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Delayed cord clamping in Nepal-Evidence for implementation

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Abstract

Rana, N. 2019. Delayed cord clamping in Nepal-Evidence for implementation. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1557. 66 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0611-7.

The aims of this thesis were to investigate effects of timing of umbilical cord clamping on newborn health, and on infant outcomes up to 12 months of age in a high-risk population and to explore the context of implementing changed umbilical cord clamping practices in Nepal.

A randomised controlled trial with 540 late preterm and term infants born by normal vaginal delivery was set up at a maternity hospital in Kathmandu, Nepal. Infants were enrolled in two parallel groups (1:1 ratio), randomised to early (ECC) (≤60 seconds) or delayed cord clamping (DCC) (≥180 seconds).

To get a deeper understanding of barriers and enablers for change in clinical practise in relation to cord clamping, a qualitative study with delivery staff was set up. Focus group discussions and key informant interviews were conducted at two major delivery hospitals in Kathmandu.

Paper I showed that DCC was an effective intervention to reduces anaemia at 8 and 12 months of age in a high-risk population, which may have major positive effects on infants' health and development.

Paper II utilised the Ages and Stages Questionnaire (ASQ) to assess neurodevelopment in infants at 12 months of age. The result showed DCC was associated with an improvement of the overall neurodevelopment at 12 months of age as compared to infants in the ECC group.

Paper III showed that DCC was not associated with an increased risk of hyperbilirubinemia during the first day of life or risk of jaundice within 4 weeks compared with the ECC group.

Paper IV demonstrated how a positive attitude towards DCC and a will to rely on research evidence when striving to do good are facilitators of change in clinical practice. However, the participants in the study were hesitant to apply DCC due to lack of national or institutional protocols and formal training. Consequently, they were forced to take informal decisions and rely on alternate sources of information.

In conclusion, delaying umbilical cord clamping for 180 seconds is safe and associated with a significantly reduced risk of anaemia at 8 and 12 months which may have neurodevelopmental effects at a later age and is not associated with an increased risk of hyperbilirubinemia during the first days of life or risk of jaundice within 4 weeks of age. In order to change cord clamping practices to comply with evidence and policies health-care staff needs to be better supported by the governance structures of the health system, with clear and approved guidelines made available and coherent training and support.

Keywords: Attitude, Clinical Practice, Ferritin, Haemoglobin, Iron deficiency, Iron deficiency anaemia, Iron status, Jaundice, Neonatal hyperbilirubinemia, Newborn, Neurodevelopment, Randomized controlled trial, Umbilical cord clamping.

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To my mum, son, husband and specially to all anaemic newborns

List of Papers

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

I KC A, Rana N, Målqvist M, Jarawka Ranneberg L, Subedi K, Andersson O. Effects of Delayed Umbilical Cord Clamping vs Early Clamping on Anemia in Infants at 8 and 12 Months: A Randomized Clinical Trial. *JAMA Pediatr.* 2017;171(3):264–270. doi:10.1001/jamapediatrics.2016.3971

II Rana N, KC A, Målqvist M, Subedi K, Andersson O. Effect of Delayed Cord Clamping of Term Babies on Neurodevelopment at 12 Months: A Randomized Controlled Trial. *Neonatology*. 2019;115(1):36–42.

III Rana N, Ranneberg LJ, Målqvist M, KC A, Andersson O. Effect of delayed cord clamping on risk of hyperbilirubinemia in term newborns: A randomised clinical trial. *Submitted*

IV Rana N, Brunell O, Målqvist M. Implementing delayed umbilical cord clamping in Nepal - Delivery care staff's perceptions and attitudes towards changes in the practice. *Submitted*

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Contents

Abbreviations

ACOG	The American College of Obstetricians and Gynaecologists
ASQ	Ages and Stages Questionnaires
CI	Confidence Intervals
CSPro	Census and Survey Processing System
DCC	Delayed Cord Clamping
ECC	Early Cord Clamping
FGD	Focus Group Discussion
FIGO	International Federation of Gynaecology and Obstetrics
ICM	International Confederation of Midwives
ID	Iron Deficiency
IDA	Iron Deficiency Anaemia
KII	Key Informant Interview
MNSC	Maternal and Neonatal Service Centre
NNT	Number Needed to Treat
PMWH	Paropakar Maternity and Women's hospital
SBA	Skilled Birth Attendant
SD	Standard Deviation
TcB	Transcutaneous Bilirubin
TUTH	Tribhuvan University Teaching Hospital

Glossary and definitions

Ages and Stages Questionnaires: A screening tool that helps parents provide information about the development milestones of their children. It includes series of parent-report questionnaires that span the age range of 2 to 60 months.

Anaemia: A condition that develops when blood lacks enough healthy red blood cells or haemoglobin level less than 11.0 g/dL (altitude corrected).

Bilirubin: A substance that is made each day as red blood cells break down.

Delayed cord clamping: Umbilical cord clamping after 180 seconds.

Early cord clamping: Umbilical cord clamping within 60 seconds.

Ferritin: A universal intracellular protein that stores iron and releases it in a controlled fashion.

Gestational age: Number of intrauterine weeks of a foetus calculated from the mother's last menstrual period.

Haemoglobin: Is the iron-containing oxygen-transport metalloprotein in the red blood cells (erythrocytes).

Hyperbilirubinemia: An elevated level of the pigment bilirubin in the blood.

Iron deficiency: Ferritin level in blood less than 12 μg/L.

Jaundice: A yellowish pigmentation of the skin and whites of the eyes due to high bilirubin levels.

Iron deficiency anaemia: Ferritin and haemoglobin levels below the respective cut-offs i.e. ferritin level of less than 12 μg/L and haemoglobin level of less than 11.0 g/dL.

Late-preterm: Infants born between 34 completed weeks to 36+6 weeks of gestation.

Neonatal period: First 28 days after birth.

Neurodevelopment: Neurodevelopment is a term referring to the brain's development of neurological pathways that influence performance or functioning.

Skilled birth attendant: An accredited nurse midwife who has been educated and trained to proficiency in the skills needed to manage normal (uncomplicated) pregnancies and childbirth.

Term birth: Infants born at or after 37 completed weeks to 41+6 weeks of gestation.

Transcutaneous bilirubin measurement: A measurement to find out how much bilirubin is in in your child’s blood without using a needle.

Introduction

The aim of this thesis is to compare the effects of timing of umbilical cord clamping on risk of hyperbilirubinemia, anaemia at 8 and 12 months and subsequent neurodevelopment in late pre-term and term infants, and to explore the barriers and enablers when implementing strategies for delayed umbilical cord clamping.

Anaemia is one of the most common and widespread public health problems affecting human health as well as social and economic development in both developed and developing countries (1,2). It is characterised by a decrease in the concentration of circulating haemoglobin (1) and is a major health problem in Nepal, especially among young children and pregnant women (3). More than half (53%) of the children aged 6-59 months are anaemic, with 26% mildly anaemic, 26% moderately anaemic, and 1% severely anaemic (4). For the age group up to 12 months of age, a cross-sectional survey with 500 mother-infant pairs from Bhaktapur, Nepal, showed prevalence of anaemia in 49% of infants at the age of 2- 6 months and 72% of infants at the age of 7-12 months, with 9% and 26% of infants in respective age groups suffering from iron deficiency anaemia (IDA) (5).

Iron is a key component of haemoglobin that carries oxygen to all part of body and thus iron deficiency (ID) affects all body functions (6). Young children are at particular risk of IDA since their rapid growth leads to high iron requirements in combination with low iron intake (7). Globally, 43% of children below 5 years of age (approximately 273 million persons) have anaemia, where approximately 42% is attributable to ID (8). Children with anaemia and ID have associated impaired neurodevelopment, affecting their cognitive, motor, and behavioural abilities (9,10). Food fortification and iron supplementation is used in treatment (11) but delayed cord clamping (DCC) has been proposed as a safe intervention and is also associated with higher haemoglobin concentration and reduces the risk of IDA (12) .

The foetal-placental circulation

During pregnancy, blood circulates continuously through the umbilical cord to and from the foetus and the placenta which brings oxygen and nutrition to the foetus from the mother's blood (13). At the time of birth, the infant is still attached to the mother through the umbilical cord and is separated from the placenta by clamping the cord (14). Umbilical cord circulation continues for several minutes after birth and if the cord is clamped early, it may interfere with the completion of a normal physiologic neonatal transition (15,16). Timing of cord clamping is considered to have a positive effect on placental transfusion rate and therefore neonatal and infant circulation (17).

Placental transfusion usually occurs within 2 minutes, but sometimes continues up to 5 minutes after birth and if early cord clamping (ECC) is avoided after delivery, around 30% to 40% (roughly 25-30 ml/kg) of blood volume is transfused to the baby (18). The rate of the transfusion is largely influenced by uterine contractions, gravity, lung aeration, spontaneous inspiration and crying in the newborn (19,20). Neonatal benefits associated with the increased placental transfusion include better cardiopulmonary adaptation and higher haemoglobin concentrations, additional iron stores and prevention of ID in early infancy, up to 6 months of life (14,21–24). Distribution of the blood volume in the placenta and the foetus before and after birth in the placenta and infant after early and delayed cord clamping is presented in Figure 1.

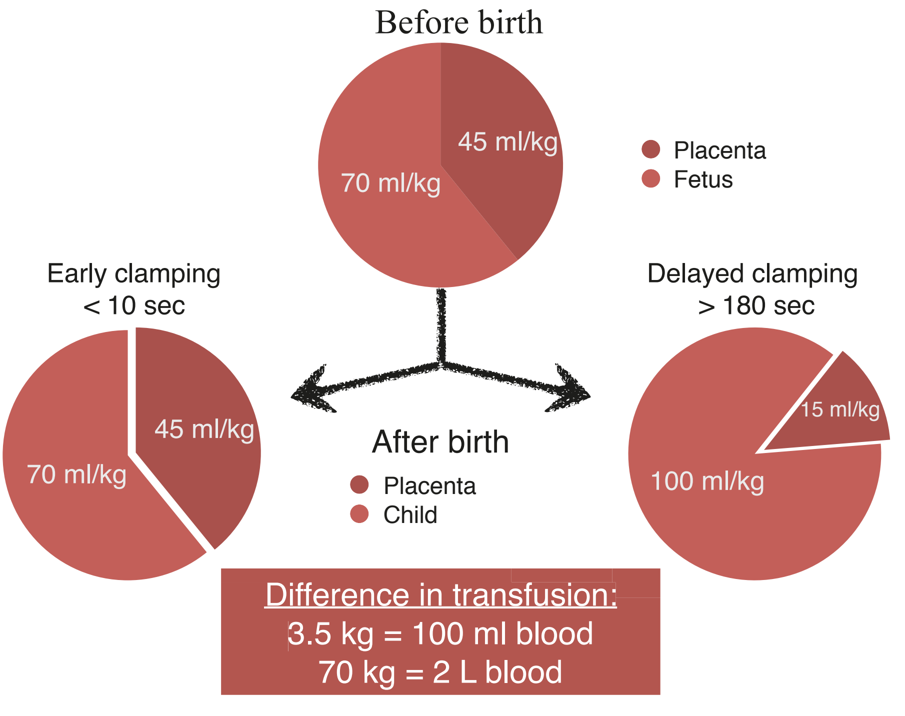

Figure 1. Distribution of the blood volume in the placenta and in the foetus before birth, and after birth in the placenta and infant after early cord clamping (left) and delayed cord clamping (right) (25).

Early and delayed cord clamping-definitions

Debate about the appropriate time to clamp and cut the umbilical cord has been ongoing for many decades (26). Different definitions of ECC have been used, with the time varying from immediately to within one min after delivery of the baby. ECC, which is generally carried out in the first 60 seconds after birth (most commonly in the first 15-30 seconds) has been common practice in delivery care around the world (27). However, evidence of multiple benefits of waiting for more than one minute to cut the cord has been increasing (14,18,28–30) and recent World Health Organization guidelines for active management of the third stage of labour no longer recommend immediate cord clamping. The current recommendation is to practice DCC, i.e. to wait for at least 60 seconds after birth before clamping the cord (27).

