Umbilical cord clamping - from the first decision to the short- and long-term outcomes

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Manuela Isacson

LUND
UNIVERSITY

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Abstract:

Term infants receive a placental transfusion of approximately 30% of their total blood volume after birth, when umbilical cord clamping (CC) is delayed. Delayed CC increases iron stores and improves neurodevelopment up to 4 years. The aim of this thesis was to increase the scientific evidence for some of the current knowledge gaps in umbilical cord management after birth.

A prospective observational cohort study in Sweden explored the association between time to CC and neonatal and maternal short-term outcomes. The Infant and Young Child Development (IYCD) tool assessed neurodevelopment in two-year-old Nepalese children who had been resuscitated with an intact cord vs after early CC as part of a randomised controlled trial (RCT). Midwives' decision-making process when a non-vigorous neonate is born in Sweden was evaluated with an inductive-descriptive design and analysed with thematic analyses. Neurobehavioral outcome at 10 years of age after a RCT comparing early and delayed CC was explored by using a screening questionnaire for attention deficit hyperactivity disorder.

We found no adverse effects of CC ≥ 3 min compared to CC < 3 min in 904 neonates with gestational age ≥ 35 weeks. Resuscitation with intact umbilical cord was associated with significantly higher total IYCD scores compared to resuscitation after early CC. Interviews with 14 midwives generated the overarching theme, *"The balancing act of clamping the umbilical cord"*. No difference in neurobehavioral outcome at 10 years of age was seen between children subjected to early versus delayed CC.

This thesis addressed some of the existing knowledge-gaps regarding delayed CC and found that delayed CC in Sweden was not associated with adverse outcomes. In Nepal, intact cord resuscitation was associated with slightly improved neurodevelopment compared to resuscitation after early CC. Exploring knowledge gaps on delayed CC can help develop guidelines and programmes about optimal neonatal care.

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Grown-ups never understand anything by themselves, and it is tiresome for children to be always and forever explaining things to them The Little Prince

Table of Contents

Abstract

Background: Term infants receive a placental transfusion of approximately 30% of their total blood volume after birth, when umbilical cord clamping (CC) is delayed. Delayed CC increases iron stores and improves neurodevelopment up to 4 years. The aim of this thesis was to increase the scientific evidence for some of the current knowledge gaps in umbilical cord management after birth.

Methods: A prospective observational cohort study in Sweden explored the association between time to CC and neonatal and maternal short-term outcomes. The Infant and Young Child Development (IYCD) tool assessed neurodevelopment in two-year-old Nepalese children who had been resuscitated with an intact cord vs. after early CC as part of a randomised controlled trial (RCT). Midwives' decision-making process when a non-vigorous neonate is born in Sweden was evaluated with an inductive-descriptive design and analysed with thematic analyses. Neurobehavioral outcome at 10 years of age after a RCT comparing early and delayed CC, was explored by using a screening questionnaire for attention deficit hyperactivity disorder.

Results: We found no adverse effects of CC ≥ 3 min compared to CC < 3 min in 904 neonates with gestational age ≥ 35 weeks. Resuscitation with intact umbilical cord was associated with significantly higher total IYCD scores compared to resuscitation after early CC. Interviews with 14 midwives generated the overarching theme, *"The balancing act of clamping the umbilical cord"*. No difference in neurobehavioral outcome at 10 years of age was seen between children subjected to early versus delayed CC.

Conclusion and future research: This thesis addressed some of the existing knowledge-gaps regarding delayed CC and found that delayed CC in Sweden was not associated with adverse outcomes. In Nepal, intact cord resuscitation was associated with slightly improved neurodevelopment compared to resuscitation after early CC. Exploring knowledge gaps on delayed CC can help develop guidelines and programmes about optimal neonatal care.

Overview of the four studies in this thesis

Study 1	
Aim	To investigate whether delayed cord clamping (CC) beyond 3 min is associated with increased short-term risks for the neonates and their mothers
Study design	Prospective observational cohort
Setting	Two labour wards in Region of Halland, Sweden
Participants	Expected vaginal birth ≥ 35+0 gestational weeks
Data collection	Primary outcomes: admission to neonatal ward, need for phototherapy, and maternal postpartum blood loss in relation to CC time
Study 2	
Aim	To evaluate neurodevelopmental outcomes at 2 years of age in children randomised to resuscitation after immediate CC or with an intact umbilical cord
Study design	Two-year follow-up of a randomised controlled trial (RCT)
Setting	Paropakar Maternity and Women's Hospital in Kathmandu, Nepal
Participants	Children born after uncomplicated singleton pregnancy, expected vaginal delivery at 33 – 41 gestational weeks and in need of resuscitation. All 231 resuscitated children were eligible for follow-up
Data collection	Neurodevelopment assessed by the World Health Organization tool Infant and Young Child Development
Study 3	
Aim	To improve knowledge about midwives' decision-making process when a non-vigorous neonate is born, with emphasis on the CC decision
Study design	Qualitative interview study of midwives, using the Critical Incident Technique, evaluated with an inductive-descriptive design and analysed with thematic analyses
Setting	Personal telephone interviews
Participants	Midwives currently working in Swedish labour wards
Data collection	Semi-structured telephone interviews in Swedish that were digitally recorded and transcribed verbatim
Study 4	
Aim	To explore potential long-term neurodevelopmental effects of early vs. delayed CC in school-aged children who were vigorous at birth
Study design	10 year follow-up of a RCT comparing early (standard) vs. delayed CC (intervention)
Setting	The hospital of Halland, Sweden
Participants	Children included in the Cord Clamping Trial (uncomplicated pregnancy, healthy mother, vaginal birth, gestational age 37-41 weeks) who were also part of the longitudinal Halland Health and Growth Study
Data collection	Neurobehaviour assessed by Swanson, Nolan and Pelham scale IV (SNAP-IV), a screening tool for attention deficit hyperactiviy disorder

Popular science summary

Your first three minutes

Pexels. Marck Rodriquez

Before you were born, your lungs were filled with water and your normal oxygen level was much lower than the one you have now. The moment you were born, your body only had a couple of minutes to adapt to an independent life breathing air. When you were born, you also received a last placental transfusion from your umbilical cord that affected you for months, maybe years later – if your umbilical cord was not clamped immediately.

This thesis is about the umbilical cords that are not clamped immediately after birth; it is about the umbilical cords that are allowed to provide the newborn with a last placental transfusion. When this is allowed – which takes about 3 minutes – the time when the cord is clamped is called *delayed cord clamping*. Each paper in the thesis targets different aspects of delayed cord clamping.

If the umbilical cord is clamped a couple of minutes after birth, rather than immediately after, it provides the newborn with a placental transfusion equivalent to 30% of the newborn's total blood volume. In animals who are not breathing when they're born, allowing for this continued placental transfusion while helping them to start breathing results in a smoother transition and adaptation to the new life outside the womb. In humans, delayed cord clamping improves iron stores, myelination (which allows the electrical impulses to transmit efficiently along the nerve cells) and fine motor performance in 4-year-old children.

In one of our studies, we found an association between the children who were resuscitated while the umbilical cord was still providing them with blood (*intact cord resuscitation*) and better performance in developmental tests at 2 years of age. This is an important finding because newborns that need assistance to start breathing, i.e. newborns in need of resuscitation, are currently resuscitated after the umbilical cord is clamped. The current recommendation is that newborns in need of resuscitation have their cord clamped early, because the evidence for delayed cord clamping in non-

breathing newborns is not considered sufficient. Our study on intact cord resuscitation was performed in Nepal and preceded a larger multicentre study in Sweden. In order to better understand midwives' criteria for umbilical cord clamping, midwives were interviewed about their decision-making process when a non-vigorous baby was born. Intuition and experience were important determinants for the midwives' decisions, as well as the constant balancing of knowledge, evidence and opinions, the current birth history, the appearance and perception of the newborn, and the underlying belief that mothers and newborns shouldn't be separated.

The three first minutes of extrauterine life can make a major difference for the infant's iron stores. But does it make a difference after a decade? One of the main knowledge gaps on delayed cord clamping is the lack of evidence regarding the long-term outcomes. The worldwide acknowledged International Liaison Committee on Resuscitation states that a task force knowledge gap on cord management is *"whether the demonstrated reduction in early iron deficiency seen after late cord clamping improves long-term neurodevelopment".* Therefore, we explored the long-term outcomes of delayed cord clamping in 10-year-old children, which has not been done previously in any study. However, we did not find any differences in neurobehavioral screening scores between children who were subjected to early compared to delayed cord clamping.

Pexels, Abhi Nikam

Every human being on earth had their cord circulation stopped at some point in life. But we still don't know if and how the later cord clamping affects us in the long run. We don't know if the newborn's nutritional status or underlying risks for jaundice should be taken into consideration when clamping the cord. We don't know if the timing of cord clamping affects newborns that don't breathe, and we don't know if the cord clamping time has implications for the future in the non-breathing newborns. This thesis intended to answer some questions and raise new focus areas of research. We all had our umbilical cord circulation ended at some point – if it was delayed and we were full-term we know it improved our early iron stores, and if we were premature, it might even have increased our chances of survival. One thing is sure: the day when you were born, your first three minutes mattered.

List of Papers

Paper I

Winkler A, **Isacson M**, Gustafsson A, Svedenkrans J, Andersson O. Cord clamping beyond 3 minutes: Neonatal short-term outcomes and maternal postpartum hemorrhage. Birth. 2022;49(4):783-91.

Paper II

Isacson M, Gurung R, Basnet O, Andersson O, Kc A. Neurodevelopmental outcomes of a randomised trial of intact cord resuscitation. Acta Paediatr. 2021;110(2):465-72.

Paper III

Isacson M, Andersson O, Thies-Lagergren L. Midwives' decision-making process when a non-vigorous neonate is born - a Swedish qualitative interview study. Midwifery. 2022;114:103455.

Paper IV

Isacson M, Hellström-Westas L, Domellöf M, Dahlgren J, Roswall J, Andersson O. Neurobehavioral outcomes at 10 years of age following delayed umbilical cord clamping. Manuscript.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADHD	Attention Deficit Hyperactivity Disorder
CC	Cord Clamping
CI	Confidence Interval
CIT	Critical Incident Technique
DAZ	Development for Age Z-score
ERC	European Resuscitation Council
HIV	Human Immunodeficiency Virus
ID	Iron Deficiency
IDA	Iron Deficiency Anaemia
ILCOR	International Liaison Committee on Resuscitation
IYCD	Infant and Young Child Development
LMIC	Low- and Middle-Income Country
ODD	Oppositional Defiant Disorder
PPH	Postpartum haemorrhage
RCT	Randomised Controlled Trial
SD	Standard Deviation
SNAP-IV	Swanson, Nolan and Pelham Scale, 4th Edition
WHO	World Health Organization

Introduction

Every year, approximately 134 million neonates are born in the world (1). Each of these neonates need to immediately adapt and transition to the extrauterine life, and for each of these births a decision is made on when to clamp and cut the umbilical cord.

The transition of a foetus to newborn extrauterine life is one of the most dramatic processes in biology. Major hemodynamic changes take place, and the newborn starts oxygenating the blood through breathing with the lungs. During this transition, the circulating blood in the placenta can be further transferred to the newborn if the umbilical cord is not clamped or cut immediately after delivery – a process called "placental transfusion" (2-5). Delayed, also referred to as deferred/late/physiological, cord clamping (CC) is a CC time that has allowed for a placental transfusion to take place (2, 3).

