registries.[112-114]
The annual birth rate in Denmark is approximately 60 000. The majority (97.5%) of births take place in a public hospital, approximately 80% of births are vaginal, 9-10% are planned CS and 10-11% are emergency CS. Almost half of births (47%) are first time births and 6% of infants are born before GA 37+0.[115,116]
All pregnant women and infants in Denmark are offered free and comprehensive antenatal obstetric and neonatal care.
In Denmark, the due date is established by an ultrasound examination early in the second trimester (crown–rump length between GA 11+2 and GA 14+1) in more than 90% of pregnancies and in most of the remaining pregnancies, the due date is estimated according to fetal biometrics in a late second-trimester ultrasound examination.[117]

The rate of perinatal death (WHO definition: stillbirth and neonatal death within the first 7 days) in the last ten years in Denmark was 5.5 ‰ (stillbirth = 3 ‰ and neonatal death within 7 days = 2.5‰).[118]
The stillbirth rate in Denmark is low and similar to the other Nordic countries. The neonatal mortality rate equals rates in France, Germany, and The Netherlands. However, the rate in Denmark is higher than in the other Nordic countries (2.5 ‰ versus 1.3‰ in Norway, 1.4‰ in Sweden, 1.3‰ in Finland, and 1.4‰ in Island (2021)).[119]

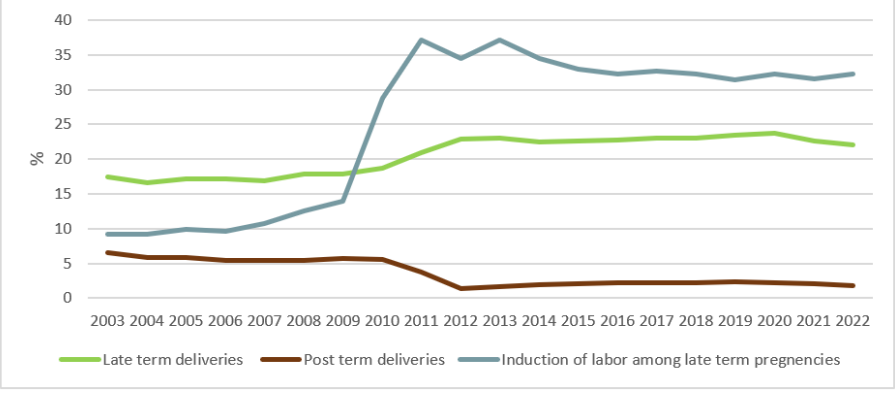
Figure 3 Perinatal death in Denmark (2021) compared to other European countries.[119]



The rate of stillbirth and neonatal death in Denmark has decreased over the last 25 years from 8‰ in 1997 to 5‰ in 2022.[115]
In 2022, the total number of stillbirths in Denmark was 158 and the total number of neonatal deaths (day 0-6) was 95. Between GA 37+0 and 42+0 weeks, the total number of stillbirths was 60 and the number of deaths within day 0-6 was 15.[115,116]
The proportion of infants with UC-pH <7.0 was 0.4–0.5%.
The total annual number of children diagnosed with CP in Denmark is 110–130 corresponding to a rate of 1–2‰. An unknown number of CP cases is caused by birth-related hypoxia. Other causes are preterm birth, infection, or stroke but often the cause is not known.[120]

Since 2011, the national recommendation in Denmark has been induction of labour between GA 41+3 weeks and GA 41+5 weeks, intending that all births occur before GA 42+0 weeks. In case of high-risk pregnancies (e.g., maternal BMI >35 kg/m^2, maternal age >40 years, and GDM), the recommendation is induction of labour at GA 41+0 weeks.[3]
The proportion pregnancies reaching GA 41+0 weeks in 2022 was 22.1 % and in 32.3 % of these cases labour was induced. As illustrated in Figure 4, the clinical practice in Denmark changed in 2011/2012 after the recommendation on induction of labour changed from induction at GA 42+0 weeks to induction at GA 41+3–41+5 weeks.

Figure 4 Change in the proportion of births after induction of labour and late term and post term births after implementation of a new recommendation on induction of labour in late term pregnancies.



3.2 DATA SOURCES

All Danish citizens receive a unique personal identification number at birth or immigration (Central Person Register, CPR number) and are registered with this number in The Danish Civil Registration System (DCRS). The DCRS is an administrative register which holds individual-level information on name, gender, date of birth, vital status, place of birth, place of residence, citizenship, and identity of family.[112] The CPR number enables linkage between mother and infant(s) and is used in all registries and for linkage of data between registries.

The Danish National Patient registry (DNPR) holds data on diseases, examinations, in-hospital medical treatments, and surgical procedures from all Danish nonpsychiatric hospitals since 1977 and on psychiatric inpatients, emergency department and outpatient specialty clinic contacts since 1995.[113]
Data on maternal characteristics (e.g., maternal weight, height, smoking status, obstetric history, relevant comorbidities, and mental illness) are registered in the DNPR by the midwife or obstetrician at the beginning of pregnancy and are updated at each antenatal visit. For each contact to the hospital during pregnancy one primary diagnosis (A-diagnosis), possible secondary diagnosis (B-diagnosis) and interventions are registered. (Classification of Diseases, 10th Revision-ICD-10). Entering of data into the registry is mandatory.[113]
Infant diagnosis and interventions are registered in the DNPR using the child's CPR number.
Registers in Statistics Denmark hold information socioeconomic variables at individual level.
The Income Statistics Register holds individual-level information on annual income and the Danish Population`s Education Register holds information on the highest completed level of education.[114]

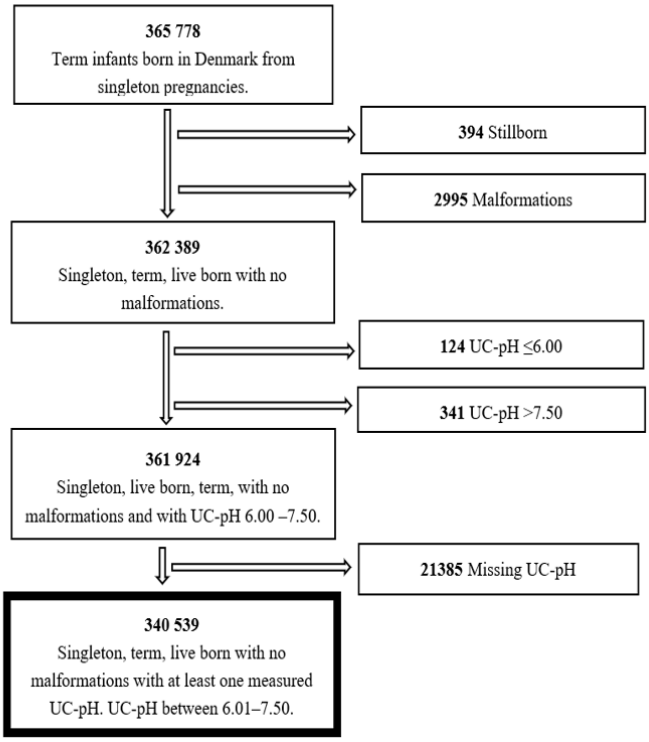
3.3 STYDY POPULATION

The study population in this thesis was women giving birth in Denmark between 2009 and 2018 and their infants. We excluded infants with malformations of heart, lungs, or nervous system.

Study I: In the first part of the study, we included all live singleton hospital births in Denmark with GA above 24+0 weeks, with registered GA. In the second part of the study, we included only births from GA 35+0 weeks.

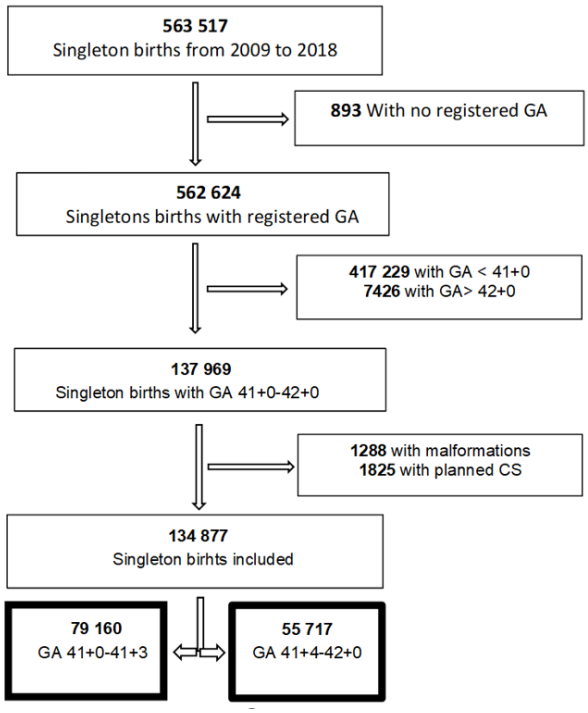
Study II: In study II, we included live born singleton, term infants (from GA 37+0 weeks) with at least one measured UC-pH (between 6.01 and 7.50).

Figure 5 Study population, Study II.



Study III: In study III we included singleton births without major congenital malformations, with registered GA, and with intended vaginal delivery at GA 41+0–42+0 between 2009 and 2018.

Figure 6 Study population, Study III



Study IV: This study population resembled the population in the Swedish Post-term Induction Study (SWEPIS).[10] The population included singleton live births at GA ≥41+0 weeks, cephalic presentation, and maternal age above 18 years of age. We excluded women with a previous CS, insulin dependent diabetes (IDDM), pregnancy-related hypertensive disorders (hypertension and/or preeclampsia), oligohydramnios and giving birth to SGA infants (<2 standard deviations (SD)). Moreover, we excluded woman with induction of labour *and* prelabour rupture of membranes (PROM).

3.4 STUDY PERIODS

The overall study period was from 2009 to 2018. In the individual studies, we chose the periods that were most relevant concerning validity of data or clinical relevance.

In the first part of Study I, we included births from 2009 to 2018 in the evaluation of the implementation of universal UC-pH measuring. In the second part of study, we included births after universal UC-pH measurement was implemented (2014–2018).
In Study II we included infants born after 2012, since therapeutic hypothermia treatment was not offered at all neonatal departments in Denmark before 2012.
The study period in Study III was from 2009 to 2018 in the main analysis but we compared the risk of complications before and after the change in the recommendations for induction of labour in 2011 in a sensitivity analysis.
In Study IV, the study period was from 2014 to 2018. The study period started after the new recommendation on induction of labour before GA 42+0 weeks was fully implemented.

3.5 OUTCOMES

In Study I, the outcomes of interest were UC-pH measured from both umbilical artery and vein, UC-pH from only one vessel (or two measurements with a difference ≤ 0.02 units) and missing UC-pH.[30]
In Study II, the outcomes were neonatal morbidity and mortality within the first 28 days after birth. The primary outcome was a composite of severe adverse neonatal outcomes including neonatal death, therapeutic hypothermia, treatment with inhaled nitric oxide, mechanical ventilation, or seizures. Secondary outcomes were individual components of the primary outcome and specific clinical outcomes including Apgar scores, CPAP, meconium aspiration syndrome, and hypoglycaemia.
In Study III, the neonatal outcomes resembled outcomes in Study II. However, the composite outcome did not include seizures and we also report on fetal acidosis, use of central venous catheter as well as SGA (-1 SD or -2 SD) and large for gestational age (LGA) (+2 SD). Birth and maternal outcomes were suspected fetal distress during birth, scalp pH/lactate sampling, maternal fever, operative vaginal birth, emergency CS, shoulder dystocia, uterine rupture, 3rd-or 4th-degree perineal tear and post-partum haemorrhage ≥1000 ml.
In Study IV, the composite outcome in the main analysis resembled the primary outcome in the SWEPIS including stillbirth, neonatal death (days 0–27), 5-minute Apgar score, Apgar score <7, UC-pH <7.00, intracranial hemorrhage, seizures, meconium aspiration syndrome, mechanical ventilation, therapeutic hypothermia, and obstetric brachial plexus injury. Secondary outcomes were individual components from the composite outcome and macrosomia (birthweight ≥4500g). Maternal outcomes were epidural, planned and emergency CS, operative vaginal birth, shoulder dystocia, 3rd-or 4th-degree perineal tear and postpartum haemorrhage (>1000 mL).