Effect of early versus delayed cord clamping

The methods of ECC and DCC have different advantages, which can oppose each other. Two main proposed advantages of ECC are: a reduction of maternal postpartum haemorrhage as part of the active management of third stage labour (31), and facilitation of blood gas sampling from the umbilical cord (32). On the other hand, ECC has been suggested to result in an artificial loss of stem cells at birth and could increase the possibility of both neonatal and age-related diseases, whereas DCC is perhaps the most effective and non-invasive way of transplanting stem cells in order to treat those diseases (33).

As an advantage, DCC in term infants increases the early haemoglobin concentration and iron storage in newborn infants reducing the rate of neonatal anaemia (34,35) and preventing the development of ID before 6 months of age (23). The improved iron stores at four to six months after DCC suggest that IDA could be reduced at eight to twelve months of age but this possibility did not occur among infants aged 12 months in a Swedish study, possibly due to small sample size and low frequency of IDA (37). An observational study found a 22% reduction in anaemia among infants aged 8 months after a change in hospital policy (28).

In conflict with these benefits, DCC has increased the risk of polycythaemia, hyper-viscosity, hyperbilirubinemia, and transient tachypnoea of the newborn or maternal haemorrhage (14,22). Therefore, comparative risks and benefits of timing of cord clamping are still a subject of debate and unclear (14). The effects of placental transfusion are presented in Figure 2.

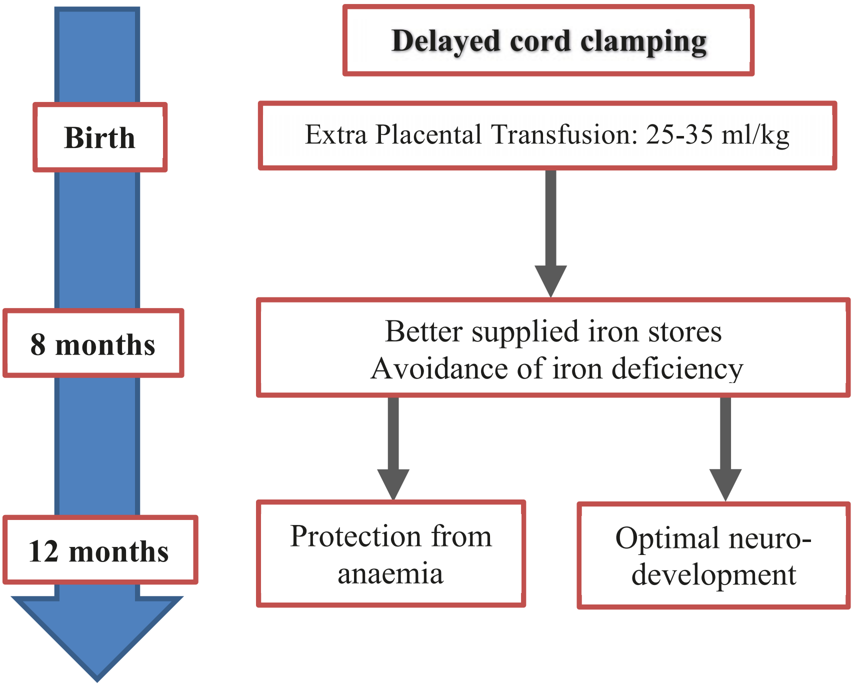

Figure 2. The effects of placental transfusion (25).

Iron deficiency and iron deficiency anaemia

Infancy and early childhood are at high risk of ID due to high iron requirements for rapid physical growth, early period of brain development and low iron intakes (38). Two meta-analyses conclude that iron supplementation helps to improve psychomotor and mental development in infants and children (39,40). A Swedish trial showed that early iron supplementation to marginally low birth weight infants significantly reduced the prevalence of behavioural problems at 3.5 years of age (41) and therefore suggests iron supplementation in all low birth weight children for long-term effects on behavioural functions (42).

Iron plays a critical role in rapid growth and development of the central nervous system in the first year of life (43). ID is highly prevalent and widespread micronutrient deficiency especially among infants and young children in low-income countries and they have adverse effects on cognitive and motor development (44,45).

A large number of studies have investigated the consequences of ID on neurocognitive development in infants and children. IDA in early infancy and young children is associated with adverse effects on neurocognitive, motor, socio-emotional and neurophysiologic development, impairments in learning, memory, myelination and long-lasting cognitive and behavioural deficits

(7,9,46,47). The possible seriousness of ID is often ignored, but it can lead to a poor neurodevelopmental outcome, poor physical growth and recurrent infections (48). In addition, it is also associated with psychosocial, economic and biomedical disadvantages (49). A cohort study among Icelandic children of 1 and 6 years of age evaluated the possible association between iron status and development at 6 years. They concluded that ID at 1 year may be associated with lower fine motor development scores and haemoglobin levels might affect expression and gross motor score at 6 years of age (50).

There are limited interventions available for the prevention of ID and anaemia in early infancy, and DCC can contribute by increasing the iron endowment at birth (51). A previous Swedish study on DCC ≥3 minutes after delivery showed higher scores for prosocial behaviour as well as fine-motor function and personal social development among 4-year-old children compared to ECC within 10 seconds after delivery (30). Therefore, reducing the prevalence of anaemia, especially among infants, is an urgent global need.

Relationship between cord clamping time and hyperbilirubinemia

Hyperbilirubinemia is one of the most common problems requiring evaluation and treatment in newborn infants (52), particularly in East Asian populations compared to white populations (53). Most jaundice in newborns is benign, but there is the possibility of developing toxicity of bilirubin and in rare cases, acute bilirubin encephalopathy or kernicterus (54). The bilirubin level can be measured either by blood sample or by bilirubinometer. Transcutaneous bilirubin (TcB) measuring devices are considered to be a sufficiently accurate and non-invasive method to estimate bilirubin concentrations in neonates, do not inflict pain to the neonate and are cost-effective and fast (55,56).

A Cochrane meta-analysis in 2013 discovered that jaundice requiring phototherapy is less likely in the ECC group than those in the DCC group (14). Whereas in 2012, a review of all published randomised controlled trials (n=15) since 1980 could not find any association between DCC and hyperbilirubinemia (15).

Recommendations from professional organisations

How to practice umbilical cord clamping is also discussed in many high-income countries. In Europe, as well as in other parts of the world, ECC is perhaps the dominant practice but it varies substantially both between and within countries (57,58). In order to reduce postpartum haemorrhage, the International Federation of Gynaecology and Obstetrics (FIGO) and the International

Confederation of Midwives (ICM), as well as a Cochrane report, have previously recommended immediate cord clamping together with controlled cord traction and administration of an oxytocic drug (59).

In recent years support for DCC has been increasing (22,34) the FIGO/ICM as well as a Cochrane report revised their statement and omitted ECC as a part of active management of third stage labour (34,59). The Society of Obstetricians and Gynaecologists of Canada recommended that even though the possible increased incidence of neonatal jaundice requiring phototherapy must be weighed against the potential benefits of DCC in term newborn infants but for premature newborn infants, DCC of at least 60 seconds is recommended since there is less risk of intraventricular haemorrhage and the need for transfusion if the cord is clamped late (60). Recently, the World Health Organization and also The American College of Obstetricians and Gynaecologists (ACOG) published a Committee Opinion (#684), recommending DCC for at least 30-60 seconds in term and preterm infants except for conditions when immediate umbilical cord clamping is necessary (27,61).

Delayed cord clamping in practice

Even though there are published benefits primarily to both infant and mother, there is little evidence of practicing DCC routinely in hospital settings (29). Health-care providers tends to clamp the cord either as they were clinically trained to or according to organisational practice where they work (29). Immediate or early cord clamping is a deeply rooted practice in maternity care and if they had to elect to wait to clamp, they feel like the whole world is in slow motion (62). New structures make them feel uncomfortable, strange and at variance, consequently, shifting to a new routine takes time and patience (62).

In 2014, U.S. obstetricians were surveyed on their attitudes and beliefs towards umbilical cord clamping and 88% of the physicians stated that their hospitals did not have a policy for cord clamping and they did not know the optimal timing for cord clamping (63). Even though the majority of the delivery care staff were aware of the new guidelines, they still practiced ECC and this knowledge gap could be rectified through the implementation of a nation and hospital-wide policy (64).

There are examples where DCC is regularly and successfully applied even among distressed infants demonstrating the feasibility in clinical practice (65). It is possible to introduce DCC even if acceptance is slow and requires education and quality feedback (66).The beliefs and knowledge of the individuals involved are critical components for the evolution of practice changes (62) where research can play a vital role in shifting towards evidence-based practice (67). Besides that, strong leadership is needed to provide strategies in the development and implementation of DCC (29). Nurses and nurse midwives can be leaders in educating in the evidence surrounding DCC and by dispersing misconceptions or myths (62).

Aims of the thesis

The overall aims of this thesis were to investigate effects of timing of umbilical cord clamping on newborn infant health, and on infant outcomes up to 12 months of age in a high-risk population and to explore the context of implementing changed umbilical cord clamping practice in Nepal.

The specific objectives are:

Study I
To evaluate effects of delayed vs early umbilical cord clamping on anaemia in infants at 8 and 12 months (Paper I), neurodevelopment at 12 months (Paper II), and risk of hyperbilirubinemia during first month of life (Paper III).

Study II
To explore barriers and enablers for implementation of delayed umbilical cord clamping in Nepal.

Methods

Studies in this thesis include both quantitative and qualitative methods. A randomised controlled trial comparing DCC with ECC was conducted at Paropakar Maternity and Women's Hospital (PMWH). The first three papers were based on the randomised controlled trial. In order to explore barriers and enablers for implementation of DCC, focus group discussions (FGDs) and key informant interviews (KIIs) were performed. Overview of papers included in the thesis is presented in Table 1.

Table 1. Overview of papers included in the thesis (ECC – Early Cord Clamping (≤60 seconds after delivery), DCC – Delayed Cord Clamping (>180 seconds after delivery)).

Paper	Study design	Study setting	Sample size	Outcome
I	Randomised controlled trial	Paropakar Maternal and Women's Hospital (PMWH)	At 8 months: ECC-188 DCC-212 At 12 months: ECC-157 DCC-177	Delayed cord clamping (DCC) reduced anaemia at 8 and 12 months
II	Randomised controlled trial	PMWH	At 12 months: ECC-159 DCC-173	DCC was associated with better overall neurodevelopment at 12 months
III	Randomised controlled trial	PMWH	At discharge: ECC-270 DCC-270	Timing of cord clamping was not associated with risk of hyperbilirubinemia or jaundice during the first 4 weeks of life.
IV	Qualitative study: Focus Group Discussions (FGDs) and Key Informant Interviews (KIIs)	PMWH and Tribhuvan University Teaching Hospital	12 KIIs 8 FGDs (34 participants)	Positive attitude towards DCC and a will to rely on research evidence when striving to do good are facilitators of change in clinical practice

Paper I, II and III

Study setting

This randomised controlled trial was conducted in Nepal at PMWH, Kathmandu, a tertiary government hospital providing obstetrical and gynaecological services. It also serves as a central referral maternity centre for Nepal with an annual birth rate of approximately 20,000. This hospital provides antenatal, delivery and postnatal care for women and newborn and other obstetrical and gynaecological services. It also provides academic programmes such as postgraduate diplomas and masters in obstetrics and gynaecology. The hospital is equipped with 415 inpatient beds and serves as the central referral hospital and training site for reproductive health including neonatal health in the country.

Study design

A trial design including two parallel groups (1:1 ratio) randomised to DCC (≥180 seconds) or ECC (≤60 seconds) was applied. The cut-off for ECC was based on an observational study in the same hospital, which showed a mean ± SD umbilical cord clamping time of 61 ± 33 seconds (68).

Study population

The hospital has two delivery units: the labour room for high-risk vaginal deliveries with the human resources of nurse midwives and obstetricians and the low-risk vaginal delivery unit, Maternal and Neonatal Service Centre (MNSC) staffed by nurse midwives. In caesarean section cases, delivery takes place in the operating theatre. The criteria for admission to the MNSC includes uncomplicated pregnancies, no complication at admission, and healthy mothers (no clinical history of hypertension, infection, diabetes, or any chronic medical condition), expected vaginal delivery, gestational age of 34 to 41 weeks, and singleton pregnancy. Women were eligible to participate in the study if they were assigned to the MNSC. Recruitment took place during all the hours of the day and all days of the week. The exclusion criteria were predefined as serious congenital malformations, syndromes, or other congenital disease that could affect the outcome measures.