Historical context

> *If the secundines be wholly excluded before the pulsation in the navel string is stopped, no bad consequences will ensue, the circulation will still be carried on betwixt the child and the placenta as perfectly as if it were in the womb, till the child's lungs are fully expanded and the necessary alterations have taken place*
> *- White, 1773.*

In 1773 Charles White described how the placental circulation continues outside the womb (Figure 1) (6). However, the knowledge about the placental transfusion and CC has not been a quick journey. About a century after White wrote about the placental circulation, in 1875, Pierre Budin published the first study on

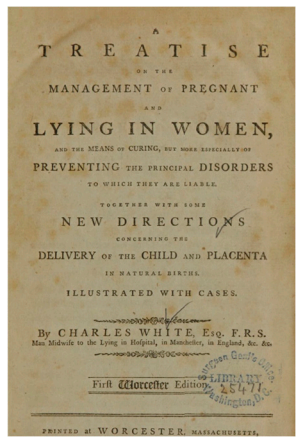
A
TREATISE
ON THE
MANAGEMENT OF PREGNANT
AND
LYING IN WOMEN,
AND THE MEANS OF CURING, BUT MORE ESPECIALLY OF
PREVENTING THE PRINCIPAL DISORDERS
TO WHICH THEY ARE LIABLE.
TOGETHER WITH SOME
NEW DIRECTIONS
CONCERNING THE
DELIVERY OF THE CHILD AND PLACENTA
IN NATURAL BIRTHS.
ILLUSTRATED WITH CASES.
By CHARLES WHITE, Esq. F.R.S.
Man Midwife to the Lying in Hofpital, in Manchefter, in England, &c. &c.
First Worcester Edition.
PRINTED at WORCESTER, MASSACHUSETTS,

Figure 1. From the front page of *A Treatise on the Management of Pregnant and Lying-In Women,* White C. London, 1773. With permission from the National Library of Medicine.

CC (7). In the mid 20th century, several studies observed a placental transfusion that was completed at around 3 min after birth (4, 8). Despite this knowledge, the common practice at the time was early CC (9). Early CC was advocated as part of active management of the third stage of labour, which was implemented in an attempt to reduce postpartum blood loss (10).

Foetal-placental circulation and the placental transfusion

The foetus depends on the blood circulation from the placenta, through the umbilical cord, to be able to receive oxygen and nutrients, and to be able to remove carbon dioxide and other waste products. During pregnancy, the total blood volume of the foetal-placental compartment is approximately 115 mL/kg of foetal weight (5).

There are different ways of indirectly assessing the placental transfusion. One way is to simply compare birth weights between early and delayed clamped neonates (11). Another way is to assess the residual placental blood volume, which has been done by for example collecting the residual placental blood volume in a cylinder and relating it to the neonate's total blood volume increase (8, 12), exemplified in Figure 2.

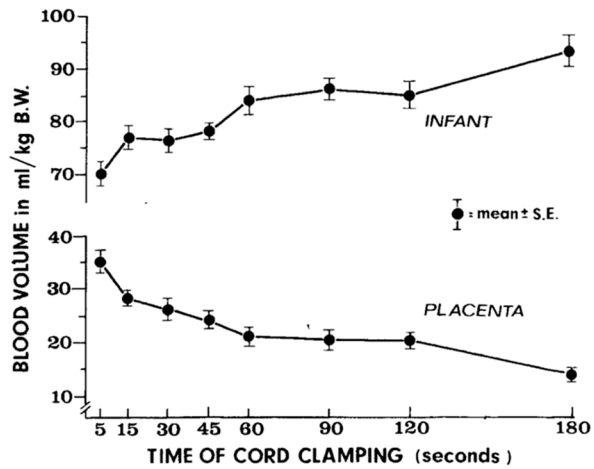

Figure 2. Relation between infant's blood volume and residual placental blood volume. From Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet. 1969;2(7626):871-3. With permission.

A third way of indirectly assessing the placental transfusion is by serial weights of the same neonate directly after birth. Farrar et al. weighed 26 neonates by using digital scales, Figure 3 (13). With the neonate's umbilical cord still intact, they recorded average weight every two seconds. They found that the placental transfusion provided the neonate with on average 83 to 110 mL of blood, depending on the statistical analysis used and if artefacts (such as sharp spikes in the graph below, Figure 3, when the neonate was placed on the scales) were removed. In most neonates the placental transfusion ceased 2 min after delivery, although for some it continued up to 5 min.

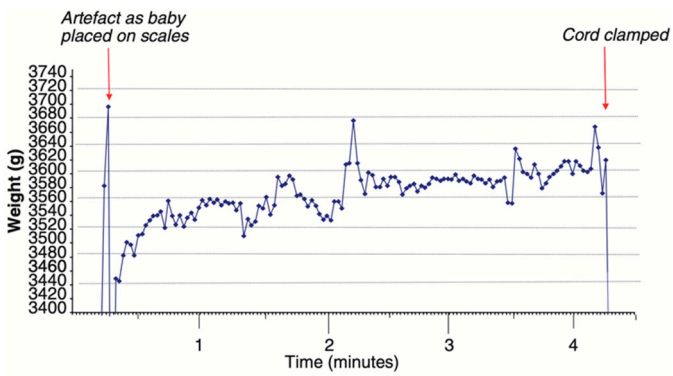

Figure 3. Weight change from birth to cord clamping. From Farrar D, Airey R, Law GR, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: weighing babies with cord intact. BJOG. Jan 2011;118(1):70-5. With permission.

After almost 150 years of research quantifying the placental transfusion, the expected amount of blood being transfused to the neonate when delaying CC has been concluded to be approximately 15-30 mL/kg (14). This means that when the cord is clamped 3 - 5 min after birth, term infants receive a placental transfusion of up to 40% of their total blood volume (13).

Delayed cord clamping

There is no single definition as regards timing of umbilical CC. Early CC is often defined as CC within or up to 30 - 60 s after delivery (15), but the definition of delayed CC varies even more. The American College of Obstetricians and Gynecologists (ACOG) recommend delayed CC for at least 30 – 60 s in healthy term neonates (16). However, a Cochrane review

from 2013 and the latest guidelines from the International Liaison Committee on Resuscitation (ILCOR) acknowledge that most studies that compared early and delayed CC, defined delayed CC as ≥ 60 s (15, 17). In practice, CC often takes place after cessation of cord pulsations (15, 18). Further, an approach where CC takes place after ventilation is established, often referred to as physiological CC, has also been proposed (19).

Several experimental studies have demonstrated the effects of immediate versus delayed CC, and these have mostly related CC to the start of ventilation (i.e., CC prior to or after ventilation is established). In a lamb study, immediate CC before ventilation was established resulted in a rapid decrease in arterial and cerebral oxygen saturation as well as a sudden increase in blood pressure and cerebral blood flow. In contrast, CC after ventilation led to a smoother transition (seen as a more stable blood pressure and cerebral blood flow) (20). In another lamb study, Bhatt et al. showed that a more stable cardiovascular transition was achieved when ventilation was established prior to CC, because it avoided large changes in heart rate, arterial flow, and blood pressure as seen when the cord was clamped prior to ventilation (21). The decrease in adverse cardiovascular responses following CC when ventilation preceded CC, led Bhatt et al. to the conclusion that the indicated decrease in pulmonary vascular resistance (because lung aeration during ventilation increases pulmonary blood flow) prior to CC has a profound impact on the cardiovascular system after birth.

In human studies, a similar increase in oxygen saturation has been seen (22). However, in contrast to the animal models (21), an initially lower heart rate has been observed in neonates receiving intact cord resuscitation and/or physiologically-based CC (i.e., CC after established ventilation/breathing) compared to neonates who have been resuscitated after immediate CC or had their cord clamped prior to ventilation (22-24).

The physiology and transition during delayed CC are summarized and described in Figure 4 (25).

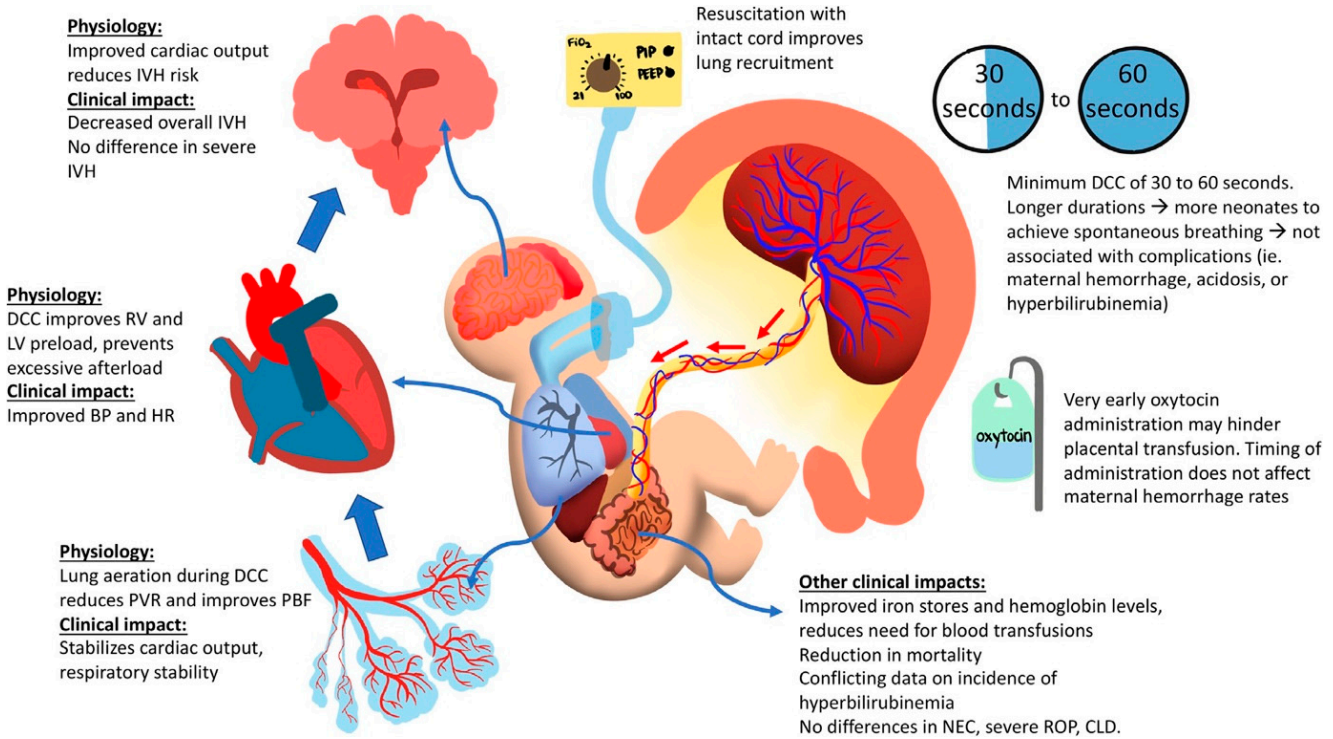

Figure 4. A newborn's "life line" - A review of umbilical cord management strategies. From Koo J, Katheria AC, Polglase G. Semin Perinatol. 2022;46(6):151621. With permission. The figure shows the multiple effects of delayed versus early umbilical cord clamping. Abbreviations: BP= blood pressure; CLD= chronic lung disease; DCC= delayed cord clamping; HR= heart rate; IVH= intraventricular hemorrhage in preterm infants; LV= left ventricle; NEC= necrotizing enterocolitis; PBF= pulmonary blood flow; PVR= pulmonary vascular resistance; ROP= retinopathy of prematurity; RV= right ventricle.

Intact cord resuscitation

Today, international guidelines recommend delayed CC in vigorous neonates (17). It has been proposed that also infants requiring immediate resuscitation after birth may benefit from a placental transfusion after delayed CC, and that resuscitation could be initiated with an intact umbilical cord (3, 26). The suggestion is based on data demonstrating the benefits of delayed CC and the results from experimental animal studies, showing a smoother transition when ventilation is established prior to CC (as mentioned above) (20, 21, 27). Furthermore, resuscitation with an intact cord is considered a simple, easily implemented and cost-neutral approach with potential high impact on neonatal outcome (3).

There are currently different opinions on the optimal timing of umbilical CC in neonates requiring resuscitation after birth. The European Resuscitation Council (ERC) Guidelines state, since 2021, that CC should ideally take place after the lungs are aerated, and that non-vigorous neonates can have delayed CC if appropriate support/resuscitation is possible (28). The Swedish recommendations from 2022 are more cautious, stating that CC needs to be performed so that resuscitation can be started within 60 s from birth, as there is not enough evidence for intact cord resuscitation (29). The latest, limited update from the American Heart Association does not give a clear answer regarding optimal umbilical cord management in non-vigorous neonates but concludes that the topic is a priority for future research (30).