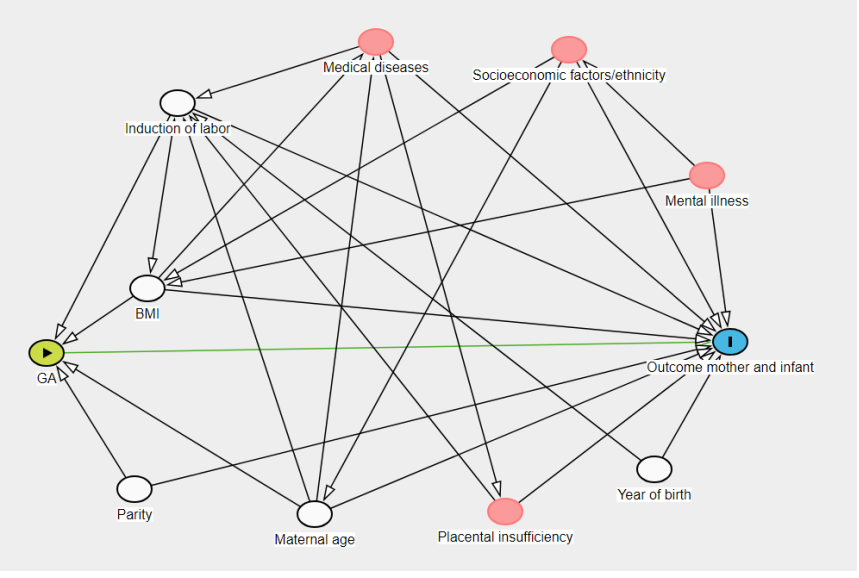
3.6 COVARIATES

A full list of covariates included in the study designs and analyses are presented in Table S2.[10,54,76,121-135]

In Study II, the correlation between fetal hypoxia/acidosis and neonatal morbidity and mortality is complex and the risk of introducing bias by stratification is high.[136-137] We reported the unadjusted crude results in the main analysis and in a sensitivity analysis with adjustment for potential confounding factors in two models. In the first model we adjusted for infant sex assigned at birth, GA, and year of birth and in the second with adjustment for infant sex assigned at birth, GA, year of birth, intrapartum fever, birthweight < -2 standard deviations, and IDDM.[76-78,130,132,134]

The most important risk of confounding in Study III was induction of labour. Since the recommendation for uncomplicated pregnancies in Denmark is induction of labor in the last days of GW 41, induction of labour before this is always on an indication. The main reasons for induction in the first days of GW 41 is either conditions known to be associated with increased risk of adverse outcome (high BMI, GDM or advanced maternal age) or pregnancy-related complications (e.g., hypertension or signs of placental insufficiency). In the last days of GW 41, the indication is most often advanced GA according to the Danish recommendation. In the main analysis we adjusted for maternal age, BMI, parity, year of birth and induction of labour.[94, 138] The causal model of Study III is presented below.

Figure 7 Directed acyclic graph (DAG) illustrating the causal relationship between GA and adverse outcomes. Figure from supplementary material of Study III.



In Study IV we adjusted for parity, maternal age BMI, GDM, SGA (below 1 SD) and LGA (above 2 SD) in the RS analysis and the same variables were used in the PS analysis.[121-124, 129,133,139]

Besides the covariates described above, we obtained data on characteristics of the pregnant woman, the birth and the infant; these were reported if relevant. Maternal characteristics were parity, maternal age, BMI, smoking in pregnancy, IDDM, GDM, hypertension, preeclampsia, medical diseases other than hypertensive disorders and diabetes, pregestational medical conditions, pregnancy-induced medical conditions, placental insufficiency, recurrent pregnancy loss, mental illness, abuse, previous CS, and socioeconomic status (income, ethnicity, and educational level). Characteristics of the child were GA, birthweight and sex assigned at birth. Characteristics concerning the birth were induction of labour, intrapartum fever, vaginal birth from breech presentation, operative vaginal birth, emergency CS and serious birth events.
Pregestational medical conditions (Study I) included IDDM, thyroid diseases, neurological diseases, respiratory diseases, and anaemia.
Pregnancy-induced medical conditions (Study I) included GDM, hypertension, preeclampsia/eclampsia, and intrahepatic cholestasis of pregnancy.
Medical diseases other than hypertensive disorders and diabetes (Study III) included respiratory diseases, hypothyroidism, hyperthyroidism, polycystic ovary syndrome, gastrointestinal diseases, and neurological diseases.
Placental insufficiency included pathological signs on the cardiotocography, intrauterine growth restriction (<-2 SD), low amniotic fluid volume, or abnormal doppler indices of fetal vessels.
Serious birth events included shoulder dystocia, uterine rupture, placental abruption, cord prolapse, and vasa praevia.
Income was reported as equivalized disposable income, which is the total household income after tax and other deductions, divided by the number of household members converted into equalised adults; household members are equalized or made equivalent by weighting each member according to age, using the modified OECD equivalence scale.[140]
Ethnicity was defined as Danish origin/descendant or immigrant.

3.7 DATA HANDLING

Statistical analyses were performed in STATA version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.). All

individual-level data were anonymized and handled at a restricted server at Statistics Denmark.

3.8 STATISTICAL ANALYSIS

Study I: In the first part of the study, we calculated the total proportion of births with UC-pH measured from either none, one or two umbilical cord vessels each year from 2009 to 2018.
For selected outcomes we compared the proportion of births with measured UC-pH from both umbilical cord artery and vein in two periods: 2009–2010 and 2014–2018. Since the proportion births with two measured UC-pH depended on GA, we calculated the proportion of births with one or two UC-pH measured from GW 24 to 42 in a sub-analysis.

In the second part of the study, we used binary logistic regression models to identify pregnancy, birth, and infant characteristics in births with missing/one UC-pH measured compared to births with UC-pH measured from both umbilical cord artery and vein (reference).[141] In a sub-analysis, we compared births with missing UC-pH to births with at least one pH measured (reference). To avoid bias from low GA, we restricted the population to include births from GA ≥ 35+0 weeks in the second part of the study, and we included only births from 2014 to 2018 after the proportion of births with UC-pH measured from both umbilical cord artery and vein had reached a plateau. Results were estimated as crude risks and risk ratios (RR) with 95% CIs

Study II: Baseline characteristics were reported as frequencies and percentages for categorical variables and means with SD for numerical variables.
Robust Poisson regression models were used to estimate the difference in adverse neonatal outcomes between the UC-pH groups.[142] Results were estimated as crude risks and crude risk ratios with 95% CIs.
To evaluate the robustness of the results, we completed several sensitivity analyses. We analysed the risk of adverse neonatal outcomes after multiple imputation for missing data on UC-pH (multiple imputation by chained equation (MICE)) and we performed a multiple poison regression with adjustment in two models; one model was adjusted for infant sex assigned at birth, GA, and year of birth and a the second model was adjusted for infant sex assigned at birth, GA, year of birth, intrapartum fever, birth weight < -2 SD, and IDDM.[143] We performed an analysis restricted to cases with UC-pH measured from both the umbilical cord artery and vein.
Finally, we analysed births with missing UC-pH according to baseline characteristics and outcomes.

Study III: Baseline characteristics were reported as frequencies and percentages for categorical variates and mean with interquartile range for numerical variables.

Binary logistic regression models were used to estimate the difference in complications between births at GA 41+0–41+3 weeks and births at GA 41+4–42+0 weeks.[141]
The results were reported as crude risks, risk differences, risk ratios (RRs) and adjusted RRs with adjustment for maternal age, BMI, parity, year of birth, and induction of labour.
In a pre-planned sensitivity analysis, we compared the risk of complications before and after implementation of new recommendations for induction of labour in 2011. Finally, a multivariate analysis was completed adjusting for maternal age, BMI, parity, and year of birth, but not for induction of labour and we examined the occurrence of complications in a small group of births with no registered GA and with a birthweight above 3000 g.

Study IV: The exposure groups were created using RS, where we applied a generalized Poisson distribution to modulate gestational age and a Bernoulli distribution for labour induction.[142,144,145] Balancing of confounding variables (year of birth, BMI, GDM, maternal age, SGA and LGA) was built into the RS by first conducting dimensionality reduction applying multiple correspondence analysis (MCA) on unordered categorical and dichotomous variables and a principal component analysis (PCA) for the remaining variables. Afterwards, the subjects were stratified by quintiles of the principal components, RS was performed, and equal proportions of these strata were imposed between the two exposure groups. Subjects were further sampled to enable comparison of the proportions between parity and the proportion of parity of all included women in the SWEPIS. RS was executed 50 times for each group allowing up to 49 resamples of a single subject in each group. For the balance diagnostics, subjects were weighted according to number of times each subject was sampled.
Missing values were imputed using multiple imputation chained equations under the assumption missing at random.[143]
In the PS analysis, subjects were weighted to estimate the average treatment effect on the induction group. We applied trimming to avoid large individual weights.[145] This PS approach is approximately equivalent to PS matching.
Balance diagnostics and characteristics of the sampled groups were presented as frequencies, percentages, medians and inter quartile ranges (IQR) when appropriate. For the binary outcomes, the groups were compared using Poisson regression with cluster robust variance estimation with each subject representing a cluster.[142] Results were presented as RR with 95% confidence intervals (CI).

3.9 ETHICAL CONSIDERATIONS

In Denmark, ethical permissions are not required for registry-based studies. Permission to access data used for the studies was granted by the Danish Data Protection Agency

CHAPTER 4. RESULTS

4.1 IMPLEMENTATION OF UNIVERSAL UC-PH IN DENMARK (STUDY I)

The study included 560 891 singleton live births in the period from 2009 to 2018. The proportion of births with measured pH from both umbilical artery and vein increased from 12.4% in 2009 to 82.8 % in 2015 declining to 76.9% in 2018. The proportion of births with at least one UC-pH reached 95.9% in 2015 declining to 95% in 2018 (Figure 8).
An increase was seen for all the investigated sub-groups, except for extremely preterm birth which only reached 46.6 % and for births with neonatal death within the first 28 days, which only reached 40.9%. We found that the proportion of births with UC-pH from both artery and vein equaled the proportion in term births if GA was above GW 32 (Figure 9)

Figure 8. Development in the proportion of births with two, one or no UC-pH in the period from 2009 to 2018. Figure adapted from Andersson et al.[147]

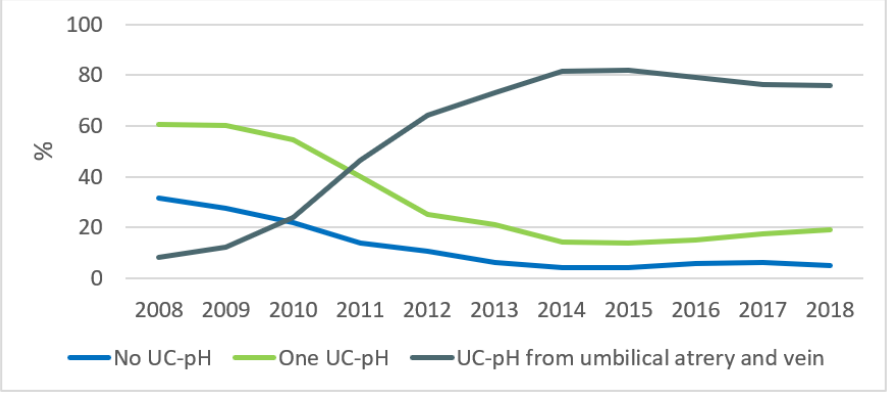


Figure 9 The proportion of births with UC-pH from both artery and vein, and at least one measurement according to GA. Figure adapted from Andersson et al.[148]