Randomisation and masking

One of the principle investigators (OA) prepared a list using the random digit generator in the Excel program (Microsoft, Seattle, WA, USA) for the 540 participants to determine their allocation into each treatment group. For concealment, the treatment allocation to each participant was not revealed. Sequentially numbered, opaque envelopes were prepared holding cards with details of the allocated group. These envelopes were kept at the research office and were brought to the delivery unit before randomisation.

For those women who had given consent to be part of the study, randomisation took place a few minutes before delivery when the nurse midwife considered vaginal delivery was imminent. The surveillance officer opened the next consecutively numbered envelope and informed the nurse midwife of the allocation. The details of sequence generation and allocation concealment were limited to the investigator, who had no clinical involvement in the trial but participated in the data analysis after the trial had ended. Allocation cards and opened envelopes were discarded once used. The surveillance officer and nurse midwife did not actively inform the mother of the allocated treatment. However, the mother might have noticed the nature of intervention. The outcome assessors were blinded to the allocation, as were the members of the research team who obtained the outcome measurements.

Follow-up

After delivery, the babies were taken care of according to standard clinical routines, and early breastfeeding was encouraged. As part of the study, the nurse midwife assessed the infant to see whether the baby has been breastfed at 1 and 6 hours. The infants stayed at the postnatal ward with their mothers for one or two days after delivery, except for those healthy babies whose mothers preferred to leave the hospital earlier or infants who required admission to the neonatal unit. The surveillance officer stationed at the postnatal ward performed TcB measurements of the child before the child and mother were discharged from the hospital, as well as 24 and 48 hours after delivery if possible. At four weeks of age, all parents were contacted by phone and interviewed according to a semi-structured questionnaire, recording health status of the baby, need of medical care and current status. At 8 and 12 months of age, infants were scheduled for a follow-up visit including blood sampling (haemoglobin and ferritin). At 12 months of age, the Ages & Stages Questionnaire (ASQ) was used to record infants' neurodevelopment. Parents were assisted in answering the ASQ.

Sample size

The sample size calculation was based on examining the effect of cord clamping on anaemia at 8 months of age. The national prevalence of anaemia was 70% at 8 months (3). To find a difference of 15% (from 70% to 55%) in prevalence of anaemia between the two randomisation groups with a power of 80%

and a type I error rate of 0.05, a group size of 176 would be needed. Considering an attrition rate of 35%, we calculated that 270 newborn infants should be included in each group, i.e. a total of 540.

Timeline

The enrolment of 540 deliveries was started between 2 October and 21 November, 2014. Eight months blood sample tests were performed from 25 May to 4 August, 2015. Similarly, enrolment for 12 months blood sample testing and ASQ assessment were carried out from 6 September to 11 December, 2015.

Data collection

When the delivery was imminent (expected within 10 min), a surveillance officer opened sealed numbered opaque envelope containing the treatment allocation. The surveillance officer measured the time from complete delivery of the infant to the first clamp on cord using a stopwatch. The nurse midwife laid the infant on the mother's abdomen until the cord was clamped. In the ECC group, the surveillance officer informed the nurse midwife when 60 seconds approached and that the cord should be clamped if not already earlier performed. In the DCC group, the surveillance officer informed the nurse midwife when 180 seconds had passed, and the cord should be clamped. If the nurse midwife recognised that the mother or the infant needed attention, the umbilical cord was clamped and cut regardless of the treatment allocation.

Information on maternal age and parity, gestational age, Apgar scores, and birth weight were recorded. The gestational age was calculated based on the recall of each woman about her last menstrual period. Birth weight was based on the weight taken on an analogue weighing scale.

Transcutaneous bilirubin measurement after birth

At discharge, a nurse midwife who was trained in the procedure measured TcB on all included newborn infants. TcB was also measured at 24 and 48 hours providing that the baby was available and had not been discharged. Bilirubin level was measured by the JM A30 bilirubinometer (Dräger Service, Germany). At four weeks of age, questions on recognisable signs (yellowish skin or eyes) and/or treatment of jaundice were included in the questionnaire. All data were entered in a data base and analysed by SPSS 22 (originally, Statistical Package for the Social Sciences, 22, IBM Corp).

Blood sampling at 8 and 12 months

At 8 and 12 months, laboratory staff collected a venous blood sample (2 mL) from the infants with a needle of a 3-mL syringe (Lifeline Services Pvt. Ltd). The blood sample was transferred into an anticoagulant-treated vial (EDTA

K3; Zhejiang Gongdong Medical Technology Co, Ltd). Blood samples were stored at room temperature and analysed the same day. A haematology analyser (ABX Pentra XL 80; Horiba Medical) was used for haemoglobin analysis, and an immunoassay system (ADVIA Centaur; Siemens Healthcare GmbH) was used for ferritin analysis.

ASQ at 12 months

The ASQ is a screening tool that helps parents provide information about the development milestones of their children. It includes a series of parent-report questionnaires that span the age range of 2 to 60 months (69). For the secondary outcome neurodevelopment at 12 months of age, the third edition of the ASQ was used. It consists of three sections: brief demographic items; 30 questions divided into five different domains (communication, fine motor, gross motor, problem solving ability, and personal-social functioning); and seven open-ended questions regarding parental concerns about their children's growth and abilities. There are three choices for each question in the second section: "Yes", "Sometimes", and "Not yet", which score 10, 5, and 0, respectively. Domain scores are then calculated by the sum of each item. According to the ASQ manual, cut-off scores for the follow-up are created by subtracting the mean score with two standard deviations (2SD). In addition, we constructed an "at risk" cut-off score by subtracting one SD from the mean score.

The English questionnaire of 12 months ASQ was first translated to Nepali and then the Nepali version was validated with the English version by a professional English translator. After that, the questionnaire was piloted with ten infants of a similar age.

Even though the ASQ is a parent-report questionnaire, in the Nepalese context it was not feasible to send questionnaires to all parents since many parents were illiterate and also all people do not have a personal postal address. Therefore, it was decided to conduct interviews with the mothers by surveillance officers from the research team using ASQ when they came for the 12-month blood test according to the study protocol. The translated questions were generally also fit for use in the Nepalese culture.

Expected outcomes

The primary outcome was prespecified as the haemoglobin level at eight months of age. The haemoglobin level was analysed by comparing means and as a categorical variable. Anaemia was defined as a haemoglobin level of less than 11.0 g/dL (altitude corrected) (to convert to grams per litre, multiplication by 10 was performed). The secondary outcomes included the following:

- Hyperbilirubinemia in term newborn infants, analysed based on gestational age and age measured in hours after birth
- Haemoglobin level at 12 months of age, analysed by comparing means and as a categorical variable with the same definition of anaemia.

- Ferritin levels at 8 and 12 months of age, analysed by comparing means and as categorical variables. ID was defined as a ferritin level of less than 12 μg/L (70).
- IDA at 8 and 12 months of age, defined as ferritin and haemoglobin levels below the respective cut-offs.

Altitude correction

We used the Centres for Disease Control and Prevention haemoglobin adjustment method to correct for altitude ($-0.32 \times (\text{altitude} \times 0.0032808) + 0.22 \times (\text{altitude} \times 0.0032808)^2$). The altitude of Kathmandu is 1400 m above sea level and was calculated in the given formula, resulting in a correction of 0.32 g/dL, which was subtracted from each of the individual haemoglobin results before making descriptive statistics and group comparisons (71).

Data management

The surveillance officer filled out all the information in the record form. The research manager verified all the record forms with the primary source of data. A data entry officer re-checked for discrepancies before entering the data into computers for all three studies. During the intervention period, the quality control team from Uppsala University provided supervision to ensure quality of data collected and to avoid data loss. A protocol for data tracking was followed.

The Census and Survey Processing System (CSPro), a public domain software package developed and supported by the U.S. Census Bureau and ICF Macro was used for quality data management. CSPro is interfaced with SPSS, which was used for statistical analysis, data management (case selection, file reshaping, creating derived data), and data documentation. Hard copies of records are stored in a filing system in a secure room. Data was checked for accuracy, consistency, and completeness in both CSPro and SPSS. An analysis plan was developed in accordance with the reporting guidelines. A baseline profile and comparison of key variables between groups was presented.

Statistical analysis

Analysis was based on intention to treat. In papers I, II and III, we used an unpaired 2-tailed *t* test for variables with normal distribution; categorical variables were compared between groups using the Fisher exact test.

Consideration was paid to baseline or follow-up data that were imbalanced between treatment groups and was significantly correlated with primary and secondary outcomes. We used multivariate analysis of variance (MANOVA) and logistic regression analysis, as appropriate, to control for this imbalance.

Calculations of the Spearman rank correlation coefficient (ρ) were used to determine variables that were associated with the ASQ total score at 12 months. Variables with a correlation significance of $p < 0.05$ for each outcome were then entered into a linear regression model.

Owing to attrition rates at 8 and 12 months, we also analysed data using the multiple imputation method in SPSS to reduce possible biases from missing data and to increase precision in both papers I and II (72). Variables included in the model as predictors were: time to cord clamping, mother's age, previous pregnancies, gestational age, birth weight, sex, time from delivery, haemoglobin and ferritin at 8 and 12 months, and ASQ at 12 months. These were entered as both dependent and predictive variables, whereas age and haemoglobin and ferritin levels at 12 months of age and ASQ total score, and the domain scores (communication, fine motor, gross motor, problem solving ability and personal-social functioning) were entered as dependent variables. Imputation was carried out five times.

Data was analysed according to both intention-to-treat and as per protocol. Normally distributed data was compared by using t-test and described by mean and SD. Bilirubin values were treated both as a continuous variable and analysed with Student's T-test and linear regression and as a categorical variable analysed by Chi-square test. We chose to analyse measurements obtained between 6 and 72 hours after birth for bilirubin measured at the time of discharge. MANOVA was performed for bilirubin measured at time of discharge as this timing varied. Gestational age was significantly different between the groups and was also entered into the MANOVA model. A predictive nomogram for TcB (55) was used to assess risk of developing significant neonatal hyperbilirubinemia. All newborn infants were categorised in low, intermediate and high risk of hyperbilirubinemia.

Ethical considerations

All research involving newborn infants and small children needs careful ethical considerations, mainly since the subjects themselves cannot agree to whether or not they want to participate in the study. In particular, research that is not of immediate benefit to the patients' needs special ethical consideration. The included infants were healthy late preterm or term infants undergoing umbilical cord clamping, which is a standard procedure after birth. Previous data indicate that DCC may be beneficial. The infants were randomised to either early or delayed clamping in a hospital with the routine of performing ECC. Consequently, infants included were either subjected to standard care or an intervention with potential benefit. The study was approved by the institutional review board of the hospital and the ethical review board of Nepal Health Research Council (Reg no. 76/2014) on 5 June, 2014. The trial was registered at clinicaltrial.gov with the registration number NCT 02222805 (https://clinicaltrials.gov/ct2/show/NCT02222805) on 19 August, 2014. Written informed parental consent was obtained after assignment to the MNSC from the women who were eligible and willing to participate and they were also informed that they could withdraw from the study at any time without any need for explanation.