Preterm infants and delayed cord clamping

A recent individual participant data meta-analysis based on 48 RCT with more than 6000 preterm neonates (< 37 weeks gestational age) compared delayed CC (30 s to at least 180 s, some trials delayed CC up to 5 min) with immediate CC (mostly defined as < 10 s) and found that delayed CC reduced death before discharge (OR 0.68, 95% CI 0.51-0.91, high certainty of evidence) (31). A Cochrane review a few years earlier showed similar results, and concluded that delayed CC may reduce the risk of death before discharge (32). The Cochrane review further found a modest reduction in risk of any intraventricular haemorrhage for delayed CC (32), however, in the meta-analysis no clear evidence for infants < 32 weeks was found, and for infants ≥ 32 weeks the evidence was very low (31).

Furthermore, in the meta-analysis, there was no evidence for a difference in necrotising enterocolitis or chronic lung disease, but the need for blood transfusion was reduced (with high level of evidence for neonates < 32 weeks) (31).

A concern with delayed CC and intact cord resuscitation, especially for preterm neonates, has been increased incidence of hypothermia, as seen in preterm neonates

placed skin-to-skin (33). Increased risk of hypothermia following delayed CC was also seen in the meta-analysis for neonates < 32 weeks, but the difference was only -0.13°C (95%CI -0.2 to -0.06) (31).

Concerns with delayed cord clamping

The increased blood volume following delayed CC has been proposed to lead to increased polycythaemia and higher blood viscosity (34, 35), increased risk for respiratory distress (36) and increased risk of hyperbilirubinemia (jaundice) requiring phototherapy (15, 16).

The potential risk of hyperbilirubinemia is repeatedly highlighted in several guidelines and refers mainly to a Cochrane review that in turn refers to a more than 20 years old unpublished study (15). The Society of Obstetricians and Gynaecologists of Canada recently updated their guidelines and recommend delayed CC for 60 s – but not longer because "deferred cord clamping beyond 60 s increases the risk of hyperbilirubinemia requiring phototherapy" (37). Further, the ACOG conclude that there is a small increase in jaundice requiring phototherapy in term infants undergoing delayed umbilical CC – which requires care providers to be aware of the risk (16).

Delayed CC has also been avoided for many years because of a theoretical risk of increased postpartum haemorrhage (PPH) when waiting to clamp the umbilical cord (38). Early CC was recommended, as part of "active management", in the belief that it could reduce the risk of PPH (38).

Finally, regarding intact cord resuscitation, there are concerns that resuscitation efforts might be postponed if the cord is not clamped immediately (35).

Iron and delayed cord clamping

Delayed CC increases iron stores and reduces the risk of iron deficiency in 4-8-months-old infants (11, 39, 40). Furthermore, delayed CC has been shown to lead to greater brain myelin content during infancy (41, 42), and improve neurodevelopment at 12 (43) and 48 months (44) – theoretically because of the increased iron stores. The improved iron stores following the placental transfusion during delayed CC have been summarized by Andersson et Mercer in a "placental model" that is presented in Figure 5 (3).

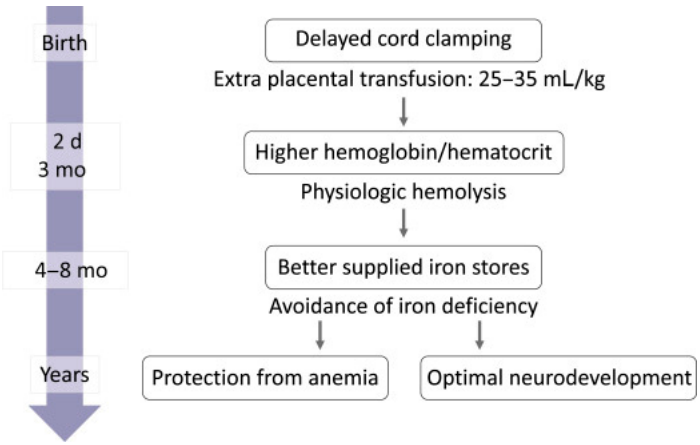

Figure 5. Effect of delayed cord clamping/placental transfusion on term infants (3). From Andersson O, Mercer JS. Cord Management of the Term Newborn. Clin Perinatol. 2021;48(3):447-70; with permission, CC BY.

If a full-term infant has a normal birth weight, is born to a mother with adequate iron stores and receives delayed CC, then the iron from birth together with the iron provided from breast milk, can be sufficient to maintain iron stores for 6 months (45). However, if any of these conditions are missing, then breast-fed infants may be at risk of ID before 6 months (45).

ID in infants and toddlers can be detrimental since this is a period of rapid neurodevelopment (46), and during this period, myelogenesis, neurogenesis and differentiation are processes that are dependent on adequate iron levels (46). Poor myelination and myelin deficit reduces processing speed in neural systems (47). The developing hippocampus seems to be especially vulnerable to ID and poor myelination, leading to reduced learning efficiency (47). ID in the late foetal period and early childhood also affects neurodevelopment with potential long-lasting effects on memory, language, cognitive and fine motor skills, as well as increased socioemotional and behavioural problems (48-51). Early ID further affects monoaminergic and glutaminergic neurotransmission (46, 52). Animal models of

ID suggest that noradrenergic, dopaminergic and serotonergic neurotransmission are affected in attention deficit hyperactivity disorder (ADHD), maybe not as a primary defect but as part of compensatory changes because of neural dysfunction in early development (53). In children born with low birthweight (2-2.5 kg), early iron supplementation has been shown to be associated with less behavioural problems in 7-year-old children (54). Further, in a setting with high prevalence of ID, iron supplementation in 6 to 12 months infants was associated with an improved adaptive behaviour at 10 years of age (55). The cycle and burden of early ID is shown in Figure 6.

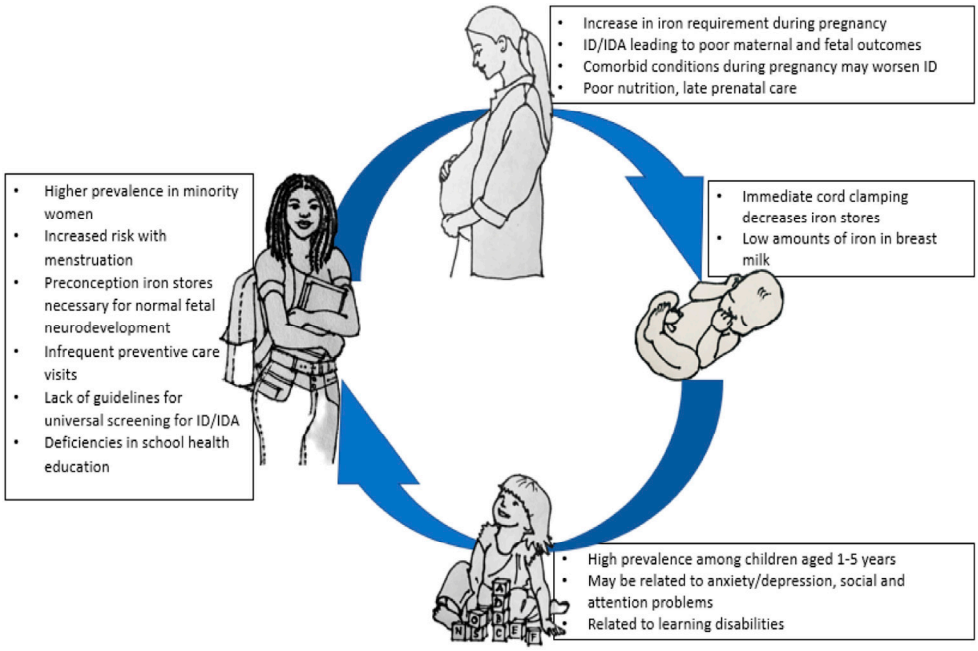

Figure 6. Burden of iron deficiency and iron deficiency anaemia. From Uduwana S, Nemerofsky S. Umbilical cord management - the first opportunity to improve healthcare disparities. Semin Perinatol. 2023;47(5):151785.With permission from Seminars in Perinatology. Abbreviations: ID, iron deficiency, IDA, iron deficiency anaemia.

However, alterations in the brain may be irreversible despite iron supplementation (49). Furthermore, concerns have been raised that the current recommended food intakes of iron far exceed those required to prevent ID, especially in high-income countries, and evidence suggest that iron overexposure leads to adverse outcomes later in life (56). Animal models have also shown that the brain responds to ID by increasing the expression of iron regulatory and transport proteins (57). If large amounts of medical iron are supplemented, there is a risk of iron overload and generation of reactive oxygen species because of the "activated system" (47). In other words, there is scientific evidence that the developing brain needs just *enough*

iron – neither too little, nor too much. Delayed CC is a physiological intervention that has the potential to improve iron stores to *just enough*.

Global aspects of delayed cord clamping

> *Delayed cord clamping is the earliest, least costly, and possibly the most critical event that can decrease health disparities and improve outcomes for minority populations.*
> *– Uduwana et Nemerofsky (58)*

Despite delayed CC and placental transfusion being studied in thousands of infants in randomised controlled trials (RCT), less research has been done in low- and middle income countries (LMIC) (59). This limits the generalisability of the current knowledge regarding the potential benefits of delayed CC. The lack of studies in LMIC means that we do not have enough evidence regarding effects of delayed CC in countries where the prevalence of ID is the highest. Iron deficiency anaemia (IDA) affects approximately 1.27 billion humans (60), and is the leading cause of years lived with disabilities in low- and low-middle socio-demographic indices (61). The global prevalence of anaemia is presented in Figure 7.

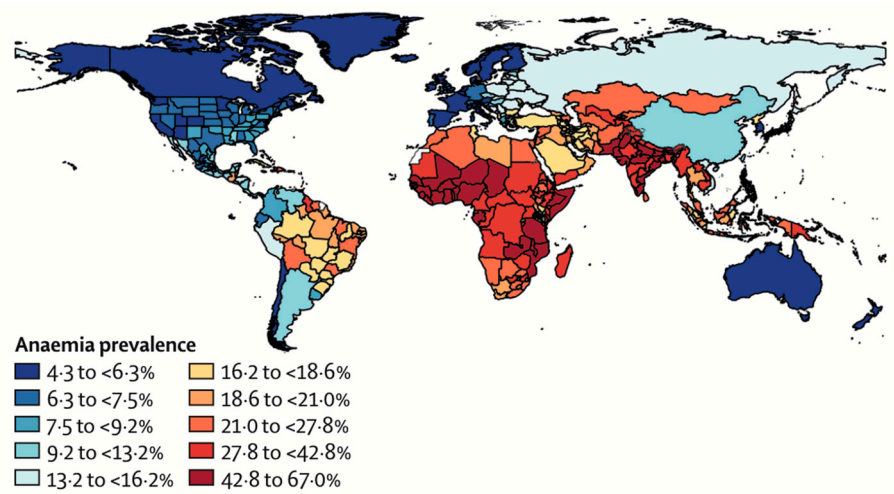

Figure 7. Worldwide prevalence of anaemia 2021 (includes females and males of all ages). The global leading cause of anaemia in 2021 was dietary iron deficiency, affecting 444 miilion males and 825 million females. Among children younger than 5 years, dietary iron deficiency was also the most common cause of aneamia. From Collaborators GBDA. Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990-2021: findings from the Global Burden of Disease Study 2021. Lancet Haematol. 2023;10(9):e713-e34. With permission from The Lancet Haematology.

ID is most prevalent in settings where iron content in the diet is low (59). In these settings, the prevalence of parasitic infections is also high (e.g., malaria and hookworm) (59), which challenges the interpretation of ferritin (and the evaluation of iron stores) because of inflammation associated increase in ferritin (62). The difficulties to interpret ferritin in these settings make it more difficult, yet very important, to study long term outcomes following ID as well as cheap, accessible ways to prevent it.

Another complicating factor is the concern that iron supplementation in malaria endemic regions would increase the risk for malarial parasitaemia, as ID seems to be protective against malaria (63). Furthermore, in regions where the prevalence of ID is high, the prevalence of human immunodeficiency virus (HIV) is also high (64). Limited research is available on the potential risk of HIV transmission to the neonate during delayed CC (59), as well as risk for malarial parasitaemia related to CC time. Regarding the theoretical risk of HIV, the World Health Organization (WHO) currently state that the proven benefits of delayed CC outweighs the theoretical, unproven harms of HIV hypothetically being passed during delayed CC, and therefore recommends delayed CC to all neonates despite their mother's HIV status (65).