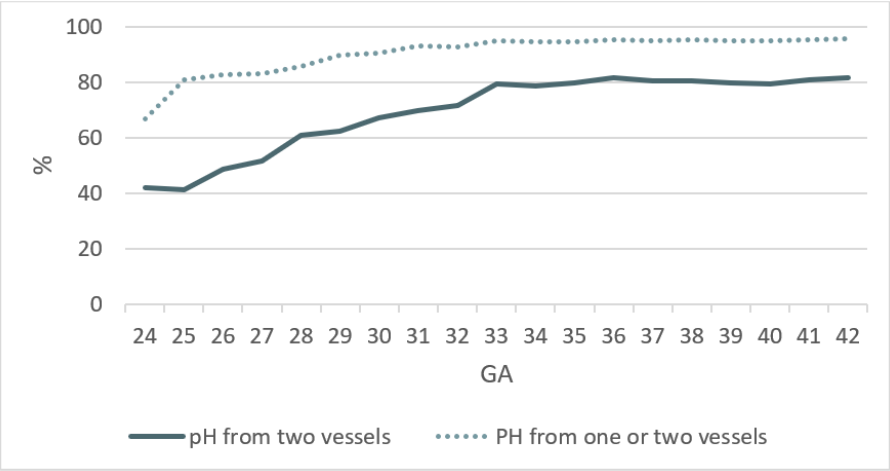


Table 6 shows a comparison between the group with UC-pH measured from both UC-pH artery and vein and missing/only one UC-pH measured among births after GA 35+0 in the period 2024–2018. In the group with missing/only one UC-pH, we found a higher occurrence of placental insufficiency (sign of fetal distress before birth), infants born SGA and seriously ill infants treated with therapeutic hypothermia or infants dying in the neonatal period. In the group with UC-pH measured from both artery and vein there was a higher occurrence of pregnancy and birth complications (BMI>35, pregnancy-induced medical conditions, fetal distress during birth, emergency CS and serious births events).

Table 5. Maternal, birth and infant characteristics of the group with missing/one UC-pH and the group with UC-pH from both artery and vein. Births from GA 35+0 in the period 2014–2018 are included. Table adapted from Andersson et al.[147]

	Missing or one UC-pH[1] **(n = 53 940)**	**UC-pH from both artery and vein** **(n = 217 633)**	**Missing or one UC-pH compared to UC-pH from both artery and vein.**
Maternal characteristics			
Age, Mean, (IQR)	29.8 (26–30)	29.8 (26–33)	
Age ≥ 40 years	1577 (2.9)	6404 (2.9)	0.99 (0.94–1.05)

BMI, mean, (IQR)	23.6 (20.6–26.3)	24.1 (20.8–26.6)	
BMI ≥ 35	2231 (4.1)	13822 (6.4)	0.89 (0.85–0.93)
Nullipara	23 081 (42.8)	94 960 (43.6)	0.98 (0.97–0.99)
Smoking	3710 (6.9)	14 828 (6.8)	1.01 (0.98–1.05)
Pre-gestational medical conditions[α]	5060 (9.4)	20 547 (9.4)	0.99 (0.96–1.02)
Pregnancy-induced medical conditions[β]	4977 (9.2)	23 267 (10.7)	0.86 (0.84–0.89)
Placental insufficiency[μ]	3104 (5.8)	11 745 (5.4)	1.07 (1.03–1.11)
Education <10 years 10–12 years >12 years	 7286 (13.5) 16 465 (30.5) 28 772 (53.3)	 28 579 (13.1) 68 189 (31.3) 116 117 (53.4)	
Income[£] (Euro) Mean, (IGR)	31 310 (21 468–37 621)	31 166 (21 786–37 494)	
Migrant status[§] (Immigrant)	9894 (18.8)	37 858 (17.5)	
Interventions in pregnancy			
Planned CS	4570 (8.5)	20 712 (9.5)	0.89 (0.86–0.92)
Induction of labor	11 960 (22.2)	53 562 (24.6)	0.90 (0.89–0.92)
Birth			
Breech (vaginal birth)	1773 (3.3)	6866 (3.2)	0.97 (0.88–1.08)
Suspected fetal distress[€]	7931 (14.7)	41 414 (19.0)	0.77 (0.76–0.79)
Spontaneous vaginal birth[‡]	42 101 (78.1)	159 884 (73.5)	1.06 (1.06–1.07)
Emergency CS	4498 (8.3)	22554 (10.4)	0.80 (0.78–0.83)
Operative vaginal birth	3134 (5.8)	16 033 (7.4)	0.79 (0.76–0.82)
Serious births events *	813 (1.5)	4098 (1.9)	0.80 (0.74–0.86)
Child			
SGA < 10th percentile	7113 (13.2)	22 831 (10.5)	1.26 (1.23–1.29)
SGA < 2.3th percentile	2212 (4.1)	6561 (3.0)	1.36 (1.30–1.43)
SGA < 1st percentile	702 (1.3)	1877 (0.9)	1.51 (1.38–1.64)
Apgar 0–3/1	533 (1.0)	2203 (1.0)	0.98 (0.89–1.07)
Apgar 4–6/1	1233 (2.3)	6523 (3.0)	0.76 (0.72–0.81)
Apgar 0–6/5	378 (0.7)	1349 (0.6)	1.13 (1.00–1.27)
CPAP	2418 (4.5)	11 548 (5.3)	0.84 (0.81–0.88)
Mecanical ventilation	241 (0.5)	820 (0.4)	1.17 (1.02–1.35)
iNO treatment	33 (0.1)	112 (0.1)	1.19 (0.81–1.75)
Therapeutic hypothermia	65 (0.1)	163 (0.1)	1.60 (1.21–2.14)
Neonatal death (<28 days)	51 (0.1)	105 (0.1)	1.96 (1.40–2.74)

Data are in n (%) or risk ratios (RR) with 95% confidence intervals (CIs).
[1] One UC-pH or two UC-pH measurements with a difference < 0.02

[α] Pregestational medical conditions: IDDM, thyroid diseases, neurological diseases, respiratory diseases, anaemia
[β] Pregnancy-induced medical conditions; GDM, hypertension, preeclampsia/eclampsia, intrahepatic cholestasis of pregnancy
[μ]Placental insufficiency; Sign of fetal distress before birth; Pathological signs on cardiotocography (CTG), intrauterine weight deviation (< - 22%), oligohydramnios or abnormal flow in the umbilical artery, the middle cerebral artery, ductus venosus or uterine artery.
[£]The equivalized disposable yearly income is the total income of a household, after tax and other deductions, available for spending or saving, divided by the number of household members converted into equalized adults; household members are equalized or made equivalent by weighting each according to age using the modified OECD equivalence scale.
[§]Migrant status; Immigrants: All patients not born in Denmark. Information on migrant status was present in 267 749/271 570 cases.

4.2 STUDY II: THE ASSOCIATION BETWEEN FETAL ACIDEMIA AND ADVERSE NEONATAL OURCOME.

Figure 10 Flowchart of the distribution of infants between UC-pH groups.

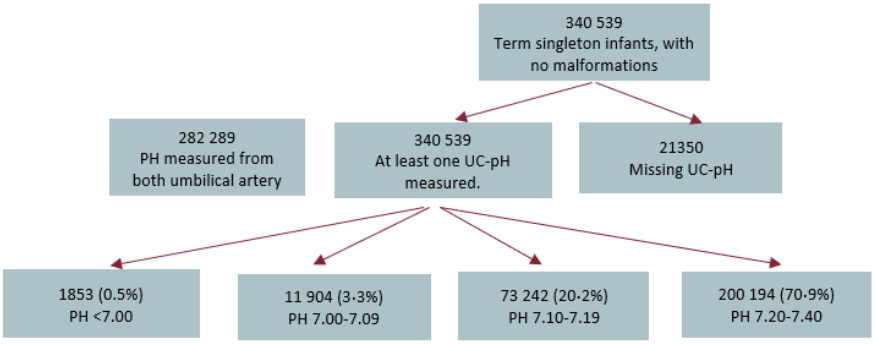


Table 6. Baseline characteristics
Infant, pregnancy, and birth characteristics according to UC-pH groups. A full list of characteristics is available in Study III.

	UC-pH <7.00	**UC-pH**	**UC-pH 7.10 – 7.19**	**UC-pH 7.20 –7.50**
GA (weeks), Mean, SD	40.2 (1.2)	40.2 (1.2)	40.1 (1.1)	40.0 (1.2)
41+0–41+6	575 (31.0)	4000 (33.6)	22 041 (30.1)	60 045 (23.7)
≥42+0	62 (3.4)	411 (3.5)	2133 (3.0)	4909 (1.9)
Sex assigned at birth (male)	1020 (55.1)	6522 (54.8)	39 468 (53.9)	127 602 (50.3)

Birthweight (g) Mean, SD	3559 (535)	3607 (491)	3615 (477)	3545 (478)
SGA <1 SD	276 (14.9)	1469 (12.3)	7645 (10.4)	27 525 (10.9)
SGA <2 SD	80 (4.3)	437 (3.7)	2200 (3.0)	7716 (3.0)
LGA >2 SD	165 (8.9)	1216 (10.2)	7729 (10.6)	24267 (9.6)
Pregnancy				
Smoking in pregnancy	123 (6.7)	668 (5.6)	4621 (6.3)	18 796 (7.4)
IDDM	15 (0.8)	115 (1.0)	659 (0.9)	1932 (0.8)
GDM	82 (4.4)	492 (4.1)	2960 (4.0)	9354 (3.7)
Hypertension	51 (2.8)	388 (3.3)	2208 (3.0)	6805 (2.7)
Preeclampsia	80 (4.3)	504 (4.2)	2923 (4.0)	8771 (3.5)
Other medical diseases[α]	248 (13.4)	1179 (9.9)	7167 (9.8)	24 342 (9.6)
Placental insufficiency[μ]	132 (7.1)	544 (4.6)	3394 (4.6)	14 212 (5.6)
Birth				
Intrapartum fever	67 (3.6)	578 (4.9)	2915 (4.0)	6275 (2.5)
Serious birth events*	163 (8.8)	437 (3.7)	1724 (2.4)	3702 (1.5)
Breech (vaginal birth)	70 (3.8)	193 (1.6)	882 (1.2)	9038 (3.6)
Operative vaginal birth	512 (27.7)	2708 (22.8)	9815 (13.4)	12 113 (4.8)
Emergency CS	490 (26.5)	1189 (10.0)	4531 (6.2)	26 814 (10.6)

Data are in n (%) or mean (SD). Birthweight data not available or valid for all infants (2575 missing)
[α]Other medical diseases: respiratory diseases, hypothyroidism, hyperthyroidism, polycystic ovary syndrome, gastrointestinal diseases, neurological disease, anemia, intrahepatic cholestasis of pregnancy.
[μ]Placental insufficiency; signs of fetal distress before birth; pathological signs on cardiotocography (CTG), intrauterine weight deviation (< - 22%), oligohydramnios or abnormal flow in the umbilical artery, the middle cerebral artery, ductus venosus or the uterine artery.
*Serious birth events: Shoulder dystocia, uterine rupture, abruptio placentae, cord prolapse or vasa previa

From the analysis of baseline characteristics, we saw that the occurrence of acidosis was higher if pregnancies were post-term or complicated by medical diseases and/or placenta insufficiency and if the birth was complicated by serious births events (shoulder dystocia, uterine rupture, abruptio placentae, cord prolapse or vasa previa).