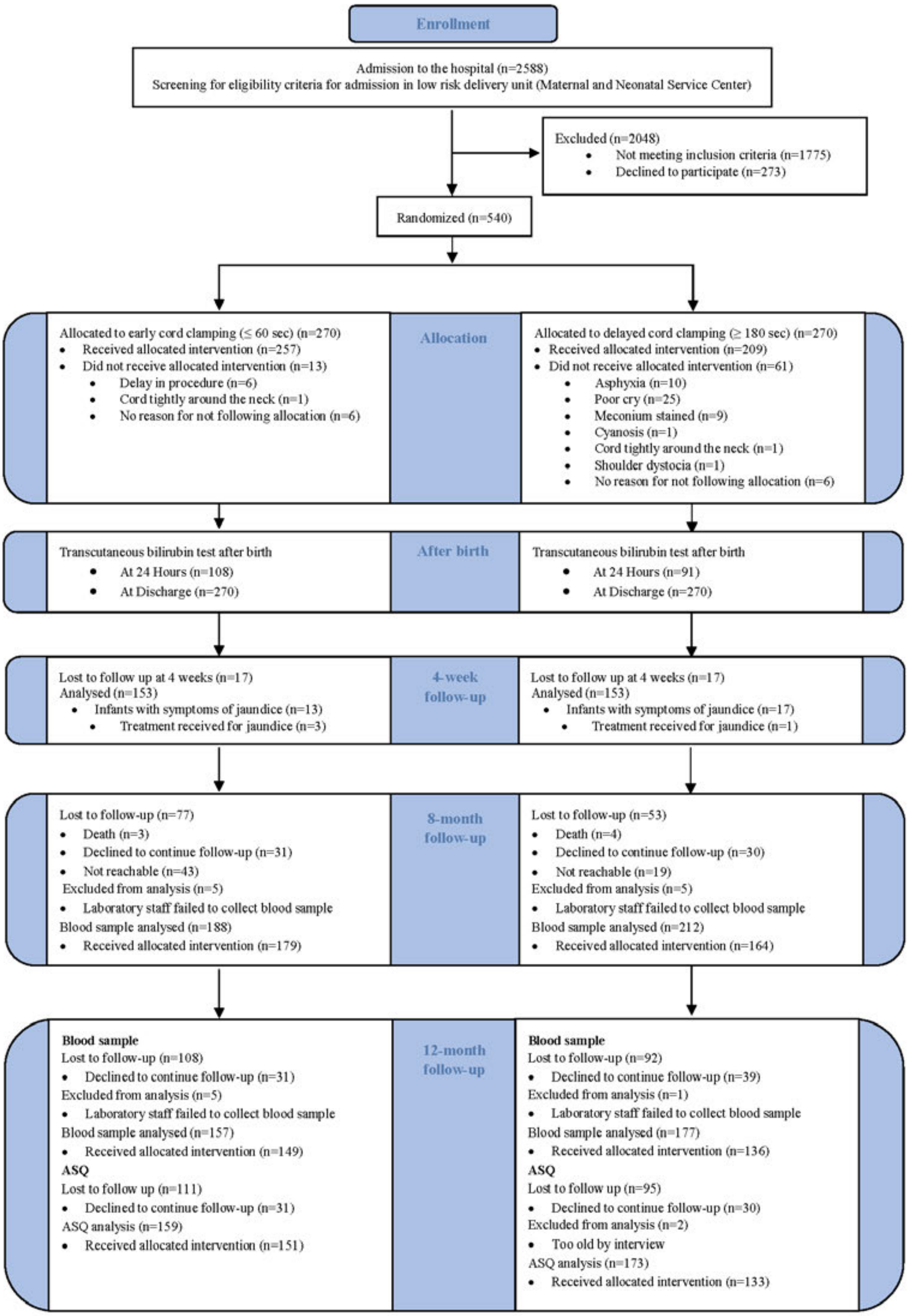

Figure 3. Trial profile (CONSORT flowchart)

Paper IV

Study settings

This qualitative study was carried out at two large referral hospitals in Kathmandu, Nepal. PMWH is a publicly funded maternity hospital for gynaecological and obstetrics services. It is one of the skilled birth attendant (SBA) training centres. Tribhuvan University Teaching Hospital (TUTH) is a non-profitable hospital with about 7,500 deliveries per year. It is a central referral hospital dealing with all types of medical services including maternity services. The hospital has two distinct functions; as a teaching hospital and as a national hospital, rendering medical care and services. The hospital is also one of the SBA training centres. The hospital has two delivery units: a high risk-labour room with human resources of nurse midwifes and obstetricians and a low risk-birthing centre run by nurse midwifes. Birthing centres at both hospitals are managed by SBA trained nursing staff except in the case of unexpected emergency cases.

Design and participants

To explore the barriers and enablers for implementation of DCC, FGD and KII were selected as preferred methods to collect data. The FGD and KII guidelines were developed with the participation and consensus of all the authors.

The nursing staff working in delivery units were invited to form a group to discuss the topic. A purposive sampling strategy was used based on the selection criteria: delivery staff involved in conducting deliveries in the labour room and birthing unit (MNSC) at PMWH; and in the labour room and birthing centre at TUTH for FGD. Only nurse midwives who were on-duty were available to participate in the discussion. Invitations were channelled through the ward in-charge of each delivery unit and they arranged the duty schedule to gather nursing staff as was possible when discussions were scheduled to take place. The ward in-charges and SBA trainers who were supervisors for the whole unit were explicitly asked not to be present during the discussions and were invited to separate KIIs. This was considered to be a suitable way to include perceptions at the managerial level and to increase the variation of the data. It also enabled them to provide their own perceptions on the study topic. The characteristics of the participants are described in Table 2.

Table 2. Characteristics of the participants of the FGD and KII from PMWH and TUTH.

	Participants (n)	Years of experience [a] Range (Median)	Participants with SBA training (n)	Degree attained (n)[b]
KIIs:				
SBA trainer/supervisors	8	19–33 (28)	8	BN (6), MN (1), M.HCM (1)
Ward in-charges	4	25–28 (27.5)	4	BN (4)
FDGs:				
Labour room (TUTH)	14	4/12-16 (6)	2	PCL (2), BN (6), BSc Nursing (5), MN (1)
Birthing Centre	4	9–22 (15.5)	3	BN (3), BSc Nursing (1)
Labour room (PMWH)	6	8–17 (14.5)	6	BN (6)
Birthing Unit	10	5–22 (12.5)	9	PCL (2), BN (8)

[a] Year of experience within health care among participants
[b] Degree attained: PCL=Proficiency Certificate Level in Nursing, BN=Bachelor in Nursing, BSc Nursing: Bachelor science in Nursing, MN= Masters of nursing, M.HCM=Masters in Health Care Management

Data collection

To create a trustworthy environment, the first author visited both hospitals and described the purpose of the study. The first author requested one of the nursing supervisors in each hospital to support in coordinating with the ward in-charge and delivery staff for setting times and availability of the participants for the discussions. The first author moderated all the FGDs and KIIs in Nepali. Four groups of delivery care nurses working in the labour room and birthing units from each hospital, altogether 8 groups in total, were included in FGDs with 3-5 participants in each group. Three KIIs from TUTH and 9 KIIs from PMWH were conducted with the ward in-charge and SBA trainers. The FGDs and KIIs lasted between 20 and 40 minutes. For the FGDs, the number of participants required to be large enough to generate a meaningful group discussion but small enough on account of difficulties in gathering together at the same time due to different duty schedules.

Before analysis, both FGDs and KIIs were recorded by voice recorder, transcribed verbatim in the local language (Nepali) and translated into English by the first author.

Data analysis

An inductive approach to the data was applied and analysis was performed through qualitative content analysis as outlined by Graneheim and Lundman (73). Transcripts were coded manually in line with the aims of the study. After coding text segments, codes were condensed into sub-categories which were given descriptions reflecting the content.

The next stage of analysis was performed by all the authors together in a back-and-forth process and the sub-categories were sorted into categories. To increase the descriptive value of the categories, some level of abstraction was used, but the authors still attempted to accurately reflect the content of the subcategories.

The first author then went back to the original text to find quotes that were representative of each category. The categories and subcategories and related quotes were finally presented to all of the co-authors to allow them to comment and agree on the findings.

Validity and reliability of tools

The instrument for data collection in this study was an interview guide with open-ended questions developed after extensive review of the literature. The tool was reviewed by the last author to check for face and content validity and translated and back-translated to and from Nepali to English.

Ethical considerations

Ethical clearance was obtained from the institutional review board of both hospitals; Paropakar Maternity and Women's Hospital (58-5-1561) and Tribhuvan University Teaching Hospital (date: 11 March 2018) and from the Nepal Health Research Council (Reg.no:17/2018) on 15 April 2018 before data collection started. All participants signed a written informed consent form before the discussion started and were reassured that the confidentiality of the information would be respected before the discussion started. The participants were informed about the possibility to withdraw from the study at any time without any sanctions or need for explanation. The study participants were at no risk of harming themselves or others by taking part in this study. Participation in the study was voluntary. Notes and audio records were kept in a safe place by the moderator. The moderator transcribed in Nepali and translated into English. The participants' anonymity was maintained throughout the data collection, analysis and reporting period.

Results

Randomised controlled trial

For the randomised controlled trial, altogether 2,588 pregnant women were admitted to the hospital during the recruitment time period, 1,775 pregnant women did not meet the inclusion criteria for the study. A total of 813 women who were admitted to the MNSC were assessed as being eligible for the study, resulting in 273 not being randomised as they declined participation. In the early clamping group, 257 out of 270 and in the delayed clamping group, 209 of 270 received the allocated intervention. Losses to follow up occurred in 4 weeks, 8 months and 12 months for various reasons, Figure 3.

Maternal and newborn characteristics

After obtaining signed consent from the pregnant women and when birth was imminent, 270 women were randomly assigned to cord clamping no later than 60 seconds (early) and 270 to cord clamping after at least 180 seconds (delayed). The mean age of the mothers was 23.6 ± 4.1 years and 291 (53.9%) of women were primipara. Almost all the mothers, 502 (93.0%) had attended antenatal care. In total, 466 (86.3%) of the 540 included received the allocated intervention (Figure 3). For the early clamping group, the median time to clamping the umbilical cord was 32 (interquartile range, 23-45) seconds and for the delayed clamping group it was 192 (interquartile range, 185-199) seconds, p<.001. At one hour of age, 533 (98.7%) babies had initiated breastfeeding. The length of stay in hospital after delivery was 20.4 (14.9 to 26.9) hours in the early and 20.2 (14.8 to 24.7) hours in the delayed clamping group. In total, 524 (97%) babies were discharged between 6 to 72 hours of birth.

There were no differences in maternal background variables detected between the two groups. There was a significant difference in gestational age. It was significantly lower in the early clamped group, mean difference 1.6 days (95% confidence interval 0.3 to 3.0). In the early clamping group, 12 (4.5%) were born before 37+0 gestational age, compared to 5 (1.9%) in the delayed clamping group, p=0.09. There were no differences in birth weight and sex of the newborns between the two randomised groups (Table 3). When analysing the 466 cases performed per protocol, there were no significant differences in maternal and newborn infants' background variables.

Table 3. Background characteristics of maternal and newborn included in the study at PMWH in Kathmandu, Nepal.

	ECC (n=270) mean (SD)	DCC (n=270) mean (SD)	p value
Maternal Characteristics			
Age (years)	23.8 (4.3)	23.4 (3.9)	0.2
No. of pregnancies	1.6 (0.8)	1.7 (0.9)	0.8
Newborn Characteristics			
Birth weight (grams)	3,015 (426)	3,029 (405)	0.7
Gestational age(weeks)	39.0 (1.2)	39.3 (1.1)	0.02*
No (%) of Female	124(46%)	135 (50%)	0.4
5-min Apgar score of 7-10, No. (%)	260 (96.3)	258 (95.6)	0.4
Data is presented as mean (SD) except for number of females. Values are means (SD) unless stated otherwise. * mean difference is -0.2 (-0.4 to 0.0)			

Main results

Bilirubin and jaundice (Paper III)

Out of the 570 newborn infants included, TcB was measured at 24 hours after delivery for only 199 (37%) and for 20 (4%) at 48 hours. At discharge, bilirubin was measured for all the infants. The mean value was not statistically different between groups at any of the time points of measurements (Table 4). While performing the analysis per protocol, values did not change considerably; the mean bilirubin in the ECC group was 87.8 ± 41.1 µmol/L and in the DCC group 85.4 ± 36.1 µmol/L respectively, p=0.52. We also adjusted bilirubin at discharge for time of measurement and gestational age, as it was significantly different between the groups. After adjustments for the time of measurement for the bilirubin at discharge, the difference between the groups was still not significant. For the ECC group, TcB was 87.1 (SE 2.3) µmol/L and for the DCC group, it was 85.8 (SE 2.3) µmol/L, and the mean adjusted difference was -1.3 (95% CI -7.8 to 5.2).