Rationale

In the last couple of years, expert organisations and scientific review studies have addressed optimal cord management, highlighting the below-mentioned gaps of knowledge.

According to a statement by the ILCOR 2021, there is a need to study (17):

- "The effects of cord-management practices on polycythaemia and hyperbilirubinemia […]" *(targeted in Study 1).*
- "Optimal cord-management practices for infants who are not vigorous or are deemed to require immediate resuscitation at birth […]" *(targeted in Study 2)*
- "Whether the demonstrated reduction in early iron deficiency seen after late cord clamping improves long-term neurodevelopment. These studies need to be performed in low-resource *(targeted in Study 2, modified, as studied in children that also needed resuscitation)* and high-resource *(targeted in Study 4)* settings".

Koo et al. (25) called out for the need of additional data to determine the optimal duration of delayed CC and the role of resuscitation during delayed CC *(questions raised in Studies 1 and 2).* Marrs and Niermeyer (66) concluded that long-term neurodevelopmental outcomes could strengthen the rationale for delayed CC *(assessed in Studies 2 and 4)*, but also that it requires collaborative efforts from teams caring for neonates and mothers to individualize cord management *(an effort to better understand the midwifery part of the team is made in Study 3)*. Rabe et al. (67) pointed out the increasing interest for stabilization of the neonate while the cord is still intact *(targeted in Study 2)*, and described the normal extrauterine transition process as a clear biological case where 'the whole is greater than the sum of its parts' *(the thesis)*.

Exploring aspects of delayed CC such as: fears regarding the practice, midwives' perceptions on caring for non-vigorous neonates, and potential long-lasting effects of delayed CC, can help develop guidelines and programmes about optimal umbilical cord management and early iron supplementation.

Aims of this thesis

The overall aim of this thesis was to increase the scientific evidence for some of the current knowledge-gaps in umbilical cord management after birth and to increase the understanding of the complexity of umbilical cord management. The aims of the respective studies in this thesis were as follows:

1. To investigate whether delayed CC beyond 3 min is associated with increased short-term risks for the neonates and their mothers.
2. To evaluate neurodevelopmental outcomes at 2 years of age in children randomised to resuscitation after immediate CC or with an intact umbilical cord.
3. To improve knowledge about midwives' decision-making process when a non-vigorous neonate is born, with emphasis on the CC decision.
4. To explore potential long-term neurodevelopmental effects of early vs. delayed CC in school-aged children who were vigorous at birth.

Methods

Study 1: The association between time to umbilical CC with neonatal and maternal short-term outcomes

Trial design

This was a prospective observational cohort study performed from April 28, 2017, to March 18, 2018, in two labour wards in the Region of Halland, Sweden. The study examined potential associations between time to CC after birth and pre-specified neonatal and maternal outcomes. The association of CC beyond 3 min and maternal or neonatal risks were specifically examined. The study was approved by the Regional Ethical Board at Lund University (2016/1052).

Participants

Pregnant women were eligible if they were expecting vaginal births at ≥ 35+0 weeks of gestation and were able to understand Swedish well enough to comprehend information about the study. Exclusion criteria were: neglected or incomplete data sheets, no measurement of CC time, and emergency caesarean delivery. At the antenatal care or at arrival to the delivery department, registered midwives handed out information about the study and the inquiry for consent.

Outcome

Pre-specified primary outcomes were: infant admission to the neonatal ward, infant need for phototherapy, and maternal postpartum blood loss and the association of each to the CC time.

Secondary outcomes were: Apgar scores at 1, 5 and 10 min, transcutaneous bilirubin level at the time for metabolic screening, respiratory distress, infection or hypoglycaemia, and the association to CC time, as well as the relation between oxytocin administration and postpartum blood loss.

Data collection

Time to umbilical CC after delivery was measured with a stopwatch, in seconds, by a midwife or assistant nurse. Except for this, only standard routine procedures were performed after birth. Clinical data (including gestational age, birth weight, Apgar score, complications such as infection or respiratory distress) were prospectively recorded at the postnatal ward. During the metabolic screening (postnatal age ≥ 48 hours), midwives made a note if the infant had been admitted to the neonatal ward. They also measured transcutaneous bilirubin (Dräger Jaundice Meter JM-105, Dräger Medical) and registered if other blood samples than the ones at metabolic screening had been taken as well as registering if phototherapy was required or administered. Estimated maternal postpartum blood loss within 2 hours after birth was recorded by measuring the volume of blood collected in a pan and weighing sheets, pads, and other textiles. The administration of oxytocin (5 IU, 8.3 μg/mL) was registered as the amount (mL) and whether it was given "before CC", "after CC" or "not administered".

Study 2: Neurodevelopmental outcomes after resuscitation with intact umbilical cord in a low-resource setting

Trial design

This study was a follow-up of a RCT performed from April 20 to August 27, 2016, at the Paropakar Maternity and Women's Hospital in Kathmandu, Nepal. Originally, neonates were randomised to either resuscitation with an intact umbilical cord, or to resuscitation after immediate CC. Neurodevelopment was assessed in surviving children at 2 years of age. The WHO Infant and Young Child Development (IYCD) tool was used to assess the child's neurodevelopment. The study was approved by the Nepal Health Research Council National Ethical Guidelines for Health Research in Nepal (reg. no. 218/2018).

Participants

Women were eligible if they were healthy with an uncomplicated pregnancy, expected vaginal births, had gestational age between 33 and 41 weeks and if it was a singleton pregnancy (all of which were the hospital's criteria for admission). The women were approached by a research assistance at the delivery ward and were informed and asked for participation in a study in which the neonate (gestational weeks 33 – 41) would be randomised to delayed or early CC. In the case of resuscitation, the delayed CC neonates would be resuscitated with an intact umbilical cord between the mother's legs and the neonates randomised to early CC would have

their cord clamped immediately and resuscitation would be performed on an adjacent table (standard treatment). All 231 children who were resuscitated in the original study were eligible for the follow-up study, subject to parental consent (22).

Outcome

The primary outcome was the total IYCD Z-score of development for age (development for age Z, DAZ, score), calculated according to the manual. Secondary outcomes were the total scores for the IYCD subdomains. We also constructed an "at-risk" cut-off score by defining the 15th percentile of the subdomains' total results.

Data collection

The IYCD estimates development up to 3 years of age, at a population level, and across cultures in the world. The IYCD is intended to compare groups, for example evaluating the impact of an intervention, rather than to screen or diagnose delayed development in an individual child. The IYCD contains four subdomains: fine/gross motor, language-cognitive and socio-emotional. The Nepalese research team members received training to use the IYCD before the study. The English IYCD version was translated to Nepali, and the interviews were conducted in Nepali.

Follow-up data were collected by telephone interviews with the children's caregivers. Three trained native speaking nurses called the caregivers and neurodevelopment was assessed by using the WHO IYCD (68) in digital tablets.

Study 3: The decision-making process when a non-vigorous neonate is born

Research design

Qualitative interview study of midwives, with an inductive and descriptive design using the Critical Incident Technique (CIT). The Swedish Ethical Review Authority advised that the study did not require review as it did not involve personal and patient data (dnr 2019-04157). Participants had the right to withdraw their participation at any time. Their confidentiality was fully maintained with nonidentifiable codes.

Participants

Midwives currently working in labour wards were eligible. In Sweden, midwives independently carry out and are responsible for normal births. The head of the labour wards in the Region of Skane and the Region of Stockholm were contacted by e-mail, and they forwarded the e-mail with study information to all the midwives working in their labour ward. The midwives made contact themselves by e-mail if they wanted to participate, i.e., a convenient and volunteer sampling strategy was applied. Also, a "snowball" technique was applied for recruitment, where already recruited midwives could forward the invitation information about the study to other midwives (69), meaning that midwives from other regions than from Skane and Stockholm also participated.

Aim

The study aimed to increase the understanding of what midwives in Sweden experience and how they reason during the decision-making process when a non-vigorous neonate is born.

In Sweden, delayed CC is standard practice in full-term, low-risk births. On the other hand, neonatal resuscitation requiring more than a short cutaneous stimulation is currently performed after CC. The decision to clamp the umbilical cord in the situation of a non-vigorous neonate is therefore strongly related to the decision that more resuscitation measures are needed. Because of this, the emphasis on the interviews was the moment when the umbilical cord is clamped.

Data collection

After acceptance (by writing an e-mail agreeing to participate), participants could choose to be interviewed by telephone, digitally or face-to-face. Semi-structured interviews following the CIT were conducted in Swedish, digitally recorded, and transcribed verbatim. The questions and citations were translated from Swedish to English by the research team.

The overall research questions were:

- What leads to the decision to clamp the umbilical cord in an acute and critical situation, and take the infant to the resuscitation table?
- What happens before the decision to clamp the umbilical cord in an acute situation?
- What is the midwife's attitude or opinion regarding CC in acute situations?

- How does the midwife experience the critical event of delivering a non-vigorous infant?
- Does the midwife have any opinion on how non-vigorous infants are handled today?

Study 4: Neurobehavioral long-term outcomes of delayed cord clamping in a high resource setting

Trial design

This is a follow-up of a RCT (the Cord Clamping study (11), N=382) including data from 10-year-old children, born at full-term during the years 2008-2009, who were randomised to early (standard) or delayed (intervention) CC. The study was approved by the Swedish Ethical Review Authority (dnr 2023-02832-02).

Participants

The subjects in this study included children who participated in the Cord Clamping Study (approved by the Regional Ethics Review Board, protocol 41/2008), and were invited to take part of a longitudinal population-based study, the Halland Health and Growth Study. In total, 280/382 (73.3%) of the children in the Cord Clamping Study participated in both studies and were invited to reply to the neurobehavioral screening questionnaire at 10 years of age.

Outcome

The primary outcome was the difference between the groups (early vs delayed CC) in total scores of the ADHD screening instrument Swanson, Nolan and Pelham Scale IV (SNAP-IV). Secondary outcomes were the differences in ADHD subtype and oppositional defiant disorder (ODD) scores and the proportion of children above the cut-off scores in SNAP-IV. The cut-offs for SNAP-IV were based on the American 95th percentiles for parent reported questionnaires (70). Further, scores in SNAP-IV were compared for sex, previous levels of ferritin and previous neurobehavioral test scores (the Ages and Stages Questionnaire, ASQ, a parent-reported developmental screening tool (71)).

Data collection

The ADHD screening tool SNAP-IV was used to evaluate neurobehavioral outcomes. The 26 items measured in SNAP-IV are grouped into: "inattention" (items 1-9), "hyperactivity-impulsivity" (items 11-19), and a combination of both, the "combined" form (70). Items for the criteria of ODD (items 21-28) are also included as these symptoms are often present in ADHD. The SNAP-IV is based on a 0 to 3 rating scale: Not at all = 0, Just a little = 1, Quite a bit = 2, and Very much = 3. The score for any subset is expressed as the average rating-per-item and is calculated by summing the scores of the items in each subset and dividing the sum by the number of items.

Data analyses

Studies 1, 2 and 4

Mean and standard deviations (SD) were used for normally distributed variables, median and ranges for skewed or ordinal variables, and numbers and percentages were used for categorical variables. Parametric and non-parametric tests were used as appropriate. Independent *t*-test (for variables with approximately normal distribution) or Mann-Whitney *U*- test (for variables skewed distribution) were used for comparisons between two groups depending on the variable distribution. Fisher's exact test was used for categorical group comparisons. Correlations were analysed by Pearson's *r* or Spearman's rho as appropriate. *P* values < .05 were considered statistically significant.

Studies 2 and 4 were follow-up studies of RCT and the sample size considered fixed. Analyses were performed both for intention to treat and for per protocol.

Study 1

The transcutaneous bilirubin values were plotted against postnatal age of the infant in a Varvarigou nomogram, giving a "low", "intermediate" or "high" risk for significant hyperbilirubinemia (significant hyperbilirubinemia is defined as the level of total serum bilirubinaemia equivalent to the phototherapy threshold, high risk as > 35 % probability of significant hyperbilirubinemia) (72).