Table 7 shows the clinical outcomes according to UC-pH and unadjusted risk ratios (RRs) depending on UC-pH values. The risk of the primary outcome defined as a composite of neonatal death, therapeutic hypothermia, mechanical ventilation, treatment with inhaled nitric oxide or seizures was 9.6% if UC-pH was <7.00 with a

steep decline to 0.9% if UC-pH was 7.00–7.09; 0.4 % if UC-pH was 7.10–7.19 and 0.2% if UC-pH was >7.20. The same pattern was seen for most of the individual outcomes of the composite outcome but for neonatal death the risk was only increased if UC-pH was <7.10. For CPAP, the decline was less steep from 39.6% if UC-pH was <7.00 to 16.6% if UC-pH was 7.00–7.09 and 5.9 if UC-pH was 7.10–7.19.

The multivariate analysis with adjustment in two models did not show any clinically relevant difference, nor did the analysis with imputation for missing UC-pH.

In the sensitivity analyses of the cases with UC-pH measured from both the umbilical cord artery and vein, we found a lower occurrence of adverse outcomes in the group with UC-pH <7.0, but nearly the same occurrence in the groups with UC-pH 7.00–7.09 and 7.10–7.19.

We analysed the group with missing UC-pH according to characteristics and outcomes and found that the occurrence of adverse neonatal outcomes resembled the occurrence in the group with UC-pH 7.10– 7.19 except for risk of neonatal death which equalled the UC-pH group 7.00–7.09.

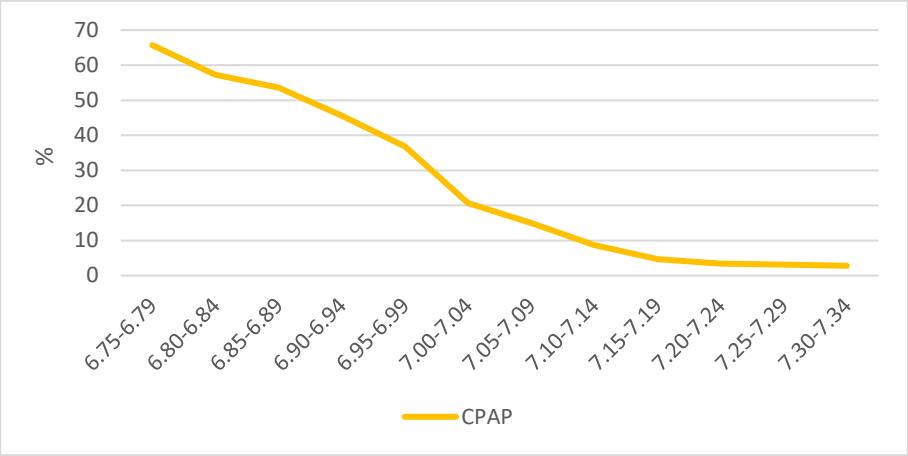
Table 7. Clinical outcomes according to UC-pH and unadjusted risk ratios (RRs) depending on UC-pH values.

	UC-pH <7.00	**UC-pH 7.00–7.09**	**UC-pH 7.10–7.19**	**UC-pH 7.20–7.50**	**UC-pH <7.00 versus 7.20–7.50**	**UC-pH 7.00–7.09 versus 7.20–7.50**	**UC-pH 7.10–7.19 versus 7.20–7.50**
Primary composite outcome*	178, 9.6	101 (0.9)	259 (0.4)	576 (0.2)	42.3 (36.0–49.8)	3.7 (3.0–4.6)	1.6 (1.3–1.8)
Individual components of the primary outcome							
Neonatal death	35 (1.9)	11 (0.1)	14 (0.0)	55 (0.0)	87.2 (57.2–>100)	4.3 (2.2–8.1)	0.9 (0.5–1.6)
Therapeutic hypothermia	116 (6.3)	28 (0.2)	38 (0.1)	42 (0.0)	>100	14.2 (8.8–22.9)	3.1 (2.0–4.9)
Mechanical ventilation	78 (4.2)	54 (0.5)	125 (0.2)	280 (0.1)	38.2 (29.8–48.8)	4.1 (3.1–5.5)	1.5 (1.3–1.9)
iNO treatment	14 (0.8)	11 (0.1)	27 (0.0)	40 (0.0)	47.9 (26.1–88.0)	5.9 (3.0–11.4)	2.3 (1.4–3.8)
Seizures	63 (3.4)	43 (0.4)	136 (0.2)	278 (0.1)	31.0 (23.7–40.7)	3.3 (2.4–4.5)	1.7 (1.4–2.1)
Low Apgar scores							
Five-minute Apgar scores <4	102 (5.5)	68 (0.6)	130 (0.2)	227 (0.1)	61.56 (49.0–77.4)	6.4 (4.9–8.4)	2.0 (1.6–2.5)
Five-minute Apgar scores <7	295 (15.9)	330 (2.8)	534 (0.7)	816 (0.3)	49.4 (43.5–56.0)	8.6 (7.6–9.8)	2.3 (2.0–2.5)
Respiratory outcomes							
CPAP	734 (39.7)	1976 (16.6)	4286 (5.9)	7442 (2.9)	13.5 (12.7–14.4)	5.7 (5.4–5.9)	2.0 (1.9–2.1)
Meconium aspiration	73 (3.9)	150 (1.3)	359 (0.5)	610 (0.2)	16.4 (12.9–20.8)	5.2 (4.4–6.3)	2.0 (1.8–2.3)
Hypoglycaemia	383 (20.7)	2449 (20.6)	4914 (6.7)	9993 (3.9)	5.2 (4.8–5.8)	5.2 (5.0–5.4)	1.7 (1.7–1.8)

Data are in n (%) or risk ratios (RR) with 95% confidence intervals (CIs).

*Composite neonatal outcome: Neonatal death, therapeutic hypothermia, mechanical ventilation, treatment with iNO or seizures.

Figure 10. CPAP treatment according to UC-pH levels



4.3 STUDY III. RISK OF COMPLICATIONS IN LATE VERSUS EARLY DAYS OF GW 41

Table 8 shows baseline characteristics of the cohort.
In the group in GA 41+0–41+3 weeks women were older, had a higher BMI and more women had medical diseases. The women in the group with GA 41+4–42+0 weeks were more often first-time mothers and their labour was induced.

Table 8. Baseline characteristics of participants according to GA group. Table adapted from Andersson et al.[130] For a full list of characteristics, please see Study III.

	GA 41+0–41+3 (n = 79 160)	**GA 41+4–42+0 (n = 55 717)**
Infant		
Sex assigned at birth (male)	39 755 (50.2)	28 873 (51.8)
Birth weight (g)., mean (IQR)	3745 (3450–4025)	3819 (3514–4110)
4001–4500	17 168 (21.7)	14 390 (25.8)
4501–5000	3300 (4.2)	3185 (5.7)
>5000	322 (0.4)	369 (0.7)
Maternal		
BMI mean, (IQR)	24.68 (21.09–26.81)	24.30 (21.19–26.45)
36–40	2405 (3.0)	698 (1.3)
>40	1052 (1.3)	260 (0.5)

Maternal age, mean (IQR)	29.87 (26–33)	29.78 (27–33)
36–40	9334 (11.8)	6270 (11.3)
>40	1311 (1.7)	404 (0.7)
First parity	33 456 (42.3)	26 628 (47.8)
Smoker	5273 (6.7)	3269 (5.9)
Prior CS	5481 (6.9)	3652 (6.6)
GDM	1506 (1.9)	137 (0.3)
Hypertension	1359 (1.7)	782 (1.4)
Other medical diseases [£]	4123 (5.2)	2782 (5.0)
Education		
<10 years	9892 (12.8)	6405 (11.8)
10–12 years	25 192 (32.6)	17 215 (31.7)
>12 years	42 241 (54.6)	30 762 (56.6)
Equivalised disposable income (EUR), mean (IQR) [β]	30 055 (21 796–35 864)	30 543 (22 053–36 478)
Etnicity		
Danish origin/descendant	33 346 (91.1)	746 226 (90.9)
Immigrant	6500 (8.9)	4627 (9.1)
Birth outcome		
Breech (vaginal birth)	538 (0.7)	252 (0.5)
Induction of labour	18 270 (23.1)	30 563 (54.9)

Data are in n (%) unless otherwise stated.

£ Other medical diseases: respiratory diseases, hypothyroidism, hyperthyroidism, polycystic ovary syndrome, gastrointestinal diseases, neurological disease

[β] The equivalized disposable income is the total income of a household after tax and other deductions, available for spending or saving, divided by the number of household members converted into equalized adults; household members are equalized or made equivalent by weighting each according to age, using the modified OECD equivalence scale.[140]

A full list of adjusted and unadjusted effect estimates is presented in Table 9 and a forest plot of the adjusted RR is presented in Figure 11.

The occurrence of most fetal complications is rare but increased with advancing GA from GA 41+0 to 42+0 weeks. The composite outcome of adverse neonatal outcomes including neonatal death within 28 days, hypothermia treatment, mechanical ventilation or iNO treatment increased from 1.7/1000 to 2.7/1000 from GA 41+0–41+3 to GA 41+4–42+0.

We found an increased risk for all maternal outcomes in except uterine rupture in GA 41+0–41+3. The risk of emergency CS increased from 11% to 15.3%. After adjusting for induction of labour maternal age, BMI, parity, and year of birth, the increase in emergency CS was 17% (adjusted RR 1.17, 95% CI 1.14–1.21).

The sensitivity analysis comparing the occurrence of outcomes before and after a new policy on time of induction introduced in in Denmark in 2011 showed a change

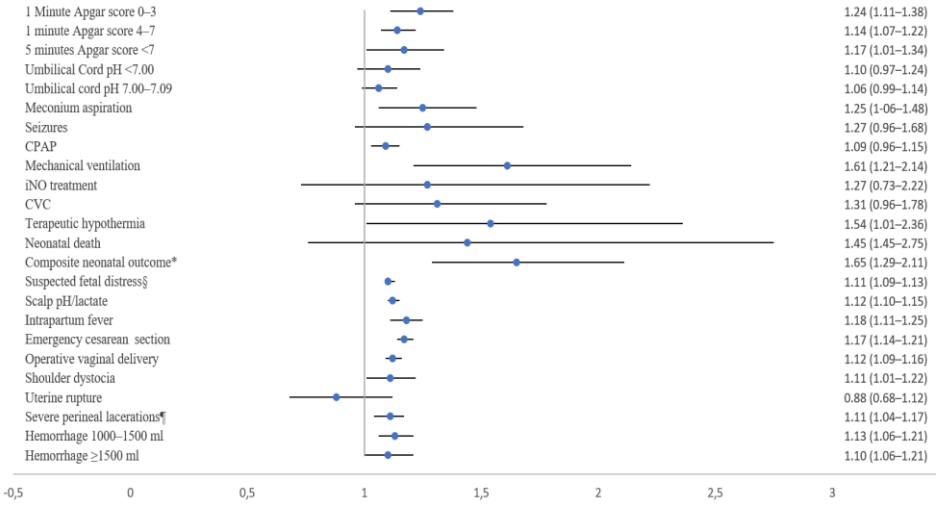
in the incidence of some outcomes. The magnitude of the change was, however, comparable between the two GA groups.