Table 4. Transcutaneous bilirubin levels at 24 hours after delivery and at discharge (Intention-to-treat).

	ECC		DCC		p-value
TcB	**Mean (SD)**	**Participants**	**Mean (SD)**	**Participants**	
At 24h	103.6 (33.1)	108	104.8 (32.3)	91	0.8
At discharge	87.3 (40.8)	270	85.4 (37.9)	270	0.6

Based on the bilirubin level and time after delivery, all the values were fitted into the predictive nomogram provided by Varvarigou et al. (55). Newborn infants were categorised into low, intermediate and high risk of hyperbilirubinemia. The number of newborn infants in the intermediate or in high-risk group was 83 (32.5%) in the ECC and 91 (35.1%) in the DCC group (p=0.58). Based on age in hours as well as gestational age, 81 (32.3%) of the ECC group and 86 (33.2%) of the DCC group had at some point in time a pathological bilirubin (p=0.78). Among neonates born before 37+0 gestational weeks, pathological bilirubin was detected in 3 (25%) in the early and in 1 (20%) in the delayed cord clamping group (p>0.99).

At the four weeks follow up, 506 of the 540 mothers were successfully contacted by telephone. According to mothers' telephone reports, a total of 30 neonates experienced symptoms of jaundice, such as yellowish skin or eyes, 13 (5.1%) were from the ECC and 17 (6.7%) from the DCC group (p=0.57). Among those who had reported jaundice, 3 (1.2%) infants from the ECC and 1 (0.4%) from the DCC group (p=0.62) requested medical consultation for the symptoms of jaundice but no one reported that their neonate had received phototherapy or transfusion for its treatment.

Haematological and iron status (Paper I)

We lost contact with many of the participants after the massive destruction due to earthquakes in Nepal in 2015; many people living in the Kathmandu valley fled to their native villages and some of them did not return due to fear of aftermaths. Along with that, a blockade from India had also affected transportation within the country. As a consequence of these two major incidents, only mothers of 400 infants at 8 months and of 334 infants at 12 months of age were successfully contacted.

At 8 months

The primary outcome of this randomised controlled trial was haemoglobin levels at 8 months of age of pre-specified infant. Blood sampling took place from 25 May to 4 August, 2015. At 8 postpartum months, 188 (69.6%) in the ECC group and 212 children (78.5%) in the DCC group, in total 400 infants (74.1%) returned, at a mean ± SD age of 238 ± 8 days. The difference in return rate between the groups was statistically significant, (p = 0.02) for reasons unknown. The mean haemoglobin level was 0.2 (95% CI, 0.1-0.4) g/dL higher in the DCC group (Table 5). Anaemia prevalence in the ECC group [222 (82.2%) vs 197 (73.0%)] was higher with a relative risk of 0.89 (95% CI, 0.81-0.98) (Table 6).

Table 5. Laboratory status at 8 and 12 months of age in infants[a].

Cord clamping group, Mean (SD)				
Laboratory status	**Early (n=270)**	**Delayed (n=270)**	**Difference (95%CI)**	**p value[b]**
8 months follow-up				
Time to umbilical cord clamping, seconds	35 (2)	159 (9)	125 (116 to 133)	<.001
Haemoglobin level, g/dL[c]	10.2 (0.9)	10.4 (0.9)	0.2 (0.1 to 0.4)	0.008
Ferritin level, µg/L[d]	16.4 (2.2)	21.8 (2.1)	33 (14 to 56)[e]	<0.001
12 months follow-up				
Haemoglobin level, g/dL[c]	10.1 (1.0)	10.3 (0.9)	0.3 (0.04 to 0.5)	0.02
Ferritin level, µg/L[d]	13.2 (2.1)	15.6 (2.4)	18 (−6 to 48)[e]	0.14

SI conversion factors: To convert ferritin to picomoles per litre, multiply by 2.247; haemoglobin to grams per litre, multiply by 10.0.
[a]Results are presented after multiple imputation analysis. Data in multiple imputation analysis were based on early cord clamping (n = 188) and delayed cord clamping (n = 212) at 8 months and early cord clamping (n = 157) and delayed cord clamping (n = 177) at 12 months. Early clamping was defined as 60 seconds or less; delayed clamping, 180 seconds or longer.
[b]Calculated using an unpaired 2-tailed t test.
[c]Corrected for altitude.
[d]Presented as geometric mean (geometric SD).
[e]Presented as geometric mean ratio in percentage.

One of the secondary outcomes was that the ferritin concentration at 8 months was significantly lower in the ECC groups (difference in geometric mean ratio 33%; 95% CI, 14%-56%). ID (103 [38.1%] vs 60 [22.2%] infants) and IDA (90 [33.3%] vs 52 [19.3%] infants) were significantly high prevalent in the ECC group. The relative risk of having ID was 0.58 (95% CI, 0.44-0.77) in the delayed group, with a number needed to treat (NNT) of 6 (95% CI, 4-13); the relative risk for having IDA was also 0.58 (95% CI, 0.42-0.78), with an NNT of 7 (95% CI, 5-6).

At 12 months

At the age of 12 months, 334 infants (61.9%) returned for blood tests from 6 September to 11 December, 2015 where 157 (58.1%) infants were from the early and 177 (65.6%) infants were from the delayed group with a mean ± SD age of 357 ± 17 days. Mean haemoglobin was 0.3 (95% CI, 0.04-0.5) g/dL higher in the delayed group (Table 5). Anaemia was less prevalent in the DCC group, with a relative risk of 0.91 (95% CI, 0.84-0.98), resulting in an NNT of 12 (95% CI, 7-78). No difference was found in the serum ferritin level or prevalence of ID or IDA between the groups (Table 6).

Table 6. Proportion of infants with haemoglobin and serum ferritin outside reference limits at 8 and 12 months of age[a].

Cord Clamping Group, No. (%)					
Laboratory status (definition)	**ECC (n=270)**	**DCC (n=270)**	**p value[b]**	**RR (95%CI)**	**NNT (95%CI)**
8-month follow-up					
Anaemia (Haemoglobin < 11.0 g/dL)[c]	222 (82.2)	197 (73.0)	0.01	0.89 (0.81-0.98)	11(6–54)
Iron deficiency (Ferritin < 12 µg/L)	103 (38.1)	60 (22.2)	<0.001	0.58 (0.44-0.77)	6 (4-13)
Iron deficiency anaemia (Haemoglobin < 11.0 g/dL and Ferritin < 12 µg/L)	90 (33.3)	52 (19.3)	<0.001	0.58 (0.42-0.78)	7 (5-16)
12-month follow-up					
Anaemia (Haemoglobin < 11.0 g/dL)[c]	232 (85.9)	210 (77.8)	0.02	0.91 (0.84-0.98)	12 (7-78)
Iron deficiency (Ferritin < 12 µg/L)	116 (43.0)	96 (35.6)	0.09	0.83 (0.66-1.03)	NA
Iron deficiency anaemia (Haemoglobin <11.0 g/dL and Ferritin < 12 µg/L)	102 (37.8)	82 (30.4)	0.8	0.80 (0.63-1.03)	NA

Abbreviations: NA, not applicable; NNT, number needed to treat; RR, relative risk.
SI conversion factors: To convert ferritin to picomoles per litre, multiply by 2.247; haemoglobin to grams per litre, multiply by 10.
[a]Results are presented after multiple imputation analysis. Data in multiple imputation analysis were based on early cord clamping (n = 188) and delayed cord clamping (n = 212) at 8 months and early cord clamping (n = 157) and delayed cord clamping (n = 177) at 12 months.
[b]Calculated using the Fisher exact test.
[c]Haemoglobin level was corrected for altitude.

Ancillary analyses at 8 and 12 months

At 8 months of age, all infants were partially breastfed. Weaning foods were equally common between groups, except for fruit that was given to 48 of 188 infants (25.5%) in the ECC and 27 of 212 infants (12.7%) in the DCC group (p = 0.003). We found no difference in occasions of respective feedings per day between groups. At 12 months of age, 298 of the 334 infants (89.2%) were still partially breastfed. The other types of food and feeding occasions did not differ between the groups. The parents did not report giving iron supplements to any infant.

Gestational age was not statistically balanced between treatment groups (Table 3), and at 12 months the mean ± SD age of the infant at the time of blood sampling also differed significantly between groups, being at 355 ± 17 days in the ECC and 359 ± 17 days in the DCC group ($p = 0.02$). To control this difference, we performed a MANOVA for the scale variables and logistic regression for categorical variables, entering gestational age as a covariate when analysing variables from the 8 and 12-month blood samples and adding age as a covariate in the analyses of 12-month blood samples. The results from the MANOVA and logistic regression analysis did not change the results significance.

We found a significant difference between groups regarding protocol adherence, as 13 infants (4.8%) in the ECC group had their cords clamped after 60 seconds and 61 infants (22.6%) randomised to DCC had their cord clamped before 180 seconds. To control for this difference, we performed the analysis again including only infants treated according to their assigned allocation group (per protocol). This analysis resulted in an overall more pronounced difference between the early and delayed group, but did not change the results in a way that would affect the conclusions of the study.

Neurodevelopment at 12 months (Paper II)

In total, 334 out of 540 infants (61.9%) returned for ASQ assessment at 12 months between 6 September and 11 December, 2015. Two of them were excluded from the assessment as they exceed the specified age interval. Among the 332, 159 (58.9%) infants belonged to ECC and 173 (64.1%) to DCC groups. The ASQ assessments were done (mean ± SD) 355 ± 21 days for early group and 360 ± 23 days for the delayed group. Among the 332 infants, 180 (54%) were male. There were no significant differences in distribution of sex between the groups.

The mean weight was 9,177 ± 1,096 in the ECC (n=155) and was 9,181 ± 1,138 in the DCC group (n=168) at 12 months of age, where mean weight gain with SD was 6,112 ± 1,004 and 6,108 ± 1,049 in respective groups. There were no significant differences between the groups regarding maternal or infant baseline date.

After multiple imputation analysis, more children in the ECC group were 'at risk' of having affected neurodevelopment measured by ASQ total score, 21 (7.8%) versus 49 (18.1%) in the delayed group, relative risk 0.43 (0.26 to 0.71) and had lower mean total score ± SD, 287.2 ± 10.1 vs 290.4 ± 10.4, $p<0.01$. Significantly fewer infants in the DCC group were at risk of having neuro-developmental impairment when comparing total score, and in the domain 'communication', 'gross motor' and 'personal social' (Table 7).

Table 7. At risk (-1SD) ASQ at 12 months of age in infants who were randomised to early (≤60 seconds after delivery) or delayed (≥180 seconds) umbilical cord clamping after multiple imputation.

	ECC (n=270)	DCC (n=270)	p value	RR (95%CI)	NNT (95%CI)
Total score < 279	49 (18.1)	21 (7.8)	<0.001	0.43 (0.26-0.71)	10 (6-23)
Communication < 56.8	46 (17.0)	22 (8.1)	0.003	0.48 (0.28-0.79)	11 (7-34)
Gross motor < 49.3	49 (18.1)	30 (11.1)	0.03	0.61 (0.39-0.95)	14 (8-141)
Fine motor < 55.5	42 (15.6)	32 (11.8)	0.26	0.76 (0.48-1.20)	
Problem solving <52.0	56 (20.7)	40 (14.8)	0.09	0.71 (0.48-1.05)	
Personal social < 55.4	54 (20.0)	29 (11.1)	0.004	0.54 (0.34-0.83)	11 (7-35)

Abbreviations: NNT, number needed to treat; RR, relative risk.
Data are shown as n (%) or with 95% confidence intervals (CI). Results are presented after multiple imputation analysis. Data in multiple imputation analysis were based on ECC (n = 157) and DCC (n = 173), p-value by Fisher's exact test.

The ASQ total score at 12 months had significant correlations with the randomised group; infant's sex, breastfeeding within the first hour of life, haemoglobin and ferritin at 12 months of age. When the 12-month ASQ questionnaire was answered, the age of the infant correlated positively with the total score. In multivariate linear regression analysis, the randomisation group and haemoglobin levels at 12 months of age remained significant predictors, as well as postnatal age. In this model, the adjusted ASQ total score was lower in the ECC group (Table 8).