ANOVA was used for comparisons of more than two groups. Bonferroni correction was chosen to adjust for multiple comparisons. Outcomes were dichotomized (yes/no) to for example: Apgar score <7 at 5 min, signs of distress/infection/hypoglycaemia, admission to the neonatal ward, phototherapy, "high risk of hyperbilirubinemia", maternal PPH > 500 mL, severe PPH > 1000 mL and oxytocin administration before/after CC. Time to CC was dichotomized to ≤ 3

min versus > 3 min and used as the grouping variable. Variables that were identified to correlate (variables with $P < .10$ were included) with the primary outcomes were used in the logistic regression models.

Study 2

The IYCD manual suggested a summary score of the participant's developmental score and their age to create a Z-score of development for age. The raw score, obtained during the interview, and the decimal age, calculated by the digital tablets used during the interviews, were copied into a spreadsheet provided by the IYCD tool, to calculate the development for age Z-score. We used IBM SPSS Statistics for Macintosh, version 25.0 (Armonk, NY: IBM Corp).

Study 4

For comparison of continuous test scores, the mean difference between early and delayed CC was calculated and Students t-test was used for *P* value estimation. No variables correlated with the outcomes, so regression analyses were not performed. We used IBM SPSS Statistics for Macintosh, version 29.0 (Armonk, NY: IBM Corp). Results were presented as mean (SD) according to the SNAP-IV manual but because of the skewed distribution of variables, non-parametric tests were also performed.

Six cases had missing values, that consisted of the missing answers to 6 different singular questions, one extra case that had no answers in 2 questions. The SNAP-IV manual did not have any guidelines on handling missing values. We replaced missing data with the mean value in the subtype of SNAP-IV for the specific case (post hoc).

Study 3

The first and last author read all interviews thoroughly several times to become familiar with data and identify patterns. Thematic analysis, as described by Braun and Clarke, was performed (73). Initial codes were generated manually, and a preliminary coding scheme developed. Codes were grouped into potential subthemes and themes. The data set was re-read, codes re-coded and themes refined in regular meetings by two researchers (to ensure credibility). Trustworthiness was further achieved by addressing dependability/confirmability (describing the research steps, keeping the records throughout the study) (74, 75). Transferability will always be a judgement made by the reader; however, we have tried to fully describe the experiences and the context.

Ethical considerations

Study 1 (approved by the Regional Ethical Board at Lund University, 2016/1052) and Study 2 (approved by the Nepal Health Research Council, reg. no. 218/2018) involved infants and children who could not actively decide on whether they wanted to participate in the study or not. Children rely on parents to make good decisions for them, and all children were included after informed parental consent. Regarding Study 4, parents had given consent to the original study (approved by the Regional Ethics Review Board at Lund University, protocol 41/2008), and the study was further approved by the Swedish Ethical Review Authority (dnr 2023-02832-02).

The observational design of Study 1 implied no extra distress on data collection or intervention for the participants. The idea of an observational study is that the participants should receive the same care as they would have received if not part of a study. However, there is a risk that practitioners handle included infants differently because they are being observed. A similar risk of bias exists with interview studies such as Study 3. Further, in Study 3, the interviews about difficult decisions could be emotionally stressful for the midwives/participants. However, we considered that an increased understanding in midwives' reasoning would outweigh eventual negative feelings of recalling a tough decision. An increased understanding in the decision-making process could improve the care of the most vulnerable neonates and help midwives take the right decisions in the future. All midwives were informed that answers would be anonymised. Informed consent was achieved prior to the study. According to the Swedish Ethical Review Authority, Study 3 did not require review as it did not involve patient data or personal data (dnr 2019-04157). However, the Declaration of Helsinki was followed for this study, as well as for the other studies.

In Studies 2 and 4, birthing women and their neonates were randomised to either early or delayed CC in hospitals where the routine at the time was to clamp the umbilical cord before resuscitation or as early CC. Both studies were performed when the existing knowledge about the routines was that they were equal to current practices, but there were indications that they could be beneficial for the neonate. In Study 4, an ethical concern was that parents gave informed consent to participate in the Cord Clamping study (dnr 41/2008, dnr 23/2012) and Halland Health and Growth Study (dnr 299/2007, dnr 2018/141), separately. However, the study did not involve any efforts from participants as all data was already collected. The data was kept in two separate data bases following usual safety routines (pseudonymisation and handling with study-id). The information and aims of the studies that had been given to the families were in accordance with the aim of Study 4 ("long-term outcomes of delayed CC"). As consent was given for this aim in the original trial and all data was already collected – there was no additional consent for Study 4. This was approved by the Swedish Ethical Review Authority on July 10, 2023 (dnr 2023-03832-02).

Results

Study 1: The association between time to umbilical CC with neonatal and maternal short-term outcomes

In total, 904/1000 (90.4%) mother-neonate dyads were included (Figure 8). The gestational age was (mean ± SD) 40.1 ± 1.2 weeks. CC was performed at a mean and median time of 6 min (range 0-23.5) postpartum.

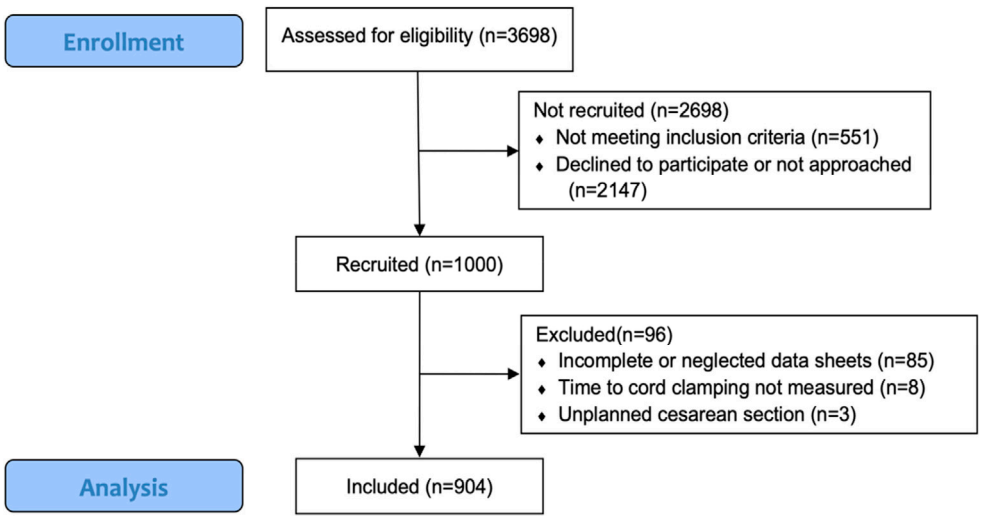

Figure 8. Flow diagram describing eligibility and inclusion of women and their neonate.
From Winkler A, Isacson M, Gustafsson A, Svedenkrans J, Andersson O. Cord clamping beyond 3 minutes: Neonatal short-term outcomes and maternal postpartum hemorrhage. Birth. 2022;49(4):783-91. With permission from Wiley.

Pre-specified outcomes relating to umbilical CC time ≤ 3 min compared to > 3 min are presented in Table 1.

Table 1. Prespecified neonatal outcome characteristics comparing umbilical cord clamping ≤ 3 min versus > 3 min.

	Time to umbilical cord clamping			
	≤ 3 min (n=63) N (%)	**> 3 min (n=841) N (%)**	**Odds ratio (95% CI)**	***P***
Apgar score <7 at 5 min	2 (3.2)	0 (0)	NA	.005
Admission to neonatal ward	7 (11.1)	19 (2.3)	0.2 (0.1-0.5)	
Respiratory distress	4 (6.3)	7 (0.8)	0.1 (0.0-0.4)	
Infection	1 (1.6)	7 (0.8)	NA	.44
Hypoglycemia	2 (3.2)	3 (0.4)	0.1 (0.0-0.7)	
Phototherapy	0 (0)	6 (0.7)	NA	>.99
At high risk of hyperbilirubinemia requiring phototherapy	14 (22.6)	132 (16.4)	NA	.22

Abbreviations: CI, confidence interval; min, minutes; N, number; NA, not applicable.
Group comparisons by Fisher's exact test when odds ratio is NA.

Transcutaneous bilirubin (at the time of metabolic screening) was measured at a median (range) postnatal age of 53.2 (47.1-115.1) hours in 866 (95.8%) neonates and there was no correlation between CC time and transcutaneous bilirubin level (Spearman's rho .021, $P = .54$). As only 6 neonates (0.7 %) needed phototherapy, being in the "high" risk for significant hyperbilirubinemia was used as a dependent variable to gain more robust models (post hoc analysis), and no significant difference was seen (Table 1). The risk stratification was assessed by using a predictive nomogram for transcutaneous bilirubin levels in relation to postnatal age as proposed by Varvarigou (72).

An Apgar score < 7 at 5 min was more prevalent in the CC ≤ 3 min group (3.2% vs. 0%, $P = .005$). Neonates presumed to be the most hypoxic with CC < 30 s were excluded in a post hoc analysis, but the CC group > 3 min was still associated with higher Apgar score at 5 min compared to the group with CC time 30 s - 3 min. There was no information regarding hereditary haemolytic diseases such as glucose-6-phosphate dehydrogenase deficiency (G6PD).

There was a negative correlation between CC time and maternal postpartum blood loss, Spearman's rho -0.115, $P < .001$ and the mean (SD) postpartum blood loss was significantly less in the group with a CC time > 3 min, 399 (292) mL, compared to the group clamped ≤ 3 min, 477 (326) mL, mean difference 78 mL (95% Confidence Interval, CI, 2 – 153). The frequency of PPH was twice as high in the ≤ 3 min group, odds ratio (OR) 2.1 (95% CI 1.2 – 3.6). There was no significant difference in postpartum blood loss when oxytocin was administered before or after CC.

Study 2: Neurodevelopmental outcomes after resuscitation with intact umbilical cord in a low-resource setting

The mean (SD) age at follow-up was 24.8 (0.8) months. In total, 84/134 (62.7%) of the children who had been resuscitated with intact cord and 54/97 (55.7%) of the children resuscitated after early CC (standard care) were followed up. The trial profile is presented in Figure 9.

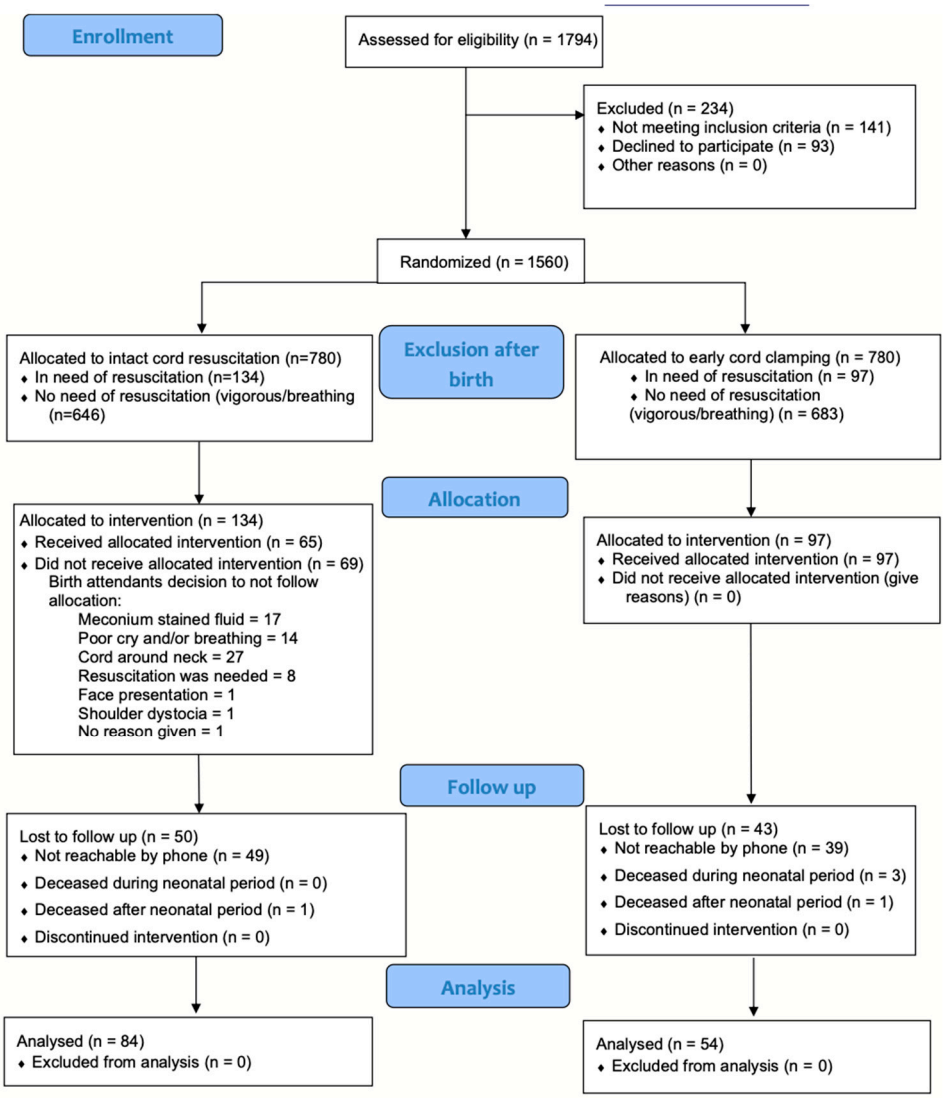

Figure 9. CONSORT flow diagram of trial profile. From Isacson M, Gurung R, Basnet O, Andersson O, Kc A. Neurodevelopmental outcomes of a randomised trial of intact cord resuscitation. Acta Paediatr. 2021;110(2):465-72. With permission from Acta Paediatrica.