Table 9. Birth outcome at GA 41+0–41+3 and GA 41+4–42+0. Values are numbers (percentages) unless otherwise stated. Table adapted from Andersson et al.[130]

	Study population		**Risk ratio (95%CI) Adjusted for maternal age, BMI, parity, year of birth and induction of labour**
	GA 41+0–41+3 (n = 79 160)	**GA 41+4–42+0 (n = 55 717)**	
Neonatal outcome			
1-min Apgar score <4	791 (1.0)	711 (1.3)	1.24 (1.11–1.38)
1-min Apgar score 4–6	2375 (3.0)	2038 (3.7)	1.14 (1.07–1.22)
5-min Apgar score <7	490 (0.6)	405 (0.7)	1.17 (1.01–1.34)
UC-pH <7.00*	684 (1.0)	548 (1.1))	1.10 (0.97–1.24)
UC-pH 7.00–7.10*	1845 (2.6)	1477 (2.9)	1.06 (0.99–1.14)
Meconium aspiration	345 (0.4)	299 (0.5)	1.25 (1.06–1.48)
Seizures	120 (0.2)	101 (0.2)	1.27 (0.96–1.68)
CPAP	3296 (4.2)	2629 (4.7)	1.09 (1.03–1.15)
Mechanical ventilation	107 (0.1)	110 (0.2)	1.61 (1.21–2.14)
NO treatment	32 (0.0)	23 (0.0)	1.27 (0.73–2.22)
CVC	101 (0.1)	91 (0.2)	1.31 (0.96–1.78)
Therapeutic hypothermia	52 (0.1)	50 (0.1)	1.54 (1.01–2.36)
Stillborn	48 (0.1)	29 (0.1)	0.88 (0.53–1.44)
Neonatal death	21 (0.0)	22 (0.0)	1.45 (0.76–2.75)
Composite outcome$^{\pi}$	138 (0.2)	152 (0.3)	1.65 (1.29–2.11)
SGA <10th percentile	8198 (10.4)	6408 (11.5)	1.02 (0.99–1.06)
SGA <2.3th percentile	2075 (2.6)	1599 (2.9)	0.96 (0.89–1.02)
LGA >90th percentile	6249 (7.9)	3969 (7.1)	0.95 (0.91–0.99)
Birth outcome			
Suspected fetal distress§	18 778 (23.7)	16 168 (29.0)	1.11 (1.09–1.13)
Scalp pH/lactate	12 966 (16.4)	11 744 (21.1)	1.12 (1.10–1.15)
Intrapartum fever	2,545 (3.2)	2,534 (4.6)	1.18 (1.11–1.25)
Emergency CS	8684 (11.0)	8503 (15.3)	1.17 (1.14–1.21)
Operative vaginal birth	7260 (9.2)	6293 (11.3)	1.12 (1.09–1.16)
Shoulder dystocia	1085 (1.4)	848 (1.5)	1.11 (1.01–1.22)
Uterine rupture	191 (0.2)	115 (0.2)	0.88 (0.68–1.12)
Maternal outcome			
3rd or 4th grade perineal tear	2799 (3.5)	2,257 (4.1)	1.11 (1.04–1.17)
Haemorrhage†			
1000–1500 ml	2215 (4.0)	2016 (5.1)	1.13 (1.06–1.21)
>1500 ml	1044 (1.9)	918 (2.3)	1.10 (1.00–1.21)

Data are n (%) and adjusted risk ratios (RR) with 95% confidence intervals (CIs)
*Only birth with at least one UC pH measured were included (N 121 445).
¶ Composite neonatal outcome: Neonatal death (0–28 days), therapeutic hypothermia, mechanical ventilation, or NO treatment
§ Suspected fetal distress: Pathological signs on cardiotocography (CTG), meconium-stained amnion fluid, pathological result of a scalp blood sampling, sign of asphyxia on US scan or a significant event on ST analysis (STAN). Registration was made when leading to an intervention.
† The volume of haemorrhage after birth was measured and reported from 2012. The results are based on data from 2012 (N 95 509).

Figure 11. Adjusted risk ratios for birth outcomes at GA 41+4–42+0 compared to GA 41+0–41+3. Figure adapted from Andersson et al.[130]



4.4 STUDY IV. REPRODUCABILITY OF A LABOUR INDUCTION STRATEGY USING RS

After RS, we included 8273 births in the induction group and 32 445 births in the expectant management group.
The RS population resembles the SWEPIS population except that the SWEPIS population included more women >35 years of age and women were more often diagnosed with psychiatric disorders and higher educated. More women were smokers in the RS population (Table 11). The population in the PS analysis differed markedly concerning maternal age, BMI, and parity.

Table 10 Descriptive statistics for the primary population (SWEPIS), in the RS analysis and PS analysis.

	SWEPIS		RS Analysis		PS Analysis	
	Induction	**Expectant management**	**Induction**	**Expectant management**	**Induction**	**Expectant management**
	(n=1381)	(n=1379)	(n=8273)	(n=32445)	(n=3468)	(n=51521)
Maternal age	31	31	30	30	30.0	30.0
(Median (IQR))	(28–35)	(28–34)	(26–33)	(26–33)	(26.0-35.0)	(26.0-26.0)
Maternal age >35 years	21.9	20.2	18.6	16.9	27.1	31.2
Height (cm)	167	168	168	168	168	168
(Median (IQR))	(163–172)	(163–172)	(164–173)	(164–173)	(164-173)	(164-173)
Weight at first antenatal visit (kg).	67	68	66	66	72.0	73.0
Median (IQR)	(60–77)	(60–77)	(60–76)	(59–75)	(63.0-93.5)	(63.0-93.0
BMI	23.9	24.0	23.4	23.2	25.2	25.4
(Median (IQR))	(21.6–27.1)	(21.7–27.4)	(21.1–26.7)	(21.–26.4)	(22.2-33.3)	(22.1-32.9)
Maternal BMI >30	12.3	14.4	14.3	11.6	31.7	34.8
Parity (nulliparous)	55.2	54.6	54.6	55.5	45.5	45.9
GA	289	292	288	291	288	290
(Median (IQR)	(288–289)	(289–294)	(288–289)	(290–293)	(287-289	(288-292)
Smoking	2.5	3.1	7.5	5.0	7.7	5.8
Psychiatric disorders	9.5	10.8	3.4	2.6	3.5	2.7
Induction of labour	85.5	33.1	85.9	34.0	100	35.3
Educational level						
Level 1: <10 years	4.4	4.6	13.4	10.8	14.1	11.8
Level 2: 10–12 years	31.0	32.6	32.6	29.2	35.1	33.2
Level 3: >12 years	64.6	62.8	54.0	60.0	50.8	55.0

Values are percentages and risk ratios unless otherwise stated.

Table 11. Infant and maternal outcome in SWEPIS, RSA and PSA

	SWEPIS			RS analysis			PS analysis		
	I	**EM**	**Induction versus expectant management**	**I**	**EM**	**Induction versus expectant management Adjusted results[µ]**	**I**	**EM**	**Induction versus expectant management Adjusted results[µ]**
Infant outcome									
Composite outcome[α]	2.4	2.3	1.06 (0.65–1.73)	2.5	2.2	1.18 (0.95–1.45)	2.1	2.0	1.05 (0.80-1.36)
Stillborn	0	0.4		0.2	0.1	1.76 (0.83–3.72)	0.0	0.1	0.46 (0.06-3.60
Neonatal death	0	0.1		0.0	0.1	0.31 (0.06–1.58)	0	0	-
Five–minute Apgar score<4	0.2	0.1	2.98 (0.31–28.66)	0.3	0.2	1.25 (0.58–2.70)	0.6	0.2	1.27 (0.51-3.14)
Five–minute Apgar score <7	1.3	1.2	1.27 (0.76–2.11)	0.9	0.7	1.17 (0.83–1.54)	0.7	0.7	0.94 (0.59-1.51)
UC- pH <7.00	2.1	1.5	1.36 (0.61–3.05)	0.6	0.6	1.01 (0.67–1.54)	0.6	0.7	0.89 (0.54-1.47)
Therapeutic hypothermia	0.1	0.1	0.50 (0.05–5.48)	0.1	0.1	0.60 (0.26–1.36)	0.1	0.1	1.48 (0.51-4.31)
Seizures	0.2	0.2	0.33 (0.03–3.18)	0.2	0.3	0.67 (0.30–1.52)	0.2	0.2	0.87 (0.35-2.18)
Meconium aspiration	0.1	0.2	0.66 (0.11–3.96)	0.6	0.5	1.13 (0.79–1.62)	0.6	0.5	1.15 (0.67-1.98)
Mechanical ventilation	0.2	0.4	0.60 (0.14–2.49)	0.1	0.2	0.83 (0.45–1.52)	0.2	0.1	1.31 (0.56-3.10)
Brachial plexus injury.	0.3	0.1	3.98 (0.45–35.56)	0.2	0.1	2.44 (0.89–6.84)	0.3	0.1	3.18 (1.34-7.29)
Macrosomia	4.9	8.3	0.60 (0.45–0.80	4.2	5.4	0.78 (0.67–0.90)	6.6	7.6	0.90 (0.76-1.00)
Maternal outcomes									
Epidural	52.8	48.5	1.09 (1.01–1.17)	38.9	31.5	1.24 (1.19–1.28)	39.7	31.0	1.28 (1.22-1.35)
Emergency CS	10.0	10.6	0.98 (0.94–1.01)	13.7	12.9	1.07 (0.98–1.16)	13.1	12.4	1.06 (0.96-1.17)
Planned CS	0.4	0.2		0.5	1.1	0.47 (0.32–0.70)	0.5	1.3	0.37 (0.22-0.62)
Operative vaginal birth	6.4	6.6	0.97 (0.73–1.28)	10.4	10.7	0.98 (0.89–1.07)	8.5	8.7	0.97 (0.86-1.09)
Shoulder dystocia	0.4	0.3	1.50 (0.77–1.19)	1.5	1.4	1.08 (0.82–1.41)	1.6	1.6	0.95 (0.70-1.30)
3rd or 4th degree perineal tear	2.9	3.6	0.80 (0.53–1.19)	2.8	3.3	0.85 (0.71–1,02)	2.7	2.9	0.93 (0.75-1.16)
Haemorrhage ≥1000 ml	10.1	10.6	0.96 (0.77–1.19)	11.3	10.9	1.04 (0.95–1.14)	11.9	10.3	1.15 (1.04-1.28)

I: Induction of labor, EM: expectant management

[α]Composite outcome in SWEPIS: Stillbirth, neonatal mortality, five-minute Apgar score below 7, pH less than 7.00 or metabolic acidosis (pH <7.05 and BE >12 mmol/L) in the umbilical artery, hypoxic ischemic encephalopathy, intracranial haemorrhage, convulsions, meconium aspiration syndrome, mechanical ventilation within 72 hours or obstetric brachial plexus injury.

Composite outcome in Rejection Sampling Study: Stillbirth, neonatal death (days 0–27), Apgar score <7/5, pH less than 7.00, intracranial haemorrhage, convulsions, meconium aspiration syndrome, mechanical ventilation, hypoxic ischemic encephalopathy (hypothermia treatment) or obstetric brachial plexus injury.

CHAPTER 5. DISCUSSION

5.1 MAIN FINDINGS

The main findings of the four studies were:

Study I: Implementation of universal measurement and central registration of UC-pH was a comprehensive process lasting 4-5 years before a plateau was reached at 77–83% from 2015. The proportion of births with at least one UC-pH reached 9596%. Missing UC-pH from one or both vessels was associated with less complicated pregnancies, SGA, seriously ill infants treated with therapeutic hypothermia, and with neonatal death.