Table 8. Predictors of the ASQ total score at 12 months of age: results of multivariate linear regression analysis.

	B (95% CI)	p-value
Intercept	253.5 (288.3 to 278.6)	< 0.001
Male	–1.9 (–4.2 to 0.3)	0.09
Randomisation	–2.8 (–5.1 to –0.6)	0.02
Breastfed within first hour	–13.6 (–27.8 to 0.7)	0.06
Haemoglobin at 12 months	1.8 (0.6 to 3.1)	0.004
Ferritin at 12 months	0.09 (–0.5 to 6.3)	0.09
Age at test	0.08 (0.03 to 0.13)	0.002

CI, confidence interval. $F = 7.8$; $p < 0.001$; $R^2 = 0.111$; $n = 326$

When analysis was restricted to the infants who received the allocated intervention, the DCC group (n = 132) still scored higher in both communication and personal-social than the ECC group (n = 151), with mean difference (95% CI) of -0.7 (-1.3 to -0.2) and -1.5 (-2.3 to -0.6) at p=0.009 and 0.001, respectively.

Barriers and enablers for implementation of DCC (Paper IV)

For this study, recruitments for FGDs and KIIs took place from 22 April to 20 May, 2018. Altogether, 8 groups of delivery care nurses working in the labour room and birthing units from both hospitals were included in FGDs. Twelve KIIs with ward in-charges and SBA trainers who were supervisors for the whole unit and SBA trainers in PMWH and TUTH were conducted. From the analysis of FGDs and KIIs, we found six categories and 18 sub-categories (Table 9).

Table 9. Categories and their corresponding subcategories from both FGD and KII.

Categories	**Sub-categories**
Medical and physical constraints	Maternal medical condition
	Foetal medical condition
	Physical setting
Habitual practice	Routine work
	Need for reminders
	Need to have knowledge about benefits
	Change through practice
Forced to informal learning	Lack of refresher training
	Peer learning, and informal information
Lack of coherence	Lack of team work
	Lack of trust among team
Need to bring uniformity	Knowledge update through coaching and orientation
	Request for authorised protocol
	Supervision, monitoring and evaluation
	Use flex chart, poster and pamphlet to raise awareness
Opportunities for change	The will to do good
	Research as authority
	Trust in hierarchical system

The discussion revealed constraint to perform DCC due to maternal or foetal medical conditions, which makes it difficult to wait to clamp the cord. Also, sometimes the mother is not ready to keep the newborn on her abdomen, either because she is uncomfortable or afraid or just not cooperative. Besides maternal and foetal conditions, physical conditions were barriers to DCC, e.g. in the operating theatre the delivery bed is small and it is difficult to keep the baby on the mother's abdomen, the room temperature is low especially in winter, and sometimes due to lack of manpower and heavy work load delivery staff cannot wait for DCC.

> *"...some mothers would get afraid and say don't keep it on my abdomen...they would say "I don't want to hold the baby"." (Birthing centre in-charge)*

Sometime it is difficult to adopt new guidelines due to habitual practice as the medical staff in attendance gets stressed and feels the need to cut the cord before any other procedure. It is more difficult to adopt new routines for more senior staff as they have been carrying out old practices for a long time. They forget the new practice, and they require reminders more frequently at the beginning; reminders, especially from ward in-charge and SBA trainer/supervisors.

> *"Very senior sisters, they themselves don't want to change, they want to do how they have been practicing it." (SBA trainer/supervisor)*

> *"They remember only after we remind them about delaying the cord clamping" (Nurse in-charge)*

Inadequate knowledge about the benefits and disadvantages of DCC, and lack of formal information through coaching or training made delivery staff hesitant to bring intervention in practice. Due to lack of refresher training opportunities and knowledge updates for SBA trained staff, they are left to rely on informal learning and are forced to take their own initiative to learn new ideas through peer learning, self-education and in-service learning. Therefore, there should also be a demonstration to begin with and they should be supported to practice regularly until it becomes a new habit. Along with that, it is necessary to have self-motivation to adopt change.

> *"We had SBA training 2-3 years back, we don't have training that often so... if it was frequent then we would have been updated too but there is not much training, that's why" (Nurse in-charge)*

> *"There should be simulation and at the beginning they should have supervisors with them, that would help them to learn it gradually" (Nurse midwife)*

> *"It's all about practice and if they get into practice then it continues." (SBA trainer/supervisor)*

"More than that, it should come from their inner heart, from their attitude" (SBA trainer/supervisor)

There is lack of coherence within the team. There is no proper teamwork and trust among the team members, which forms a barrier to creating uniformity. Delivery staff feel that the medical doctors regard themselves as superior to them and that they don't have to follow what nurses say, even though it is about the latest information that the doctors are unaware of.

"It would have helped to have the same thoughts because even though we are a different team, our goal is the same, only our way is different.... patient comfort, condition of patient, safe mother and child.... It would have been better if that could have happened" (SBA trainer/supervisor)

"If doctors are involved in a delivery then they ask, "Who said delayed cord clamping?" (Nurse midwife)

"Yes, they feel superior.... 'we are doctors and you are just a nurse. Why should we listen to nurses?' We feel it, we have the same value as they have but they seem to feel that, 'nurses are our assistants'." (SBA trainer/supervisor)

Onsite coaching, refresher training for those who have already received SBA training and orientation to all delivery staff nationwide can help to bring uniformity in clinical practice. DCC should be included in the nursing curriculum and SBA training manual and thus be formalised. Standardised protocol at the national level and within the hospital guides and puts pressure on delivery staff to follow and adopt new guidelines. The protocol should be disseminated through official written documents or letters so that they reach all over the country and information can be spread quickly in an authorised way.

"Those who are exposed to conducting delivery should formally know about it. Small orientations or one- or two-day packages as per content volume." (Nurse midwife)

"It should be included in the SBA course. Secondly, it should be included in the bachelor's and master's curriculum and after that every hospitals and periphery level should provide orientation." (Nursing in-charge)

"It would be best if we could make it a protocol, if this is possible. It would be useful for ever, everyone would read it and apply it. It would go to every place and everyone would do their work as per the protocol." (SBA trainer/supervisor)

“There should be authorised instructions and then everyone would do it.” (Nurse midwife)

DCC should be included in the partograph and have regular supervision and monitoring from a higher level, since it is difficult to bring change without effective supervision and monitoring. Developing a flex chart, poster and pamphlet, and advertising through radio, television and other social media could be methods of raising awareness. These methods will not only raise awareness among delivery staff but also among the general public, which would help to encourage delivery staff to perform DCC.

“It might also help if we were to make a habit of noting the timing of the cord clamping in the partograph.” (Nurse midwife)

“In my experience, without follow up, without supervision and monitoring, it is impossible to achieve 100% adaptation” (SBA trainer/supervisor)

“We can do advocacy, it will be effective to do it through television or radio, now everyone has Facebook.” (Matron)

“If the mother knows about it through the media, radio, then they might be reminded to delay doing it.” (Nurse midwife)

Besides all those constrains and barriers, there are also opportunities to bring about change both within the hospitals as well as in the whole country. Willingness to do good among healthcare staff is one such opportunity. This provides the staff with self-motivation and this would make it easy to bring about change. The participants displayed the understanding that they are already working for the betterment of mothers’ and children’s health and they feel happy to change their practice if it is good for mother and child. Another opportunity was the staff’s trust in research and the authority of scientific evidence.

“We conduct delivery with the good health of the mother and baby in mind therefore, if delayed cord clamping helps the baby then we will do it for the benefits it provides. This is how I get motivated.” (Nurse midwife)

“Everyone accepts good things” (SBA trainer/supervisor)

“We have to accept this for scientific reason” (Nurse in-charge)

However, to bring research findings into implementation, it should be authorised by a higher authority, either at government level or hospital level, providing instructions for the change. The power of hierarchical structures was put forward, not only in relation to protocol development (need to bring uniformity), but also as an opportunity to implement change through authority and direction.

"It should be the hospital director, then after that the matron and then supervisors and then after that the in-charge, and then after the in-charge all the duty station staff who should receive information and should tell them its advantages." (Matron)

"It should go through the Ministry, the Nepal Government. The Nepal Government is the valid authority" (Matron)

Discussion

The umbilical cord clamping time may have an important impact on a high anaemia prevalence population, as shown by the results in this thesis and previous studies. Even small benefits for each individual may have greater impacts when multiplied in a larger population. Previous cord clamping studies have shown reduced ID at 4 and 6 months of age (14,23,24,74). This trial was set out to take a broad approach to the subject especially in a low-income setting with high prevalence of ID and anaemia, and tried to evaluate a wider range of proposed effects of delayed versus early cord clamping.

Anaemia among children under 5 years of age is one of the major public health problems affecting low, middle and high income countries where anaemia resulting from IDA has adverse effects on cognitive and motor development resulting in fatigue and low productivity (8). Iron content in the body has a positive effect on cognition and psychomotor outcomes (75). As there is a high global IDA prevalence among infants, there is the possibility of IDA affecting children's development not only at an individual development level but also in terms of national development (76). ID has a direct effect on the development of the brain and an indirect effect on poor long-term behavioural and developmental outcome. It also plays a major role in the dopamine system and in alteration of social/emotional and neurocognitive functions (9). One of the cross-sectional studies in Nepal showed that 52% of children aged 6–35 months were anaemic, 1 in 3 children had depleted iron storage, and 16% had IDA (77). Therefore, a reduction of 10 % would mean an annual reduction of 60,000 infants with anaemia in Nepal (78).

DCC at birth increases neonatal mean venous haematocrit by about 30% extra blood volume to the newborn which reduces neonatal anaemia (35,79). It has the possibility to improve infants' and children's health and development by increasing neonatal iron storage and reducing anaemia prevalence at birth (35). A randomised clinical trial with the intervention of DCC after 180 seconds compared with clamping before 10 seconds in 338 term infants, (Andersson et.al. 2011) found improved iron status, reduced prevalence of ID and neonatal anaemia but it did not show difference in an overall neurodevelopment at the age of 4 months (24,36). There was no difference in haemoglobin or iron status at 12 months of age, most likely due to the unexpected low prevalence of anaemia (11%-15%) and ID (3%-5%) at that age (37). At the age of 12 months, there was no affect found on neurodevelopment (37) whereas the

DCC group showed improved scores in fine motor and social domain at the age of 4 years, especially in boys (80).

In 2017, the Committee Opinion #684 stated that DCC in term infants showed an increase in the incidence of jaundice requiring phototherapy. The ACOG recommends that obstetric care providers ensure that there is mechanism to monitor and treat neonatal jaundice in place before adopting DCC (61). The ACOG recommendation was based on the Cochrane systematic review from 2013 (14). In contrast, a meta-analysis of 15 studies found ECC within the first 10 seconds compared with DCC with a minimum of 2 minutes had no significant difference in mean serum bilirubin levels within the first 24 and 72 hours after birth in term babies (22).

In 2011 in a randomised controlled trial, Andersson et.al. showed similar bilirubin concentrations in two groups of ECC (≤ 10 seconds) and DCC (180 seconds) and no differences in the proportion of infants with hyperbilirubinemia (24). Another randomised controlled trial including (n=73) newborn infants, showed DCC at 5 minutes compared with immediate cord clamping did not increase the incidence of hyperbilirubinemia or symptomatic polycythaemia at up to 48 hours of age (81). In a study of newborn infants with congenital heart disease (n=30), DCC 110-130 seconds after birth showed a trend towards higher peak serum bilirubin levels compared to ECC <10 seconds after birth (82). In a controlled before-and-after study on newborn infants of HIV-infected mothers (n=64), delayed cord clamping 2 minutes after birth compared with ECC within 30 seconds did not show increased risk of neonatal jaundice (83). Similarly, a recent cross-sectional, retrospective study with 398 participants showed no association with neonatal jaundice or need of phototherapy due to delayed clamping in term neonates (84).