The main reasons for loss at follow-up were related to the inability to contact the caregivers. There was no difference in background characteristics between the group of infants resuscitated with an intact cord and those resuscitated after early CC. Neither was there a difference in background characteristics between the children that took part in the follow-up compared to those that were lost at follow-up.

The intention to treat analysis showed that children resuscitated with an intact umbilical cord had higher development for age Z-score, DAZ-score (primary outcome) compared to the group resuscitated after early CC, (P = .04). If protocol violations were excluded, the difference in DAZ-score was unaltered between the two randomisation groups, but the significance was lost (P = .25), Table 2.

Table 2. Infant and Young Child Development (IYCD) scores at two years of age in children who had been randomised to either resuscitation with an intact cord or after early cord clamping (CC). Values are in median (range) unless stated otherwise.

	Intention to treat			*Per protocol*		
	Intact cord resuscitation (n=84)	**Resuscitation after early CC (n=54)**	***P***	**Intact cord resuscitation (n=4)**	**Resuscitation after early CC (n=54)**	***P***
Development for age Z-score	1.0 (0.1 - 2.1)	0.9 (-2.0 to 1.8)	.04	1.0 (0.2 - 2.1)	0.9 (-2.0 to 1.8)	.25
Total raw score	57 (49 - 64)	56 (34 - 62)	.07	56 (49 - 64)	56 (34 - 62)	.28
Motor (gross and fine) score	18 (13 - 20)	17 (11 - 20)	.05	17 (13 - 20)	17 (11 - 20)	.08
Language-cognitive score	20 (14 - 22)	20 (10 - 22)	.82	20 (14 - 22)	20 (10 - 22)	.68
Socio-emotional score	19 (15 - 25)	18 (11 - 22)	.07	19 (15 - 25)	18 (11 - 22)	.29

Abbreviations: CC, cord clamping; IYCD, Infant and Young Child Development tool.

There was no difference in the motor, language-cognitive and socio-emotional domains. No significant difference was seen between groups when comparing infants considered to be at risk (lowest 15th percentile, Figure 10).

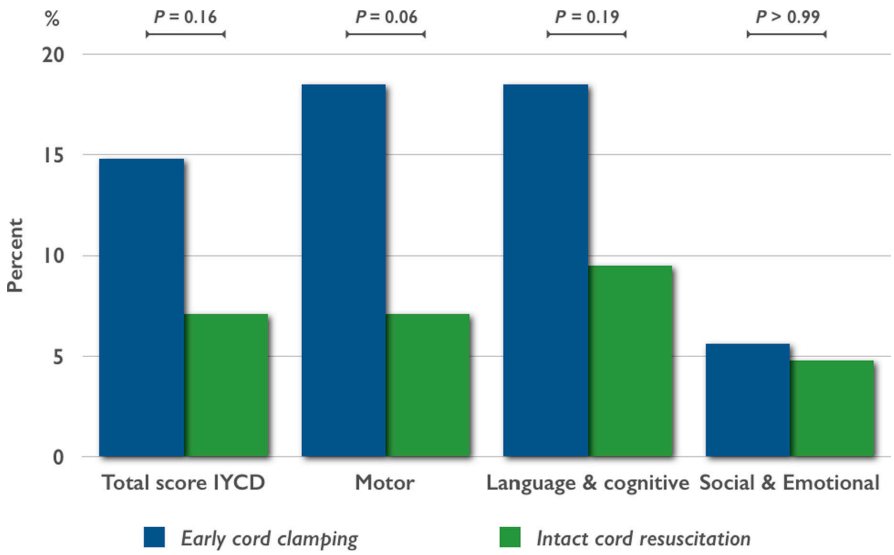

Figure 10. Proportion of children with IYCD scores below the 15th percentile, indicating risk for developmental delay at two years of age. Blue bars show children resuscitated after early CC (standard care), and green bars children resuscitated with an intact cord. Total scores and scores in each of the three domains motor, language-cognitive and socio-emotional are shown. From Isacson M, Gurung R, Basnet O, Andersson O, Kc A. Neurodevelopmental outcomes of a randomised trial of intact cord resuscitation. Acta Paediatr. 2021;110(2):465-72. With permission from Acta Paediatrica.

Study 3: The decision-making process when a non-vigorous neonate is born

The emphasis of the study was to elucidate the decision-making by midwives, as regards timing of umbilical CC.

In total, 14 midwives were interviewed. Their median age was 46 years (range 27 to 67) and the mean and median years working at a birthing unit was 14 years (range < 1 to 40). An overarching theme, *"The balancing act of clamping the umbilical cord"*, was generated. This described how the midwife balanced the different clinical signs, historical background, their own and the parents' feelings, and other team members' or professions' opinions, when they decided to clamp the umbilical cord (Table 3). The midwives cooperate with the neonatal team and the obstetricians, at the same time as they consider two individuals, the neonate and the mother. Intuition and experience were important in the decision-making process of when to clamp the umbilical cord.

Table 3. Overarching theme with themes and subthemes

The balancing act of clamping the umbilical cord		
Assessing the neonate in need of resuscitation	**Valuing own knowledge and experience**	**Influencing decision-making**
Holding the neonate	Interpreting the physiology of the neonate	Presence of others
Looking at the neonate	Intuitive decisions and experience	Obstacles due to organization of rooms and equipment
Taking maternal risk factors in account		

With permission from Midwifery.

It was common to trust that the infant had a satisfactory level of oxygen as long as the umbilical cord had some pulsations.

> *If I have good pulsations in the cord and a good heart rate, I think the baby has enough oxygen delivery and that we at least don't have a severe asphyxia* (midwife 8).

When midwives tried to balance different tasks at the same time, such as calming and explaining to the parents, medically take care of mother and neonate, maybe having to run out with the neonate – this led to feelings of stress and not being enough.

> *I really don't like to have to leave the [birthing] room, taking the baby with me and having to run out with it. But those decisions are usually taken so fast. You want to calm the mother before, but there is no time for that, it's always hard when you have to leave the room* (midwife 8).

The midwives expressed that resuscitation in the birthing room would make their decisions easier. All midwives highlighted the importance of trying to not separate mothers and neonates and trying to not cut the umbilical cord too early.

> *I think most of us wish there would be a mobile equipment for the resuscitation so that the clamping and cutting of the umbilical cord didn't have to happen* (midwife 12).

Study 4: Neurobehavioral long-term outcomes of delayed cord clamping in a high-resource setting

In total, 280/382 (73.3%) of the children in the Cord Clamping Study received the neuropsychiatric screening questionnaire SNAP-IV and were included in Study 4. Of these, 139/280 (49.6%) responded to the questionnaire, Figure 11, and 130/139 (93.5%) were per protocol. Results are presented as intention to treat but similar results were found when data was analysed per protocol. Means (SD) are presented. Non-parametric tests showed similar results.

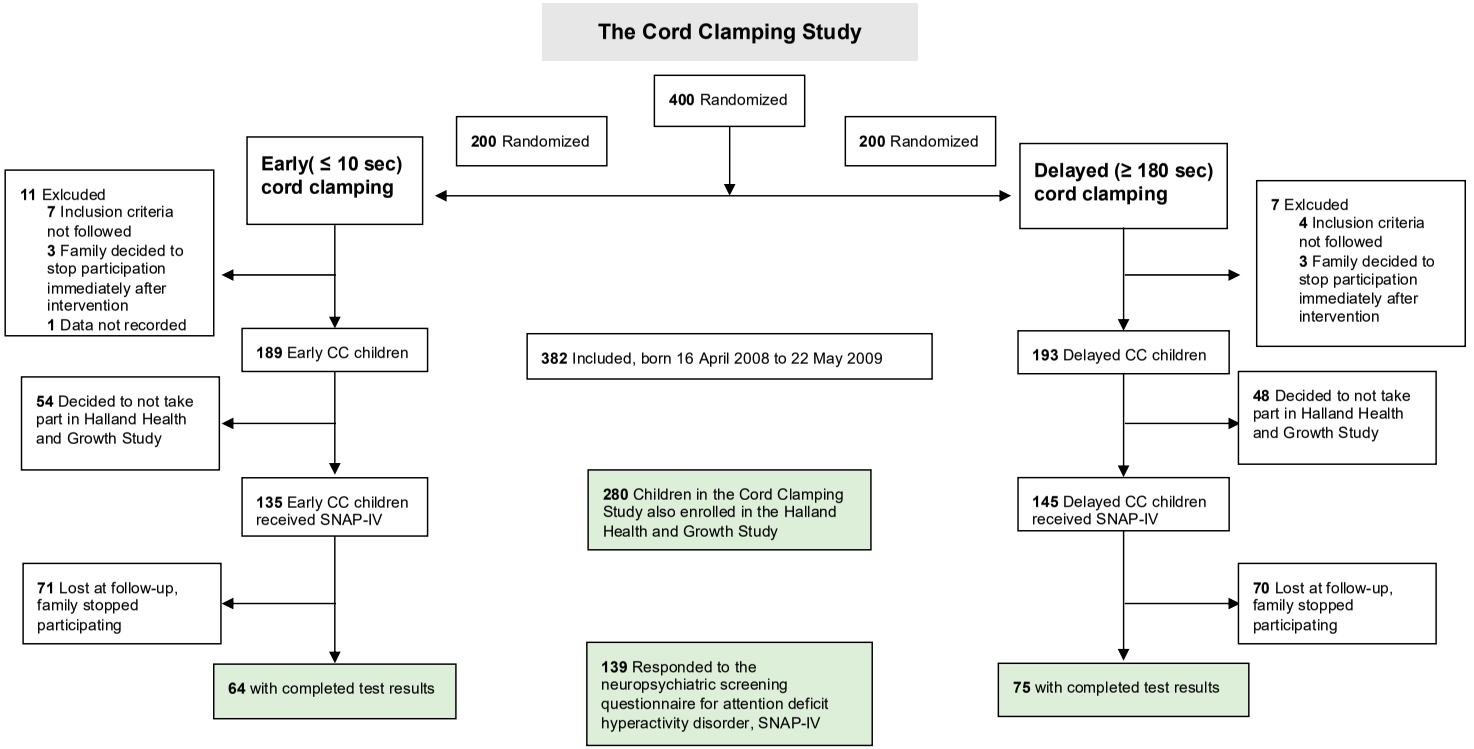

Figure 11. Consort flow diagram of Study 4, The Cord Clamping Trial. At 10 years of age, parents to 139 children responded to the neurobehavioral screening questionnaire Swanson Nolan and Pelham Scale IV (SNAP-IV).