Study II: Infants with UC-pH below 7.20 had an increased risk of adverse neonatal outcome. For the composite outcome of severe adverse neonatal outcome including neonatal death, therapeutic hypothermia, mechanical ventilation, iNO treatment, or seizures, the occurrence was 0.2% if UC-pH was 7.20–7.50. The occurrence increased with decreasing UC-pH to 0.4% if UC-pH was 7.10–7.19, to 0.9% if UC-pH was 7.00–7.09 and to 9.6% if UC-pH was <7.00. The same pattern was seen for the individual components of the composite outcome except for neonatal death, which was only increased for UC-pH <7.10. Results were the same for UC-pH between 7.00 and 7.19 in the analysis only including births with UC-pH measured from both the umbilical artery and vein.

Study III: When comparing births at GA 41+4–42+0 weeks to births at GA 41+0–41+3 weeks, births in the late period were associated with an increased infant morbidity including low Apgar score, meconium aspiration, need for CPAP, therapeutic hypothermia, mechanical ventilation, and an increased risk for the composite outcome measure including iNO treatment, therapeutic hypothermia, mechanical ventilation, and neonatal death. Also, the risk of complications during birth was increased, including fetal distress, maternal fever, operative vaginal birth, shoulder dystocia, and emergency CS. The risk of maternal complications including 3rd and 4th degree perineal lacerations and post-partum haemorrhage was also increased.

Study IV: For most outcomes, it was possible to reproduce the characteristics of the population and the results from the randomized trial (SWEPIS) after RS from observational data. When compared to the PS analysis, we found that the characteristics in the populations differed markedly between SWEPIS/RS and PS analysis; results from the PS analysis, however, resembled the results from the RS analysis and SWEPIS.

5.2 COMPARISON WITH EXISTING LITERATURE

Study I: Ahlberg et al. compared maternity wards in Sweden with a policy of universal UC-pH measuring to maternity wards with a selective approach to UC-pH measuring and found that the proportion of successfully measured UC-pH in high-risk births and in births with seriously ill infants was higher in settings with universal UC-pH measure.[34] Results are comparable to results from our study where we compared the proportion of successfully measured UC-pH in the periods before and after implementing universal UC-pH.[34] As in the study by Ahlberg et al., we found a higher proportion of successfully measured UC-pH in emergency CS (from 21.1% to 81.8%) and in preterm births (GA 32+0-37+0 from 16.6% to 79.9%) and we found that the proportion of measured UC-pH among infants who were treated with therapeutic hypothermia increased from 22.2% to 71.4% after implementation of universal UC-pH

No studies were found comparing births with missing UC-pH to births with one or two UC-pH measurements.

Study II: As described in the section on adverse outcomes from acidemia, studies on the association between UC-pH and adverse neonatal outcome in term infants are sparse and heterogenous concerning stratification, exposure, and outcomes.

The design in our study is comparable to the design in the study by Yeh et al including 51 519 singleton, term, non-anomalous live infants comparing neonatal outcomes in UC-pH intervals to UC-pH 7.26–7.30. The most important difference between the study by Yeh et al. and our study was that the cohort in the study by Yeh et al. was from a selected population (52.4% of the total population) and included only infants with measured UC-pH from both artery and vein (95.7% of the 52.4%).[19]

The risk of neonatal death in the group with UC-pH <7.00 was the same as in our study (1.9%). However, Yeh et al. did not find an increased risk of neonatal death if UC-pH was above 7.00.[19]

Yeh et al found that the risk of encephalopathy with seizures was increased if UC-pH was between 7.00 and 7.10 and, to lesser extent, between 7.11 and 7.15 and 7.16 to 7.20. This resembles the results for seizures in our study except that we found a higher risk in the group with UC-pH 7.10–7.20. The risk of a 5-minute Apgar score <7 was markedly increased below 7.20 in both studies.

Even though the population in the study by Yeh et al only included 42% of the total population and the included infants in complicated pregnancies or births with suspected hypoxia, results resembled the results in our study including 94.1% of the total population where UC-pH measuring was not selective.

Study III: No studies were found comparing the occurrence of adverse neonatal and maternal outcomes in the first days of GW 41 and the last days in GW 41 after adjusting for induction of labour.
The occurrence neonatal death and treatment with mechanical ventilation in GW 41 was higher in the studies included in Table 3 compared to results from our study. Results for 5-minute Apgar score <7 resembles results in the two largest studies by Cheng et al. and Murzakanova et al.[98,101]
The design of the comprehensive study on maternal adverse outcomes by Caughey et al including 16 946 births in GW 41 resembles the design in our study. Caughey et al included all births and in the multivariate analysis they adjusted for induction of labour. They found a higher risk of emergency CS (21.2 vs.11.0/15.3), and of 3rd and 4th degree lacerations (6.7 vs 3.5/4.1) but the same increased risk of severe haemorrhage (>1000 ml) in GW 41.[100]

Study IV: Results for perinatal death in the expectant management group in the RS analysis (1.6‰) resembles results from previous randomized trials, the largest being the study from Hannah et al. including 1706 (1.2 ‰) and Keulen et al. including 900 in the expectant management group (2.2 ‰).[11,148]
Results for maternal outcomes, especially for emergency CS, in the RS and PS analysis resembles results from the randomized trials but differ from results from previous studies based on propensity score.109. [109-111]
The difference in the results in the current PS analysis and previous studies based on PS may be caused by different exposure and covariates included in the PS.
The exposure differs since, in the current study, the exposure groups were created in a more pragmatic setting, where induction of labor was allowed in the expectant management group, and women are allowed to give birth prior to induction of labor in the induction group. The covariates included in the current PS analysis included maternal age, parity, year of birth, BMI, GDM, and SGA. In the studies from Danilack et al. and Pyykönen et al. the PS included the100 or 450 most common diagnostic codes for pregnant women. Including a high number of covariates in the PS might result in an imprecise estimate of the effect and might introduce bias into the association.[110,111]

5.3 METHODOLOGICAL CONSIDERATIONS

All studies in this thesis were observational nationwide population-based cohort studies using data from Danish national registries. Some methodological considerations of validity and bias are warranted when interpreting the results.

5.3.1 Selection bias

Selection bias may occur when the inclusion of study participants depends on the exposure or the outcome.[149]
Selection bias was present in Study II where the population included infants with measured UC-pH. We know from Study I that UC-pH was not missing at random. Infants with missing UC-pH were predominantly born in uncomplicated births but also in births with severe neonatal outcomes including neonatal death. Including these infants might have affected the results. We performed an analysis with multivariate imputation for missing UC-pH and we did not find clinically relevant changes to the results.
In Study III the population included births with registered GA. Since registration of GA is mandatory in the DNPR, very few were excluded due to missing data on GA. The group with missing GA was very heterogenous and lacked registrations of other events indicating birth at term. Thus, excluding births with missing GA did not introduce selection bias.

5.3.2 Information bias

Information bias is present if data on exposure or outcomes are incorrect.[149]
The studies in this thesis rely on correct registration of characteristics, diagnoses, and interventions in the DNPR.
Registrations in the DNPR will never be flawless. Some registrations in pregnancy and after birth are optional, and others are mandatory (e.g., GA and parity), the last meaning that the registration of the birth in the DNPR cannot be completed without these registrations. This means that the mandatory registrations are always present, but we do not know if they are correct. Registrations might be missing, or registrations might not be correct concerning optional variables.
When designing the studies, we expected that the registrations for some clinical outcomes could be less precise, e.g., in shoulder dystocia, which can range from a situation with the use of a single extra (prophylactic) procedure (McRoberts manoeuvre) to severe shoulder dystocia requiring several procedures and often with severe adverse infant outcome. Similarly, in case of meconium aspiration, which is used for different conditions ranging from vomiting to severe meconium aspiration syndrome.
The validity of obstetric registrations in the DNPR was evaluated in a newly published study by Herskind et al. They evaluated registrations from 1264 pregnancies/births using medical records as the reference standard. In general, they found that the DNPR had a very high validity and completeness. The positive predictive value (PPV) was ≥0.90 in most pregnancy-related variables including parity, BMI, diabetes, and previous CS, while it was lower for hypertensive disorders. On most birth-related variables including obstetric surgical procedures (e.g., CS and induction of labour), pharmacological pain relief, and GA, the PPV

ranged from 0.98 to 1.00. A 5-minute Apgar score and birthweight had a PPV of 1.00. They did not have access to the medical record of the infants.[150] This confirms the findings from previous studies showing that registrations of interventions in general are more valid than registration of diagnoses.[151] Acknowledging this, we primarily based the composite measures in Study II and Study III on interventions. In general, we found no indications of differences in registration between different GA or UC-pH groups.

In Study IV we composed a composite measure comparable to the primary composite measure in the SWEPIS including stillbirth, neonatal death, Apgar score <7/5, umbilical cord pH <7.00, intracranial hemorrhage, seizures, meconium aspiration syndrome, mechanical ventilation, hypothermia treatment, and obstetric brachial plexus injury. Including intracranial hemorrhage and obstetric brachial plexus injury in the composite measure might increase the risk of information bias since registration of these conditions is less precise in the Danish registries.

5.3.3 Confounding

Confounding is the mix of effects of two related variables on the outcome.[149] The criteria for being a confounder is that the variable is associated with the exposure *and* the outcome and not a step on the intermediate path between exposure and outcome (a mediator).
Confounding has been a major issue in the studies in this thesis.
In our attempt to address confounding and mediation in the associations between exposure and outcomes, we used DAGs.[152]
In Study II we tried to estimate the causal association between acidemia and adverse neonatal outcome. The association is complex since adverse infant outcomes can be caused by intrapartum acidosis alone or by fetal frailty caused by diabetes, placental insufficiency, late gestational age, fever or infections, by acute obstetric situations such as shoulder dystocia, from aspiration of amnion fluid or from a combination of acidosis and one or more of these factors. [54,77,130,153] Some of these factors influence the risk of acidaemia directly (intrapartum fever/infection) or indirectly through placental insufficiency (maternal medical diseases). Besides that, the association is affected by unknown or unregistered factors such as genetic fragility and duration of birth. Adjusting for known or assumed confounding factors might introduce bias. Based on these considerations, we decided to report the crude results in the main analysis and adjusted results in two models of multivariate analysis as sensitivity analysis.

In study III the main confounding factor in the association between GA and adverse maternal and infant outcomes was induction of labour. Induction of labour was associated with GA at birth and with the occurrence of adverse infant and maternal outcomes. In the multivariate analysis, we adjusted for induction of labour along with other factors known from the literature to be confounding factors in the association (maternal age, BMI, parity).[54,121-123]

5.3.4 Composite outcomes

Composite outcomes consisting of several binary events are frequently chosen as the primary outcome in clinical trials and observational studies in neonatology and obstetrics because individual outcomes are rare and statistical power would be inadequate for any single outcome.
Ideally, components of a composite outcome have similar effect, frequency, and severity, the most important being similar severity. Interpreting results from a composite outcome is often challenging because components rarely meet these criteria.[154,155]
Another challenge with composite outcomes is that results from the composite outcomes are impossible to compare between studies because the individual outcomes included in the composite outcome differ between studies.

In Study II the composite outcome was chosen as the primary outcome since individual severe adverse outcomes were rare and the statistical power even for this large sample might be inadequate to demonstrate an association for any of the single outcomes.
The components in the composite outcome are limited to components which have comparable severity and frequency (neonatal death, therapeutic hypothermia, mechanical ventilation, treatment with inhaled nitric oxide, or seizures). Previous studies have shown that these components are associated with the exposure.
Another consideration when choosing the individual elements of the composite outcomes was the validity of registrations. The composite outcomes in study II and III included primarily intervention which is a central element in the financial reimbursement to the neonatal units and therefore are expected to be more valid.
In Study IV the composite outcome resembles the primary outcome in the SWEPIS, which was conducted for the clinical trial and used for the power calculation. The composite outcome included stillbirth, neonatal mortality, 5-minute Apgar score <7, UC-pH <7.00, metabolic acidosis (UC-pH <7.05 and BE >12 mmol/L), hypoxic ischemic encephalopathy, intracranial haemorrhage, seizures, meconium aspiration syndrome, mechanical ventilation, and obstetric brachial plexus injury. The components differed in severity and frequency (0.1% to 2.1%) and some of the components are poorly registered in the Danish registries (hypoxic ischemic

encephalopathy, intracranial haemorrhage, meconium aspiration syndrome and obstetric brachial plexus injury). In the composite measure in Study IV, we did not have the opportunity to include metabolic acidosis (UC-pH <7.05 and BE >12 mmol/L) since BE is not registered in the DNPR. Metabolic acidosis is the probably the most frequent component of the SWEPIS composite outcome.
In general, it is difficult to compare results from the composite outcomes to results from previous studies. Among the studies listed in Table S1, some of the studies report on results from composite outcomes.[40,41,69,98] The individual components of the composite outcomes differ between these studies and the included events differ in frequency and severity ranging from need for oxygen administration to neonatal death.