Concurring with these findings, our randomised controlled trial showed no significant difference in TcB levels at discharge, nor any difference in risk of hyperbilirubinemia at discharge between the groups. At four weeks follow up there was no difference in reported jaundice or in infants that were being treated for jaundice. At eight months, blood tests showed improved haemoglobin levels with a significant effect on anaemia, and with a risk reduction of 11% in the DCC group paired with a 42% risk reduction in ID. Based on this result, we had hypothesised that DCC would increase infant iron stores and haemoglobin levels up to 12 months of age. However, although anaemia was less prevalent and the mean haemoglobin concentration was higher in the DCC group, the serum ferritin level was not higher in this group compared with the ECC group at 12 months of age. The ASQ test at 12 months of age showed significant differences between the groups regarding their total ASQ scores and in communication, gross motor, and personal-social domain with higher scores in the DCC group after clamping the umbilical cord was delayed at least 180 seconds after birth, compared with early clamping within 60 seconds after birth. The regression analysis showed that haemoglobin at 12 months was significantly correlated with the total ASQ score (Table 7).

As a consequence of the beneficial results from our randomised control trail, we aimed to explore delivery care staff's perception and attitude towards changes in the practice of umbilical cord clamping in order to identify work culture barriers and enablers of improved clinical practice and implementation of the new guidelines on cord clamping. All the participants had heard about DCC but not everyone was aware of its benefits. Since it only requires waiting for a few more minutes before clamping the cord, all the participants thought DCC was easy to perform and did not need additional skills, efforts, equipment or manpower. However, as ECC is a deeply rooted practice in maternity care, changing this practice is much more important than changing the perceptions (62). Despite this clear evidence of the benefits, results indicate that delivery care staff feel hesitance towards trying to implement DCC. Medical conditions and the physical environment sometimes force them to perform early clamping and the staff tends to fall back into old routines and habits. Lack of authorised protocols and instruction together with lack of coherence within the team also prevents the effective implementation of a new practice. This is in line with a study from the USA that concluded that despite the fact that the evidence demonstrates its beneficial impacts on neonatal outcomes, obstetrician's beliefs about the appropriate timing of cord clamping are not constant (63). Participants in this study explained that it was difficult to implement a new practice as they are more comfortable with their regular practice. They however highlighted that regular practice on new clinical routines can facilitate a quicker adoption. One study says that the healthcare providers do not change their practice in a single, defined moment of time; it generally occurs after following a series of events over a period of time (67). The health system leadership needs to relate to this and continuous efforts are required, not only one-off directives. Furthermore, in the absence of refresher training and the communication of new routines, the staff is forced to rely on informal learning, listening to rumours and picking up new evidence from various channels. The willingness to do good was however put forward as an opportunity for change and paired with a high level of trust in research evidence, change can be achieved if combined with a top-down approach. In line with this finding, another study stated that obstetricians are hesitant to change routines to DCC in clinical setting and expressed the need to produce guidelines to bring DCC into obstetric practice (85). Yet another study mentioned the interpersonal variation in cord clamping practice and therefore suggested the need for clear practice guidelines regarding the optimal time of cord clamping including the health benefits of DCC both in term and preterm infants (65).

Strengths and limitations

For a randomised controlled trail, Nepal being a low-income country, some of the strengths and limitations of the study are linked to both advantages and difficulties associated with the settings. The study was performed during a comparably short inclusion time period (approximately 7 weeks), which might prevent biases that could occur due to a longer period for example; other changes in practice at the hospital, changes in staff and different light conditions during the seasons throughout the year, which might affect, in particular, the prevalence of jaundice. The study also compared a relatively late definition of ECC (≤60 seconds) with DCC of 180 seconds or more. This may explain why there were no significant weight differences between the groups, as opposed to a systematic review of term infants which found a 100 g higher weight in DCC (14).

Attrition is a major limitation to our study. We expected a high attrition rate of 35% at 8 months due to difficulties in communicating with the families included and had powered the study accordingly. The actual attrition rates included 140 infants (25.9%) at 8 months and 206 infants (38.1%) at 12 months. Though these numbers were close to the expected attrition rate they may nevertheless be associated with bias in the results. To adjust for attrition, results are presented after multiple imputation analysis.

There was a high incidence of protocol deviation occurred in the DCC group. When analysis was based on intention to treat, 22.6% of the infants in the DCC group underwent clamping before 60 seconds as the nurse midwives perceived that ECC against the allocation was required. The reasons behind the protocol deviations were; asphyxiated babies in need of immediate resuscitation, poor cry, cord round the neck tightly, and perceived signs of asphyxia in the newborn infant. Results after analysis according to intention to treat corresponds with results after analysis only including cases handled according to protocol. Furthermore, only women with relatively low-risk term pregnancies and possibly healthy newborns were included in the study, which might impair the generalisability of the study. Nevertheless, the rates of anaemia in the study group were comparable with those of earlier reports from Nepal (5).

ASQ is a screening tool designed to find children at risk of neurodevelopment disability and as such may not be optimal for the assessment of neurodevelopment in a cohort of healthy infants. The fact that the cohort consisted of low-risk pregnancies might also explain the relatively high ASQ scores in both groups as compared to populations found in other settings. On the other hand, the high mean ASQ scores might reflect a social desirability bias since data was collected through interviews rather than forms being filled in by the parents themselves. ASQ is not validated in Nepal. However, the randomised controlled design can help to diminish this bias if the bias is randomly distributed.

Another limitation was that TcB measurements were performed relatively soon after birth (median 20 hours), which could make it difficult to identify hyperbilirubinemia occurring later in the neonatal period. To overcome this limitation, all values of the bilirubin level and time after delivery were fitted to the predictive nomogram provided by Varvarigou et al. (55). Also, TcB measurements are not as reliable as measurements from blood samples but are considered to be sufficiently accurate for estimating bilirubin concentrations in neonates. It is also a cost-effective and fast method which is much more suitable in low-income countries like Nepal. We chose to also carry through a one month follow up to compensate for the rather early transcutaneous measurement. The one-month follow-up was in congruence with the measurements at discharge. Taking these limitations into account, this study is congruent with other studies on cord clamping that has measured bilirubin.

Qualitative study (Paper IV) also has some limitations worth mentioning. Due to limited time and resources, birth attendants from all the birth centres could not be included in the study. There is also always the risk of social desirability bias in this type of study, especially in a hierarchical system like Nepal. Actual perceptions and attitudes may therefore vary from self-reported, as it is not always certain that reported practices are the de facto practices. To minimise this reporting bias, efforts were made to create a safe space for the interviews and guarantee anonymity of results. SBA trainer/supervisors and other persons of authority were not present during discussions. We undertook several measures to ensure the trustworthiness as recommended in qualitative research (73).

Conclusions

Based on the findings described in this thesis, the key conclusions are:

1. Umbilical cord clamping 180 seconds after birth compared to clamping within 60 seconds reduces anaemia and ID at 8 months of age. It also results in less anaemia and a higher mean haemoglobin concentration at 12 months. This may have major positive effects on infants' health and development with minimal investments and without apparent adverse effects.
2. Umbilical cord clamping 180 seconds after birth was associated with an improvement of the overall neurodevelopment in infants at 12 months of age compared to infants whose cord was clamped within 60 seconds.
3. Timing of umbilical cord clamping was not associated with increased risk of hyperbilirubinemia during the first day of life or risk of jaundice within 4 weeks.
4. Due to poor coherence within the health system and a lack of national and institutional protocols, delivery staff have to rely on their own skills development and informal decision making. Staff is therefore hesitant to apply new routines of delayed cord clamping.

Future perspectives

This thesis has generated answers related to the question of effects of delayed cord clamping and possible implementation strategies to establish delayed cord clamping in practice. However, new evidence usually generates new questions. From our findings, we suggest future research and recommend to focus on the following areas listed below.

1. Additional research is needed to evaluate the optimal timing of cord clamping, which could be even later than 180 seconds (i.e. in conjunction with the delivery of the placenta).
2. Further research directed at studying development at later ages would give in-depth insight into long-term effects of DCC on iron status and neuro-development.
3. The Ministry of Health of Nepal needs to develop national protocols and provide orientation to all delivery care staff working in maternity care to implement DCC into practice in Nepal.

Summary in English

Anaemia is one of the most common and widespread public health problems affecting human health as well as social and economic development in both developed and developing countries. It is a major health problem in Nepal, especially among young children and pregnant women. More than half (53%) of children aged 6-59 months are anaemic, with 26% mildly anaemic, 26% moderately anaemic, and 1% severely anaemic, and where 9% of infants at the age of 2- 6 months and 26% of infants at 7-12 months are suffering from iron deficiency anaemia. Iron deficiency anaemia in early infancy and young childhood is associated with adverse effects on neurocognitive, motor, socio-emotional and neurophysiologic development, with impairments in learning, memory and myelination, causing potentially long-lasting cognitive and behavioural deficits.

Timing of cord clamping is considered to have effects on placental transfusion rate and neonatal circulation. Neonatal benefits associated with delayed cord clamping through increased placental transfusion include better cardiopulmonary adaptation and higher haemoglobin concentration, additional iron stores and prevention of iron deficiency in early infancy. Despite the published benefits of delayed cord clamping to both infant and mother, there is little evidence that it is practiced routinely in hospital settings.

The main study of this dissertation followed 540 children born after an uncomplicated pregnancy of healthy mothers. These children were randomly allocated to one of two parallel groups (1:1 ratio), either early (≤60 seconds) or delayed cord clamping (≥180 seconds). When the study started, the cut-off for umbilical cord clamping was 61 seconds, based on an observational study in the study hospital. Data on the children were collected from the time of birth to one hour after birth and until baby and mother got discharged from hospital. A telephone follow-up was conducted at four weeks of age to record health status, and sign and treatment of jaundice and haemoglobin and ferritin levels were measured at the age of 8 and 12 months respectively. An assessment of neurodevelopment using the Ages and Stages Questionnaire (ASQ) was done at the age of 12 months.

To complement the clinical trial described above we performed a qualitative study to explore delivery care staff's perceptions and attitudes towards changes in practice of umbilical cord clamping. The objective was to identify work culture barriers and enablers for improved clincal practice and implementation of the new guidelines on cord clamping. Focus group

discussions and key informant interviews were conducted and data was analysed through qualitative content analysis.

The results of the study have been presented in four scientific papers. Paper I showed that delayed cord clamping (DCC) reduces anaemia at 8 and 12 months of age in this high-risk population, which may have major positive effects on infants' health and development. Paper II revealed that DCC was associated with an improvement in the overall neurodevelopment at 12 months of age as compared to infants in the early cord clamping (ECC) group. Paper III verified that DCC was not associated with an increased risk of hyperbilirubinemia during the first day of life or risk of jaundice within four weeks compared to the ECC group. Paper IV demonstrated how a positive attitude towards DCC and a will to rely on research evidence when striving to do good are facilitators of change in clinical practice. However, the participants in the study were hesitant to apply DCC due to lack of national or institutional protocols and formal training. On account of this they were forced to take informal decisions and rely on alternative sources of information.

In conclusion, the studies have shown that delaying cord clamping for 180 seconds is a safe method to use in normal delivery and is associated with a significantly reduced risk of anaemia at 8 and 12 months, which may have neurodevelopmental effects at a later age. In order to change cord clamping practice and to comply with evidence and policies, health-care staff need to be better supported by the governance structures of the health system, with clear and approved guidelines made available and coherent training and support.

Sammanfattning på svenska

Anemi, vilket i folkmun kallas blodbrist, är ett av de vanligaste och mest omfattande folkhälsoproblemen i världen. I alla länder oavsett ekonomisk status eller utvecklingsnivå är detta något som påverkar både människors hälsa såväl som den sociala och ekonomiska utvecklingen. I Nepal är anemi ett stort hälsoproblem, särskilt bland små barn och gravida kvinnor. Mer än hälften (53%) av barn i åldern 6–59 månader är anemiska, med 26% lätt anemiska, 26% måttligt anemiska och 1% svårt anemiska. Bland barn i 2–6 månaders ålder lider 9% av järnbristanemi och vid 7–12 månader är motsvarande siffra 26%. Järnbristanemi under spädbarnstiden är förknippat med negativa effekter på neurokognitiv, motorisk, socio-emotionell och neurofysiologisk utveckling, med nedsatt inlärning, minne och myelinering som följd, vilket kan leda till långvariga kognitiva och beteendemässiga effekter.