Background characteristics for the children included in the study and the non-participants from the Cord Clamping Study were similar. There was no difference in background characteristics between the two randomisation groups early and delayed CC. Regarding ID, 5 (1.3%) of the children had ID defined as ferritin ≤ 12 µg/L at 4 months, of which only 2 were followed up in this study, and no difference was seen in SNAP-IV results. There was no difference between the early and delayed CC groups regarding total scores and sub-scores (Table 4), neither was there any difference in the cut-off scores of the SNAP-IV.

Table 4. Results of neurodevelopmental screening questionnaire SNAP-IV, comparing 10-year-old children who were included in a randomised controlled trial of early (≤10 s) versus delayed (≥180 s) cord clamping. Values are mean (standard deviation) if not stated otherwise.

	Early CC (n=64)		Delayed CC (n=75)		Mean diff. (95% CI)		*P*
SNAP-IV Scores							
Total	14.64	(13.94)	13.59	(13.41)	1.05	(-3.54 to 5.65)	.65
Inattention	6.23	(5.83)	4.97	(5.47)	1.26	(-0.63 to 3.17)	.19
Hyper./impuls.	4.19	(5.80)	3.83	(5.59)	0.36	(-1.55 to 2.28)	.71
Combined	10.42	(10.70)	8.79	(9.91)	1.62	(-1.83 to 5.09)	.36
ODD	4.23	(4.01)	4.80	(4.73)	-0.57	(-2.05 to 0.92)	.45
Average scores							
Inattention	0.69	(0.65)	0.55	(0.61)	0.14	(-0.07 to 0.36)	.19
Hyper./impuls.	0.47	(0.64)	0.43	(0.62)	0.04	(-0.17 to 0.26)	.71
Combined	0.58	(0.59)	0.49	(0.55)	0.09	(-0.10 to 0.29)	.36
ODD	0.53	(0.50)	0.60	(0.59)	-0.07	(-0.25 to 0.12)	.45

Inattention, hyperactivity/impulsivity (hyper./impuls.) and combined (combination of inattention and hyperactivity/impulsivity) forms of attention deficit hyperactivity disorder.
Abbreviations: CC, cord clamping; n, number; ODD, oppositional defiant disorder; SNAP-IV, Swanson Nolan and Pelham scale IV.
In SNAP-IV the average rating-per-item are calculated by summing the scores on the items in the subset, then dividing by the number of items in the subset, according to SNAP-IV.
Results are presented as intention to treat.

Discussion

This thesis aimed to answer some of the many unsolved issues regarding the optimal timing of umbilical CC – including long-term outcomes and effects on clinical management, and midwives reasoning about optimal timing of CC in non-vigorous infants.

The effects of umbilical CC timing on the mother giving birth and the newborn infant has gained scientific interest for almost 150 years, since Pierre Budin published his observations in 1875 (7). However, for many years the scientific interest dominated over the clinically applicability of the results. Later on, results from a RCT (published 1990) indicated that active management of the third stage of labour, which included the administration of Ergometrine but also early CC and controlled cord traction, resulted in less maternal blood loss compared to physiological management (including delayed CC but also the avoidance of Ergometrine) (76). In a Cochrane review from 2010, the active management was shown to reduce severe PPH, but the reduction in birthweight (interpreted as a reflection of the reduction in neonatal blood volume due to early CC) was also highlighted (10). Meanwhile, there were studies that demonstrated that delayed CC could be advantageous for the infants by improving early iron stores (39, 77). During the last 10-15 years, results from several studies have shown that delayed CC is advantageous for the infant without increasing the risks for the mother (39, 78, 79). For preterm infants, delayed CC may even reduce the risk of death before discharge (31, 32).

Despite benefits of delayed CC in preterm and term neonates, there have been, and still are, barriers for implementation. One of the most pronounced ones is the concern about increased risk of jaundice (80). International guidelines have continuously stated the potential increased risk of jaundice after delayed CC (16, 37) although the Cochrane analyses that initially made this statement quoted a still unpublished study (15). The ERC 2021 guidelines on the other hand conclude that the "concerns about polycythaemia and jaundice requiring intervention do not seem to be borne out in randomised trials" (28). However, ILCOR highlight that increased rates of polycythaemia after delayed CC might have to be considered in settings where resources are limited for diagnosis and treatment of hyperbilirubinemia (17).

In our prospective, observational study (Study 1) of 904 mother-neonate dyads, including late preterm and full-term vaginal deliveries, the median time to umbilical

CC was 6 min (ranging from 0 to 23.5 min) and there was no association between time to CC and bilirubin levels. Only 6 out of the 841 infants required phototherapy, but there was no substantial increase in the risk of significant hyperbilirubinemia following delayed CC neither, and this was in line with previous RCT (11, 12, 81, 82). Mercer et al. showed that delayed CC at 5 min was not associated with adverse effects, including no increased risk of jaundice or symptomatic polycythaemia (12). In a recent three-arm RCT from India, Chaudhary et al. compared CC at 30, 60 and 120 s, and found an increased duration of phototherapy and incidence of polycythaemia in the neonates who received CC at 120 s (83). However, the values of transcutaneous bilirubin, the need of phototherapy and the incidence of symptomatic polycythaemia were similar between groups (83).

The concern among health practitioners regarding increased risk of jaundice following delayed CC (80), was not expressed in our interview study with midwives (Study 3). On the contrary, midwives in Study 3 emphasized the importance of trying to not clamp the umbilical cord and to not separate mother and neonate. The strong belief about doing as much as possible to not separate mother and neonate after birth is supported in evidence and the positive effects of early skin-to-skin contact (84). The midwives in Study 3 were positive towards intact cord resuscitation and this has also been described in another interview study with midwives in Sweden (85), as well as a study with midwives from Canada (86). The midwives further expressed a wish that equipment to make intact cord resuscitation possible existed. Logistical barriers, such as lack of guidance to perform resuscitation with an intact cord and lack of equipment to facilitate the process, have been identified by Anton et al. (80). Patriksson et al. interviewed midwives during an ongoing study evaluating resuscitation with intact umbilical cord, and the midwives identified several challenges in their work environment in the labour room related to the new mobile equipment and the new teamwork required (85). However, preparation and training helped improve the practice of intact cord resuscitation (85).

In Study 1, we found no increased risk for the mothers, such as increased risk of postpartum blood loss, with delayed CC > 3 min. This agrees with other studies (79, 81), although a longer CC time was observed in our study compared to previous studies. Based on the mean and median CC time of 6 min in Study 1, and the lack of short-term adverse effects for neonates and mothers following this CC time, we considered CC as long as 6 min to be safe in low-risk births. There is a theoretical risk that extended CC times for example beyond placental delivery, leads to reverse blood transfusion back to the placenta (87), and these CC times therefore needs more studies before they can be considered safe.

There is an urgent need for long-term follow-up studies after randomised trials that evaluate outcomes after delayed compared to early CC, and this was investigated in Studies 2 and 4.

In Study 2, which was a follow-up of a RCT performed in a LMIC that included non-vigorous moderately to late preterm and term infants, we found marginally higher but significant neurodevelopmental total and motor scores in 2-year-old children who had been resuscitated with intact umbilical cord compared to after early CC. To our knowledge there are still no other published follow-up studies after intact cord resuscitation. There are several potential explanations to the improved outcomes following resuscitation with an intact umbilical cord. Firstly, improved outcomes might be related to the improved extrauterine transition seen following the continued placental transfusion (allowed by delayed CC, i.e., intact cord resuscitation) until after ventilation is established as seen in animal studies (20, 21, 27). In the original study to Study 2, the neonates who were resuscitated with an intact umbilical cord had higher oxygen saturation, higher Apgar scores and they started breathing earlier (22). These findings were in line with results from animal models, where improved and more stable systemic and cerebral oxygenation saturation were seen when ventilation preceded CC (20). Higher cerebral oxygenation following delayed CC has also been seen in a pilot study in non-vigorous neonates (88). A recent study including late preterm and term neonates, showed that intact cord resuscitation was associated with higher oxygen saturation, shorter duration of positive-pressure ventilation, and earlier onset of spontaneous respiratory effort (89). Besides what seems to be a faster recovery with intact cord resuscitation compared to resuscitation after immediate CC, the improved iron stores after delayed CC (39, 40) have the potential to improve myelination (41) and neural growth and differentiation (46) also in the neonates who are in need of resuscitation. If improved iron stores was a main contributor to the improved motor development following intact cord resuscitation in Study 2, then this is something that has been seen previously in for example a study by Shafir et al. who showed that the severity of ID, with or without anaemia, had a linear effect on gross motor function in 9-month-old infants (90).

The main theory for potential long-term benefits of delayed CC is still thought to be related to the improved iron stores (3, 39, 41), and delayed CC has been described as “the earliest, the most feasible and cost-effective intervention to decrease disparities of ID and IDA and improve early childhood outcomes in minority children” (58). There is a possibility that delayed CC makes more of a difference in improving long-term outcomes in settings with high prevalence of ID, and that we miss potential benefits by mostly studying effects of delayed CC in settings with low prevalence of ID. To be able to reach the goals of the 2030 Agenda for Sustainable Development adopted by the United Nation Member States in 2015 (91), we need attainable and equitable options that can reduce neonatal mortality and morbidity, as well as improve early development. Moving forward, the enormous burden of global ID therefore remains a problem to tackle (61, 92).

Study 4 was a 10-year follow-up of a RCT comparing early versus delayed CC in low-risk full-term infants. We did not find a relationship between the higher iron

stores following delayed CC at 4 months (11), and improved neurobehavioral/neuropsychiatric test results at 10 years of age. It is possible that this was due to some of the limitations of the study, such as the loss at follow-up and a population with low prevalence of ID. The low prevalence of ID can be compared to a RCT in Nepal where 60/270 (22.2%) had ID (ferritin ≤ 12 μg/L) in the delayed CC group at 8 months, and 103/270 (38.1%) in the early CC group (40). A follow-up to the Nepalese trial later showed that haemoglobin at 12 months was significantly correlated to total scores in the neurodevelopmental tool ASQ, in addition to the randomisation group delayed versus early CC, as well as age (43). However, opposed to the Nepalese study, Chaudhary et al. found that despite 1/5 of the neonates developed ID in a three-arm RCT comparing CC at 30, 60 and 120 s in India, there was no difference in serum ferritin between the CC groups (83). There are a lack of studies from countries with high prevalence of ID, so the opposing findings require further evaluation.

Our findings in Studies 2 and 4 show that resuscitation with intact cord/delayed CC is not associated with worse long-term outcomes, but the findings are not coherent enough to conclude that delayed CC leads to improved long-term neurodevelopment. Furthermore, there is a lack of studies to compare with, and more follow-up studies are still needed. Finally, in Study 4, it is possible that more, or other, neurodevelopmental tools would have gained a deeper insight. It is possible that a potential long-term difference between early and delayed CC will not show up as a difference in behaviour at 10 years of age, but in for example cognitive or motor functions.

Methodological considerations

The strengths of Study 1 include the prospective design and the large number of mothers and neonates included. However, a prospective design's limitation to demonstrate causal association is a major challenge. In this study, several potential biases may have gone undetected, for example compromised neonates might have had their umbilical cord clamped earlier, and since only one third of eligible neonates were included, there is a risk that midwives who were more positive to delayed CC were more active in recruiting. Another limitation is the difficulty to measure postpartum blood loss, with a risk of information bias by not recalling the correct amount. Further, in the present study, we did not have all information regarding variables leading to higher risk such as haemolytic diseases and therefore we cannot conclude that delayed CC is safe for neonates with higher risk.

Most limitations in Study 1 were related to the methodological choice, however, observational research can be a good option in cases where the exposure cannot be modified for ethical reasons. This could be the case with randomising to early or

delayed CC in vaginally born, vigorous, full-term neonates, now that delayed CC is considered better for the neonate in those cases.

Despite the limitations in this observational study, the results included a large, prospective maternal-infant cohort demonstrating that the concerns for hyperbilirubinemia and risk for phototherapy following delayed CC were not supported in these low-risk, full-term neonates.