5.3.5 External validity

The studies in this thesis were based on data from a high income setting with free and equal access to health care.
Some aspects of prenatal and intrapartum care are specific to Denmark, including routine setting of due date in the first trimester (>95% of all pregnancies), screening for malformations in second trimester, standardised approaches to intrapartum and neonatal care, and a high proportion hospital births (97.5% in 2022).[116,117]
This may limit the generalisability of our results. The risk of adverse neonatal outcomes associated with hypoxia and the risk of adverse neonatal and maternal outcomes associated with advanced GA is presumably higher in settings with more restricted access to obstetric and neonatal care.

CHAPTER 6. CONCLUSION

The aims of this thesis were to validate universal measuring of UC-pH for clinical and scientific use, to evaluate the association between UC-pH <7.20 and adverse neonatal outcomes in a setting with universal UC-pH measuring, to evaluate the risk of adverse infant and maternal outcomes in late term pregnancies, and to evaluate a RS can be used as a method to reproduce results from a randomized trial based on observational data.
Study I showed that after implementation of universal UC-pH, the proportion with the recommended measures from both umbilical vein and artery reached 76-80% and measure from one vessel reached 94%. UC-pH was not randomly missed. In the group with missing UC-pH, pregnancies and births were either less complicated (the majority) or the infants were severely ill or died. We saw that introducing universal UC-pH resulted in an increase in measured UC-pH in very acute situations and in situations where it is difficult to sample umbilical cord blood (prematurity, placental insufficiency).

Results from Study I were important when we evaluated the association between UC-pH and adverse neonatal outcomes (Study II). In Study II we saw that the risk of adverse neonatal outcomes was increased below UC-pH 7.20. The risk of the composite measure of adverse neonatal outcomes was one in 10 if UC-pH was below 7.00, one in 100 if UC-pH was 7.00–7.09 and one in 250 if UC-pH was 7.10–7.19. For some of the less serious outcomes, the decline was less steep.
Studies III and IV concerned the risk of adverse outcomes from late term birth. The subject of Study III has been a matter of much debate since the SWEPIS was published in 2019; the aim of the current study was to add information to that debate. It is known from previous studies that the risk of adverse outcomes is increased in late term birth (Table 2). We found that even though the risk of adverse infant outcomes were rare, the risk of the composite outcome was 65% higher in the last days of GW 41 compared to the first days of GW 41. According to maternal adverse outcomes, we saw an increase in risk of all outcomes (11-17%) in the last days of GW 41 compared to the first days of GW 41.
The aim of Study IV was to evaluate if it was possible to reproduce results from a randomized trial using RS from observational data. Compared to the PS analysis the strength of the RS analysis is the more pragmatic definition of the exposure groups.

6.1 PERSPECTIVES AND CLINICAL IMPLICATIONS

Results from the study on implementation of universal UC-pH may guide clinicians, administrations, and quality organisations aiming to implement universal UC-pH or UCBA. Knowledge about the timespan and in which cases it is difficult or not prioritized to collect samples is valuable in the implementation process. Further, our results may be valuable for future research on causes and consequences of intrapartum hypoxia.
Knowing the occurrence of adverse neonatal outcomes associated with different levels of UC-pH from an unselected population may lead to reconsiderations about the threshold for more intensive observation of infants with mild acidaemia to identify clinical signs of hypoxic ischemic encephalopathy earlier. The study highlights the relevance of universal UC-pH measurement.
Results from the study on the risk of adverse infant and maternal outcomes in late term pregnancies may aid administrations and clinicians to decide when to recommend or offer induction of labour in late term pregnancies and the results can be used in shared decision making.
The RS method evaluated in Study IV might be comparable or better than PS matching to predict the consequences of induction of labour at GA 41+0 weeks based on observational data.

6.2 GAPS IN EVIDENCE AND FUTURE STUDIES

The national recommendation on universal measuring of UC-pH in Denmark was fully implemented in 2014. When I planned this PhD in 2018, the oldest children born after 2014 were four years of age and the cohort would not be large enough to investigate long-term outcome caused by acidaemia. Instead, I decided to investigate the risk of complications within the first 28 days after birth acknowledging that most of the infants with neonatal complications do not have long-term complications. Now the oldest children are 10 years old, and it is possible to study the long-term outcomes based a cohort with universal UC-pH measurement and including both vigorous and non-vigorous infants. That study would be extremely valuable for neonatologists and obstetricians when planning clinical controls in childhood and when informing parents on the prognosis.
The advantages and disadvantages of induction of labour in the first days of GW 41 in uncomplicated pregnancies have been investigated in several studies. This has led to a change in recommendations to induce labour in GA 41+0 weeks in many countries. In Denmark, the subject is a matter of debate, and the discussion is concentrated on whether the evidence is sufficient to change the recommendation. Unfortunately, the SWEPIS was stopped by the Swedish authorities after including one third of the planned participants because of an unexpectedly high proportion of perinatal deaths in the expectant management group. For ethical reasons it is not possible to plan a new randomized trial, hence, further studies are needed based on observational data. In the author group, we plan to do a study on the occurrence of complications from induction of labour in uncomplicated pregnancies in 41+0 weeks in a setting like the Danish and, in collaboration with health economists to study the financial consequences of changing the recommendations.

6.3 RETROSPECTIVE CONSIDERATIONS

My clinical experience was of great value when planning the studies and interpretating the results. My experience in data management and statistical analysis on the other hand was almost non-existing and thus constituted a challenge. Even though it was hard job, and I am very far from being an expert, I have acquired useful knowledge for my future work. As an obstetrician doing research in neonatology, I also had to expand my knowledge in neonatology. I have had great help from my paediatric coauthors, from my visits at the neonatal department at Aarhus University Hospital and from attending two neonatal congresses.

When Study III was published results were interesting to the public because timing of induction of labour in late term pregnancies was debated in the media and among pregnant women. This resulted in a newspaper article describing the results. It was quite a struggle to avoid that the journalist gave too much focus to the risk of death

and severe complications. I learned a lot from that process, and I am sorry if the article introduced fear among pregnant women.

The study periods in the studies included in this thesis stopped long before the thesis was submitted (2018). Clinical practice in obstetrics and neonatology changes in a period of six years. I could have updated data during the six years, but it is a comprehensive process and in 2022 the DNPR introduced a new version of the registry, which made it difficult to get access to updated data in the years that followed.[156]

It was not my original plan to do a PhD study, but I am glad that I did. It has given me the opportunity to join PhD courses and collaborate with other PhD students, which has been very valuable. I will continue to do research at the Danish Centre for Health Services Research, which I look forward to.

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Supplementary

Table S1. Observational studies on the risk of neonatal complication among infants with acidemia compared to infants without acidemia.
Table S2. Covariates in the four studied comprised in the thesis.
Table S3. ICD10 codes

Table S1 Observational studies on the risk of neonatal complication among infants with acidemia compared to infants without acidemia.

Author, Year Journal N	Design Origin Period	Study population	Exposure	Comparison	Outcome
Gonen et al. 2023 [40] **Arch. Gynecol. Obstet.** **N=14 338**	Retrospective cohort study Israel, 2014–2022	Live, singleton, non-anomalous, term (37+0 and 41+0) low risk vaginal deliveries. Low risk: Excluded chorioamnionitis, preeclampsia, SGA, meconium stained or bloody amniotic fluid.	UC-pH <7.15	UC-pH ≥7.15	Neonatal encephalopathy with seizures and/or death, encephalopathy within 24 hours of birth, 5-minute Apgar scores and NICU admission
Lau et al. 2022 [55] **AOGS** **N=248**	Retrospective cohort study Hong Kong, 2003–2017	Liveborn infants born after GA 34 weeks with UC-pH <7.00.	UC-pH <6.9	UC-pH ≥6.90	Intact survivors, deaths, cerebral palsy and/or developmental delay.

Bligard et al. 2022 [68] **AJOG** **N=2081** **UC-pH <7.20: 252/2081**	Retrospective cohort study USA, 2004–2014	Live, singleton, non-anomalous term infants delivered by planned CS performed under regional anesthesia.	UC-pH <7.2	UC-pH ≥7.20	Primary composite outcome: neonatal death, encephalopathy, therapeutic hypothermia, seizures, intubation, and respiratory distress. Secondary outcomes: Apgar, NICU admission, seizures, respiratory distress syndrome (RDS), intubation, therapeutic hypothermia, neonatal encephalopathy, or neonatal death.
Kumar et al. 2022 [70] **J Mother Child.** **N=300**	Retrospective cohort study India, 2017–2018	Live, singleton, term, infants from high-risk pregnancies with uc-Ph <7.20. Exclusions: Low-risk pregnancy, malformations, MgSO4 before delivery and uterine rupture	UC-pH <7.20	UC-pH ≥7.20	Neonatal resuscitation NICU admission, early neonatal complications, early neonatal death.
De Bernardo et al. 2020 [74] **Ital. J. Pediatr.** **N=352**	Retrospective cohort study Italy, 2018	Term infants with body weight appropriate for gestational age, 5- minutes Apgar Score > 7, UC-pH < 7.4, BE <-8 mmol/l or lactate > 6 mmol/l.	UC-pH <7.12	PH ≥7.12	RDS
Gonen et al. 2019 [41] **AJOG** **N=3001** **PH <7.15: 79**	Retrospective cohort study Israel, 2009–2018	Singletons delivered by planned CS.	UC-pH <7.15	PH ≥7.15	Apgar score, sepsis, blood transfusion, phototherapy, respiratory or cerebral morbidity, NEC, or neonatal death. Composite outcome was more than one of complication.
Vesoulis et al. 2018 [56] **Arch Dis Child Fetal Neonatal Ed.** **N= 27 028**	Retrospective cohort study USA, 2008–2015	Infants with GA ≥36 weeks with no congenital anomalies.	UC-pH <7.00	UC-pH 7.00–7.10	Moderate/severe encephalopathy, therapeutic hypothermia, and neonatal death.