Tidpunkten då navelsträngen kläms av, s.k. avnavling, på det nyfödda barnet anses ha effekter på blodtransfusionen från placenta till barn och därmed också inverka på den neonatala cirkulationen. Fördelar som är förknippade med ökad transfusion från placenta genom fördröjd avnavling inkluderar bättre anpassning av hjärt-lungcirkulationen och högre haemoglobinkoncentrationer genom ytterligare järnförråd och förebyggande av järnbrist i tidig spädbarnsålder. Trots att det finns god evidens för att sen avnavling är fördelaktigt för både barn och mamma praktiseras det sällan rutinmässigt.

Huvudstudien som redovisas i denna avhandling har följt 540 barn födda efter en okomplicerad graviditet hos friska mödrar. Dessa barn allokerades slumpmässigt till en av två parallella grupper (1: 1 förhållande), antingen tidig (≤60 sekunder) eller sen avnavling (≥180 sekunder). När studien påbörjades var tiden till avnavling i medeltal 61 sekunder baserat på en observationsstudie genomförd på det aktuella sjukhuset. Data samlades från förlossning till dess att mamma och barn blev utskrivna från sjukhus. En telefonuppföljning genomfördes vid fyra veckors ålder och haemoglobin och ferritin mättes då barnen var 8 respektive 12 månader gamla. En skattning av barnens neurologiska utveckling gjordes vid 12 månaders ålder med hjälp av Ages and Stages Questionnaire (ASQ).

Som komplement till den kliniska studien beskriven ovan utfördes en kvalitativ studie för att undersöka förlossningspersonalens uppfattning och inställning till förändringar i praktiken runt avnavling. Syftet var att identifiera vad som hindrar respektive underlättar införandet av nya riktlinjerna för avnavling i den kliniska vardagen. Fokusgrupper och nyckelpersoner intervjuades och data analyserades med kvalitativ innehållsanalys.

Resultat från studierna har presenterats i fyra vetenskapliga artiklar. Artikel I visade att sen avnavling minskar anemi vid 8 och 12 månader i denna högriskpopulation, vilket kan ha stora positiva effekter på barns hälsa och utveckling. Artikel II visade att sen avnavling är associerad med en förbättring av den totala neurologiska utvecklingen vid 12 månaders ålder jämfört med spädbarn som hade avnavlats tidigt. Artikel III verifierade att sen avnavling inte var associerat med ökad risk för hyperbilirubinemi under de första dagarna av livet eller risken för gulsot inom fyra veckor jämfört med hos gruppen barn som avnavlats tidigt. Artikel IV avslöjade att vårdpersonalen har en positiv inställning till sen avnavling och att det finns en vilja att förlita sig på evidens eftersom man strävar efter att göra det bästa för barnet och mamman. Detta var faktorer som underlättade förändringar i klinisk praxis. Deltagarna i studien var dock tveksamma till att tillämpa sen avnavling på grund av brist på nationella eller institutionella protokoll och formella utbildningar. På grund av denna brist tvingades de ta informella beslut och förlita sig på alternativa informationskällor.

Sammanfattningsvis har studierna visat att det är säkert och fördelaktigt att vänta i 180 sekunder eller mer med att avnavla barnet vid en normal förlossning. Studierna visar också att det är förknippat med en signifikant minskad risk för anemi vid 8 och 12 månader och bättre neurologisk utveckling över lag. För att kunna förändra avnavlingsrutinerna så att de blir mer evidensbaserade måste förlossningspersonalen få bättre stöd, med tydliga och godkända riktlinjer som görs tillgänglig samt ges möjlighet till samstämmig utbildning.

सारांश

रक्तअल्पता एक सामान्य र व्यापकरुपमा फैलिएको जनस्वास्थ्य समस्या हो जसले दुबै विकसित र विकासोन्मुख राष्ट्रहरुमा मानिसको स्वास्थ्यका साथै सामाजिक र आर्थिक विकासमा असर पारिरहेको छ। नेपालमा विशेषगरी सानो उमेरका बालबालिकाहरु तथा गर्भवती महिलाहरुमा यो एक प्रमुख स्वास्थ्य समस्या हो। आधा भन्दा धेरै (५३%), ६-५९ महिना उमेरका बालबालिकाहरुमा रक्तअल्पता छ जसमध्ये २६% मा हल्का रक्तअल्पता, २६% मा मध्यम रक्तअल्पता र १% मा कडा रक्तअल्पता छ ; जहाँ ९ प्रतिशत २-६ महिना र २६ प्रतिशत ७-१२ महिनाका शिशुहरु आइरनको कमिबाट हुने रक्तअल्पताबाट ग्रसित छन्। प्रारम्भिक शिशु अवस्था र सुरुवाती बाल्यवस्थामा आइरनको कमिबाट हुने रक्तअल्पताले पार्ने प्रतिकूल असरहरु मध्ये न्यूरोसंज्ञानात्मक (neurocognitive), मोटर (motor), सामाजिक-भावनात्मक (socio-emotional) तथा न्यूरोमनोवैज्ञानिक (neurophysiologic) विकाससँग सम्बन्धित, साथै ज्ञानमा क्षति (impairment), स्मृति (memory),, माइलिनेसन (myelination), लामो अवधिको संज्ञानात्मक र व्यवहारमा कमी छन्।

नाभी च्याप्ने वा बाँध्ने (delayed cord clamping) तालिकाले सालबाट रक्तसंचार हुने दर र त्यसले नवशिशुको रक्तसंचारमा सकारात्मक असर पार्छ भन्ने बुझिन्छ। नाभी च्याप्न वा बाँध्नलाई ढिलाई गरी सालबाट रक्तसंचारमा वृद्धिसँग सम्बन्धित नवशिशुको फाइदाहरुमा मुटु र फोक्सो (cardiopulmonary) को राम्रो तालमेल र हेमोग्लोबिनको उच्च केन्द्रिकरण (concentration), अतिरिक्त आइरन संचिती र सुरुवाती शिशु अवस्थामा आइरन कमीको रोकथाम रहेका छन्। नाभी च्याप्न वा बाँध्न ढिलाईबाट मुख्यतः दुबै शिशु र आमालाई हुने फाइदाहरु प्रकाशनमा आएतापनि अस्पतालहरुमा नियमित रुपमा यसको प्रयोगको प्रमाण निकै कम छ।

यस अनुसन्धनात्मक अध्ययनले ५४० बालबालिकाहरु, जो स्वस्थ महिलाहरुको जटिल नभएको प्रसूति पश्चात् छिटो नाभी च्याप्ने वा बाँध्ने (early cord clamping) वा ढिलो नाभी च्याप्ने वा बाँध्ने (delayed cord clamping) भनेर छुट्याइएको थियो, ति समूहहरुलाई अध्ययन गरेको छ। परिक्षण योजना अन्तर्गत ढिलो नाभी च्याप्ने वा बाँध्ने (≥१८० सेकेण्ड) र छिटो नाभी च्याप्ने वा बाँध्ने (≤६० सेकेण्ड) गरी दुई समानान्तर समूह (१:१ अनुपातमा आधारित) मा विभाजन गरिएको थियो। जब अध्ययन सुरु भयो, हाल अध्ययन चलिरहेको अस्पतालमा भएको एउटा अवलोकन अध्ययनमा आधारित भएर नाभी च्याप्ने वा बाँध्ने समय ६१ सेकेण्ड निर्धारण गरिएको थियो। बच्चाहरुको तथ्याङ्क संकलन बच्चा जन्मेको समय देखि बच्चा जन्मेको १ घण्टा सम्म र बच्चा र आमा अस्पतालबाट डिस्चार्ज नभए सम्म गरिएको थियो। त्यसको ४ हप्तामा टेलिफोन सम्पर्क मार्फत् कुराकानी गरिएको थियो र हेमोग्लोबिन र फेरिटिनको जाँचहरु क्रमशः ८ र १२ महिनामा गरिएको थियो। न्यूरो विकास (neurodevelopment) को मूल्याङ्कन Ages and Stages Questionnaire (ASQ) को प्रयोग गरी १२ महिनामा गरिएको थियो।

हाम्रो परिक्षणबाट आएको फाइदाजनक परिणामहरुको माध्यबाट हामी प्रसूतिमा काम गर्ने स्वास्थ्यकर्मीहरुको नाभी च्याप्ने वा बाँध्ने तरिकामा परिवर्तन ल्याउन धारणा र दृष्टिकोण छानबिन गर्न चाहन्थ्यौं ता कि हामीले कार्यक्षेत्रसँग सम्बन्धित बाधाहरु तथा सहयोगीहरु पहिचान गरी क्लिनिकल अभ्यासमा सुधार गर्न सकौं र नाभी च्याप्न वा बाँध्नलाई नयाँ निर्देशिका लागु गर्न सकौं ।

यस अध्ययनका परिणामहरु चारवटा लेखहरु मार्फत प्रस्तुत गरिएका छन् । पहिलो लेखले ढिलो नाभी च्याप्ने वा बाँध्ने गर्नाले ८ र १२ महिनाको उमेर, जुन चाहिं उच्च जोखिम जनसंख्या हो, तिनीहरुमा रक्तअल्पता घटाउँछ जसले गर्दा शिशुको स्वास्थ्य र विकासमा प्रमुख रुपमा सकारात्मक असर हुनसक्छ भनेर देखाएको छ । छिटो नाभी च्याप्ने वा बाँध्ने समूह भन्दा ढिलो नाभी च्याप्ने वा बाँध्नेसँग १२ महिनामा हुने सम्पुर्ण न्यूरो विकास सुधार सम्बन्धित थियो भनेर दोस्रो लेखले देखाएको छ । ढिलो नाभी च्याप्ने वा बाँध्ने गर्नाले बच्चा जन्मेको सुरुको केही दिनहरुमा रगतमा बिलिरुबिनको मात्रा धेरै (hyperbilirubinemia) गराउने जोखिम हुन्छ वा जन्मेको पहिलो ४ हप्तामा जण्डिस हुने जोखिम हुन्छ भन्ने कुरालाई तेस्रो लेखले गलत पुष्टि गरिदिएको छ । क्लिनिकल अभ्यासमा ढिलो नाभी च्याप्ने वा बाँध्ने प्रक्रिया प्रति सकारात्मक धारणा र राम्रो गर्नका लागि अनुसन्धानमा आधारित प्रमाणमा भरोसाले कसरी परिवर्तनका लागि सहजीकरण गर्न सक्छन् भनेर चौथो लेखले दर्शाएको छ । तथापि, अध्ययनमा भाग लिएका सहभ(ागीहरु राष्ट्रिय वा संस्थागत प्रोटोकल र औपचारिक तालीमहरुको अभावमा ढिलो नाभी च्याप्न वा बाँध्न हिच्किचाउनुहुन्थ्यो । यसले गर्दा वहाँहरु अनौपचारिक निर्णयहरु लिन बाध्य हुनुहुन्थ्यो र वैकल्पिक सुचनाका स्रोतहरुमा निर्भर हुनुहुन्थ्यो ।

निष्कर्षमा, १८० सेकेण्डसम्म सामान्य प्रसूतिमा, नाभी च्याप्न वा बाँध्न ढिला गर्नु एउटा सुरक्षित तरिका हो र यसले ८ र १२ महिनामा रक्तअल्पता को जोखिम महत्वपूर्ण रुपमा घटाउन मद्दत गर्छ, र जसको पछिल्लो उमेरमा न्यूरो विकासमा असर हुनसक्छ । प्रमाण र नीतिमा आधारित नाभी च्याप्ने वा बाँध्ने तरिकामा परिवर्तन ल्याउन स्वास्थ्यकर्मीहरुलाई स्वास्थ्य प्रणाली अन्तर्गतमा प्रशासनिक संरचनाहरुबाट सहायता आवश्यक हुन्छ साथै प्रष्ट र स्वीकृत निर्देशिकाहरु र उचित तालीम र सहयोग उपलब्ध गराइनुपर्छ ।

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