Study 2 was a randomised study including both preterm and term infants. Although infants in the original study were randomly assigned to two resuscitation groups, the proportion of neonates requiring resuscitation was unbalanced: 97 (12.4%) in the early CC group versus 134 (17.2%) in the intact cord group (22). We were not able to find a reason for the difference. Furthermore, the allocation was followed in 97 (100%) cases in the early CC group, compared to only 65 (48.6%) cases in the intact cord group (22). It is possible that the high degree of protocol violation in the intact cord group was due to these neonates being in a more compromised state than the ones who received their allocated intervention, i.e., intact cord resuscitation. However, when we compared infants who were randomised to intact cord resuscitation but received early CC (protocol violation group), to the infants who were randomised to, and received, early CC we could not find any difference between these groups. The Nepalese staff were used to delayed CC and prior to the study an extensive training program was performed. When we analysed per protocol, the significance in our results were lost. Nevertheless, the differences between the groups were mainly unaltered, which implies that an insufficient number of subjects were left in each group.

Another limitation was the low follow-up rate in Study 2. Nepal is a LMIC (93), at the time when the study was performed it was a low income country (94) which might have affected the possibility to follow up participants. One reason to our loss at follow-up could be that we collected the data by calling the caregivers' mobile phones. In Nepal, people have cheap and easy access to new telephone SIM cards, which leads to frequent changes of phone numbers. Another reason could be the lack of routine early health check-ups and developmental infant check-ups in Nepal, as these are moments where the interviews could have taken place with the research nurses.

In a paper that systematically evaluated existing tools for assessment of early child development in LMIC, the IYCD was considered very accessible (e.g., its digital availability, the costs of the tool and required equipment) but it rated low in training (duration of training of the tool, skill level of trainers) and validity (how accurate the tool was) because the tool was under development (95). The IYCD has later been tested and compared in Brazil, Malawi and Pakistan (chosen as representatives for three different continents with a cultural diversity), and was then considered a valid and reliable estimate for neurodevelopment in young children across the three countries/continents (96). Compared to many other tools developed in western

cultures and high-income countries, the IYCD is designed for settings all over the world. We believed this would increase the probability that children from a Nepalese culture would be familiar with materials used in the IYCD compared to materials in other tools, and therefore we considered it a good option for the study.

In Study 3, strengths of the study included the variety in experiences, ages, and hospital work settings, amongst the interviewed midwives. Individual interviews were chosen to avoid influence from colleagues and to allow for a deeper exploration of the individual experience and reasoning. However, longer in-depth interviews might have provided more details regarding the decision-making. Strengths of the CIT method include the structured and flexible concept, as well as its ability to reflect on the respondents' own perspectives. Nevertheless, the CIT and other interview methods risk that the respondents have hazy memories about the event being studied, which can lead to bias. That type of bias can be minimized by observational studies, however, for Study 3, it was not considered the most appropriate method as we would not have been able to collect information on the midwives' emotions and perceptions by only observing their behaviours. Furthermore, there is a risk for biased answers because of a social desirability towards longer CC times. Finally, the wide range of things that can be said about the data in thematic analyses, although mostly seen as an advantage, can also be a disadvantage for the researcher when trying to decide what parts of their data to focus on (73). Nevertheless, we considered thematic analyses to be a good option for our study based on the advantages which include its flexible way to analyse qualitative data, that it is relatively easy to learn, and that the results can be presented in an accessible way to the public (73).

A major limitation in Study 4 was the loss of study participants at the follow-up. A main reason for the low participation was that data was collected as part of another, parallel study, the Halland Health and Growth Study (see Figure 11). This meant that not all children in the Cord Clamping Study could be included. We did not find any differences in background characteristics between the participants and the non-participants, and we therefore considered the results representative.

Another limitation was that the original trial (the Cord Clamping Study) was powered to demonstrate a difference in ferritin level between the groups (11), not a long-term neurobehavioral difference. Also, the screening questionnaire might not be sensitive enough to find a difference between the two groups, or an eventual difference between early and delayed CC might not be seen in behaviour, but for example in cognitive functions (as theorized earlier) or motor development.

Lastly, the overall low prevalence of ID in the children included in the Cord Clamping Study might lead to an overall good neurodevelopment, regardless of randomisation group.

Modelling umbilical cord clamping

The placental transfusion received during delayed CC provides the neonate with more than just iron. The larger blood volume itself is believed to have an impact on outcomes, especially during intact cord resuscitation. The potential benefits of sustained umbilical cord circulation during resuscitation are summarized in Figure 12 (3).

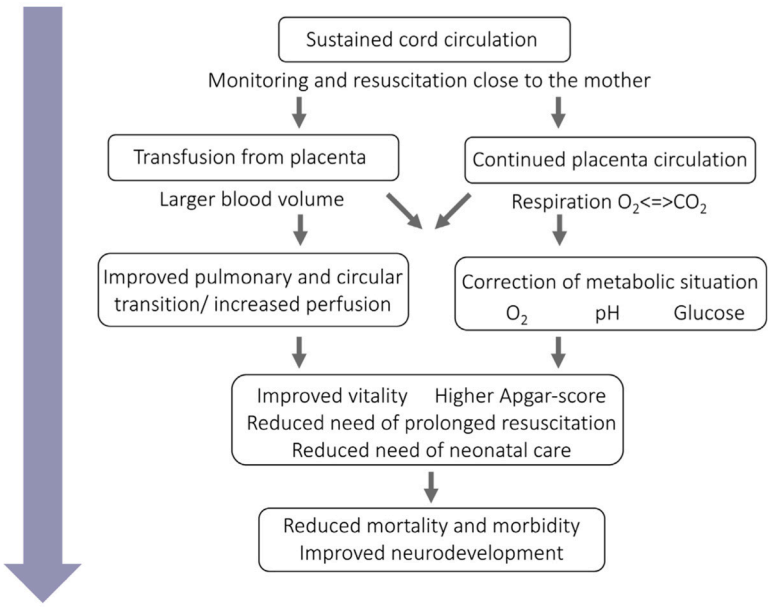

Figure 12. Potential effects of resuscitation with intact cord, i.e.with sustained umbilical cord circulation. From Andersson O, Mercer JS. Cord Management of the Term Newborn. Clin Perinatol. 2021;48(3):447-70. With permission: CC BY.

Stem cells transfused during delayed CC have been suggested as being beneficial for the neonate (97), and there are currently ongoing trials evaluating the efficacy of stem cells in treating hypoxic-ischemic encephalopathy (98). The umbilical cord stem cells are transfused in a perfect medium of proangiogenic and antiapoptotic messengers, growth stimulating factors and cytokines, all together potentially reducing inflammation (97). Further, stem cells might create a favourable environment for tissue regeneration (98), and its possible neuroprotective effect is therefore particularly interesting during intact cord resuscitation. Other suggested hypothetical reasons to an optimized brain environment and development following placental transfusion are the eventual neuroprotective effects of placental progesterone (99), and a possible regulation of catecholamine levels postpartum

(100). Further, Reid et Georgieff, hypothesized that early psychological stress leads to an inflammatory response that may affect iron metabolism and brain development (101), maybe early separation during for example resuscitation lead to a psychological stress. Mercer et al. have also proposed that the mechanical blood force created during placental transfusion would stimulate organ-specific endothelial cells to grow and repair, contributing to organ health and development (99). This has been seen in liver cells where blood flow and the following "mechanotransduction" in cells translates into liver growth and maintenance (102).

The "placental model" (presented by Andersson et Mercer, 2021, in Figure 5), is mainly based on the increased iron stores obtained after delayed CC. Here, a new theoretical placental model, based on the above-mentioned hypotheses, is summarized in Figure 13. The model has kept the theory regarding improved iron stores as the main explanation to potentially improved neurodevelopment following delayed CC; however, other potential explanations are also brought to light.

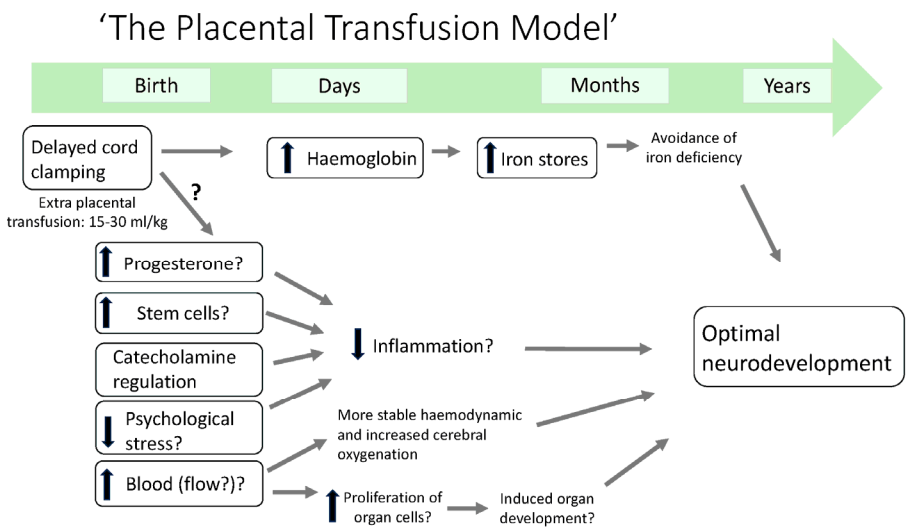

Figure 13. The Placental Transfusion Model demonstrating potential and hypothetical pathways for how delayed cord clamping/intact cord resuscitation might affect infant neurodevelopment. Illustration by M Isacson, 2024.

Finally, in their latest update, ILCOR state that *"we acknowledge the perception of early cord clamping as a medical intervention and of later clamping as a natural, or physiological, approach and the paradox that many studies defined early clamping as the control"* (17). Maybe there is a paradigm shift regarding CC, where the focus is shifting from trying to prove the benefits of delayed CC to rather avoid the potential negative effects of the "early CC intervention"?

Conclusion and future perspectives

This thesis has addressed some of the existing knowledge-gaps for optimal cord management in mothers and their newborns. Our results have also created new research questions that should be investigated to further increase knowledge of the most beneficial procedures for newborns and their mothers.

The results in **Study 1** found no adverse effects when CC was delayed to ≥ 3 min compared to < 3 min. A CC time up to 6 min seems to be safe in low-risk, late preterm and full-term vigorous neonates.

Future work following Study 1:

- Is a CC time beyond 6 min safe for low-risk neonates?
- Is delayed CC safe for high-risk neonates?

In **Study 2,** resuscitation with an intact cord was associated with slightly improved neurodevelopment at 2 years of age. However, our findings on improved neurodevelopmental outcomes following intact cord resuscitation need to be further evaluated in future trials with larger numbers of study participants and less protocol deviations.

Future work following Study 2:

- Does a smoother transition (more stable blood pressure, lower heart rate, allowance of preload until the lungs fill the heart with blood) and potential differences in cerebral oxygenation improve long-term neurodevelopment?
- What are the long-term outcomes of intact cord resuscitation in high-income countries and LMIC?
- What are the long-term outcomes of intact cord resuscitation after caesarean deliveries?

Study 3 showed that midwives in Sweden constantly balanced different factors in their decisions. The midwives were positive towards intact cord resuscitation, and they were guided by intuition and experience. Understanding caregivers' beliefs and attitudes about neonatal resuscitation could facilitate implementation of new methods.

Future work following Study 3:

- What are the attitudes and beliefs among caregivers involved in neonatal resuscitation?
- What are the mothers' and their eventual partners' experiences during, and after, intact cord resuscitation?
- What are the experiences and how is the decision-making process of midwives in settings outside the Swedish context, such as in LMIC?

In the exploratory **Study 4**, there was no association between the CC time or risk of ID, and increased ADHD symptoms in 10-year-old children. The low-risk children in this study were born at full-term, in a setting with low prevalence of ID and the study suffered from a high loss at follow up. Our question regarding long-term outcomes remain unanswered.

Future work following Study 4:

- Does delayed CC affect long-term neurodevelopmental outcomes in high-income countries and if so, how?
- What are the long-term neurodevelopmental outcomes of delayed CC in regions with higher prevalence of ID?

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