UC-pH <7.O0: 85,					
Kelly et al. 2018 [68] **Arch Dis Child Fetal Neonatal/BMJ** **N=56574** **UC-pH <7.00: 507**	Retrospective cohort study UK, 2005–2013	Live infants with GA >35 weeks, UC-pH <7.00 and/or BD >12 mmol/l on either UC blood or neonatal gas within one hour from birth.	UC-pH <6.8	UC-pH 6.9–6.99 6.8–6.89	Apgar score, intermittent positive pressure ventilation, encephalopathy, cardiac massage, NICU admission, death in delivery room
Sabol et al. 2016 [69] **AJOG** **N=26 669** **UC-pH <7.00: 133, < 7.10: 906**	Retrospective cohort study USA, 1990–2009	Live, singleton, non-anomalous, term with 5-minute Apgar scores of >7. PH measured in 86% of deliveries.	UC-pH ≤7.00 and ≤7.10	UC-pH >7.00 and >7.10	NICU admission, meconium aspiration syndrome, RDS, and neonatal sepsis.
Bouiller et al. 2015 [70] **J Gynecol Obstet Biol Reprod** **N=29 416** **UC-pH <7.00: 129**	Retrospective cohort study France, 2002–2010	Live births with GA ≥34weeks Included 82 with "real intrapartum asphyxia."	UC-pH <6.9	UC-pH ≥6.9	NICU admission, neonatal death, multiorgan failure, neonatal encephalopathy
Morgan et al. 2015 [54] **Obstet Gynecol.** **N= 323 027** **UC-pH <7.00 and BD >12 mmol/L: 1265**	Retrospective cohort study USA, 1988–2013	Singletons > GA 35 weeks	UC-pH <7.00 and BD >12 mmol/L	UC-pH ≥7.00 and BD <12 mmol/L	Apgar score, RDS, hypoglycemia, sepsis, seizures, NEC, intracranial hemorrhage and neonatal death
Georgieva et al. 2013 [75] **EJOG** **N=34 510** **UC-pH <7.00 and BD >12 mmol/L: 1752**	Retrospective cohort study UK, 1993-2008	Term singletons. UC-pH from 39.9% of all deliveries.	UC-PH centiles	-	EveREst plot showing the relation between pH and Apgar score, seizures, other cerebral problems, neonatal death, resuscitation and use of facial mask to give oxygen. A-V pH differences.
Yeh et al. 2012 [19] **BJOG** **N=51 519**	Observational cohort study UK,	Live, singleton, non-anomalous, term infants.	UC-pH <7.00, 7.01–7.05,	UC-pH 7.26–7.30	Neonatal encephalopathy with seizures and/or death, encephalopathy within 24 hours of

UC-pH <7.00: 1112	1991–2009.	PH measured in 42% of deliveries.	7.06–7.10, 7.11–7.15, 7.16–7.20, 7.21–7.25		birth, 5-minute Apgar scores and NICU admission
Silva et al.2008 [67] **J Perinat Med N=28 484** UC-pH<7.00: 87	Case control study USA, 1991–2004	Non-anomalous infants with hypotonia at birth requiring resuscitation and admission to the NICU. Controls by gestational age. GA ≥34 week.	UC-pH <7.00 and 7.00–7.10	UC-pH ≥7.00 and 7.00–7.10	Comparing cases with neonatal hypotonia and controls
Chauhan et al.2005 [76] **J Matern Fetal Neonatal Med. N=13 190 UC-pH<7.00: 87**	Retrospective cohort study USA, 1997–2002	Live, singletons with GA >34 weeks The prevalence, of pH below 7.00 was 0.6% Ph measured in 90%.	UC-pH <7.00 with organ injury.	UC-pH <7.00 and no organ injury.	NICU, neonatal organ system injury (central nervous system injury, hematologic, hepatic, renal, or cardiac) neonatal mortality.
Lavrijsen et al. 2005 [77] **Biol Neonate. N=95 UC-pH<7.00: 95.**	Retrospective cohort study. NL, 1994–2002	Term infants with severe acidemia. UC-pH collected in 49% of infants. UC-pH collected in 49%	PH <7.00	UC-pH >7.15	Seizures, neonatal death, cerebral palsy or neurodevelopmental delay.
Ghosh et al.2003 [66] **J Gynecol Obstet N=26**	Case-control study India, 1999–2001	Infants with GA 37^{+0}–40^{+6} weeks.	1 min Apgar score <6/10 and UC-pH ≤7.15.	1 min Apgar score of >6/10 UC-pH >7.15.	Admission to NICU, hypoxic ischemic encephalopathy (HIE) or neonatal death.
Victory et al. 2003 [57] **AJOG N=20 456 UC-pH <7.00: 71**	Prospective evaluation Canada, 1995–2002	Live, singleton, term infants with no major anomalies	UC-pH SD	-	Apgar less than 7 at 5 minutes, NICU admission, and need for assisted ventilation.

Heller et al. 2003 [58] **Geburtshilfe Neonatol N= 531 135 UC-pH <7.00: 1352**	? Germany, 1990–1999	Non-anomalous singletons, GA>26 weeks with neonatal death within the first week.	UC-pH <7.00, 7.01–7.10, 7.11–7.20	UC-pH >7.20	Neonatal death
Sehdev et al. 1997 [59] **AJOG N =10 705 UC-pH <7.00: 73**	Case-control study USA, 1992–1996	Neonates with an umbilical arterial pH <7.00 were divided into cases of adverse neonatal outcome or controls. Preterm births included.	UC-pH <7.00 and compli-cations*	UC-pH <7.00 and no comp.	NICU admission, length of stay, and complications.
Ingemarrson et al. 1997 [81] **BJOG N=154**	Case-control study Sweden, 19881–994.	Term infants with measured UC-pH	UC-pH <7.05	UC-pH > 7.10	Apgar score, HIE, death
Perlman et al. 1993 [60] **PEDIATRICS N=96 UC-pH <7.00: 21**	Prospektive evaluation USA, 1993	Term infants admitted to NICU.	PH <7.00	UC-pH ≥7.00	Seizures
Van den Berg et al. 1996 [44] **AJOG N=10 699 UC-pH <7.00: 84**	Retrospective cohort study. NL, 1983–1993	Non-anomalous infants 17% was preterm.	UC-pH <7.00	UC-pH >7.24	Apgar, seizures, Aspiration, NICU admission, neonatal death.
Nagel et al. 1995 [61] **AJOG N=30**	Observational cohort study NL, 1991	Neurodevelopmental assessment in children born with an umbilical artery pH < 7. UC-pH were available 64% of deliveries.	UC-pH <7.00	-	NICU admission, artificial ventilation, neonatal death, major abnormalities or minor abnormalities at age 1 to 3 years
Valentin et al. 1993 [62]	Sweden, 1982	Live born infants. Malformations not excluded.	UC-pH ≤7.00	UC-pH ≥ 7.11	Composite measure of neonatal sequelae, including severe

Arch Gynecol Obstet N=1128 UC-pH <7.00:13			≤7.10;		symptoms requiring treatment (for example, ventilation, intravenous fluids), death, or survival with sequelae

***** seizures, intraventricular hemorrhage, gastrointestinal dysfunction, RDS, sepsis or death.

Table S2. Covariates in the four studied comprised in the thesis.

Covariate	Description	Role in the study design
Year of birth		Multivariate analysis in Study II, III and IV
Parity [54]	First time mothers or multipara	Multivariate analysis in Study III and IV
Maternal BMI [121]	Calculated from pre-pregnancy weight and height	Multivariate analysis in Study III and IV
Maternal age [10,122,123]	Defined as maternal age at time of birth	Multivariate analysis in Study III and IV Excluded in Study IV: maternal age < 18 years of age
GDM [124]		Multivariate analysis in Study IV
Hypertensive disorders [54]	Hypertension and/or preeclampsia	Excluded in Study IV.
IDDM [125]		Excluded in Study IV Multivariate analysis in Study II
Previous CS [126,127]		Excluded in Study IV
Oligohydramnios [128]		Excluded in Study IV
Induction of labour [129]	Including medical induction (prostaglandins or oxytocin) or mechanical induction (artificial rupture of membranes or induction with a balloon catheter).	Multivariate analysis in Study III
Induction of labour *and* PROM	Induction of labour in case of prelabour rupture of membranes.	Excluded in Study IV
GA at birth [130,131]		Restriction on GA in all studies
Intrapartum fever [76]		Multivariate analysis in Study II
Fetal presentation [124]		Non-cephalic presentation excluded in Study IV
Infant sex assigned at birth [132]		Multivariate analysis in Study II
Birth weight deviation [133,134]	According to growth curves from Marsál [135]	Birthweight <2 SD excluded in Study IV

		Multivariate subanalysis in Study II Multivariate analysis in Study IV (weight retardation below 1 SD and LGA (above 2 SD))
Infant malformations of heart, lungs, or nervous system.		Excluded in all studies

Table S3. ICD10 codes

	ICD10
First parity	DZ340
Smoking	DZ358M18 DUT2
Prior Cesarean section	DZ358E DO342 DO757
Gestational diabetes	DO244*
Insulin dependent diabetes mellitus	DO240* DO241* DO242* DO243* DO245* DO249* DE1*
Preeclampsia	DO11 DO14 DO15
Hypertension	DO10 DO13 DO16 DI1
Placental insufficiency Study I	DO363 DO365 DO368E DO368F DO283A1 DO410
Other medical diseases: Study II ,III and IV Respiratory diseases, hypothyroidism, hyperthyroidism, polycystic ovary syndrome, gastrointestinal diseases, neurological disease	DO266G* DO992B DE03* DO992C DE05* DO993A* DG35* DG40* DO995* DJ44* DJ45* DZ980* DO996A DK50* DO996B DK51* DM05* DM06* DM32* DR768D* DE282*
Pre- pregnancy medical conditions IDDM, hypothyroidism, hyperthyroidism, polycystic ovary syndrome (PCO), gastrointestinal diseases, neurological disease, anemia, hypertension Study I	DO240* DO241* DO242* DO243* DO245* DO249* DE1* DO266G* DO992B DE03* DO992C DE05* DO993A* DG35* DG40* DO995* DJ44* DJ45* DZ980* DO996A DK50* DO996B DK51* DM05* DM06* DM32* DR768D* DE282*DO990*DO10
Pregnancy induced medical conditions. Hypertension/preeclampsia, GDM, ICP Study I	DO13* DO16* DO11* DO14* DO15* DO13* DO244* DO266G
Abortus habitualis	DO262 DN969

Abuse	DZ358M10 DZ358M11 DF101 DQ86.0 DF102 DZ358M12 DZ358M13 DZ358M14 DZ358M15 DZ358M16 DZ358M17
Minor mental illness	DO993B2 DF33 DO993B3 DO993B4 DF41* DF42* DO993B5
Serious mental illness	DO993B1 DF2* DF31* DF34*
Breech (vaginal delivery)	DO641* DUP07 DUP08 DUP09 DUP10 DUP11 DUP16
Serious births events	DO710 DO711 DO690 DO660 DO431E Study II
Intrapartum fever	DO750
Induction of labour	KMAC00 KMAC96A BKHD2*
Apgar 0–3/1 min.	DP210*
Apgar 4–6/1 min.	DP211*
Apgar 0–6/5 min.	DVA00 DVA01 DVA02 DVA03 DVA04 DVA05 DVA06
Umbilical cord pH	ZZ4232 ZZ4232A ZZ4232V
Hypothermia treatment	BMFL38B
Mechanical ventilation	BGDA0*
iNO treatment	BGXA71
CVC	BMBZ51*
CPAP	BGFC32*
Meconium aspiration	BG240
Seizures	DP90*
Hypoglycemia	DQ2 DQ30 DQ31 DQ32 DQ33 DQ34 DQ0
Malformations	DQ2* DQ30* DQ31* DQ32* DQ33* DQ34* DQ0*
Stillborn	DP95* DZ371 DO364
Suspected fetal distress during birth	DO68*
Scalp pH/lactate	ZZ4224 ZZ4227 BMBA03
Intrapartum fever	DO752
Emergency cesarean section	KMCA10A KMCA10E
Operative vaginal delivery	KMAE00 KMAE03 KMAE20 KMAE96 KMAF00 KMAF10 KMAF20 KMAF96
Shoulder dystocia	KMAH15 DO660
Uterine rupture	KMCC00 DO710
Vasa previa	DO431E
Severe lacerations (grade 3 and 4)	DO702 DO703
Hemorrhage	DO720

CPAP= Continuous positive airway pressure; CVC= Central venous catheter; NO treatment= treatment with nitrogen oxide.