THE EFFECT OF TIMING OF CORD CLAMPING ON NEONATAL HAEMOGLOBIN AND HAEMATOCRIT VALUES AT TERM: A RANDOMIZED CONTROL TRIAL.

A DISSERTATION IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE (OBSTETRICS AND GYNAECOLOGY),

UNIVERSITY OF NAIROBI.

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DECLARATION

This is to certify that the work presented herein is my original work, has not been presented for a degree course in any other university and has been supervised by senior members of the Department of Obstetrics and Gynecology, University of Nairobi, College of Health Sciences, School of Medicine, Kenyatta National Hospital, Nairobi, Kenya.

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ABBREVIATIONS

AAP= American Academy of Paediatrics

AMTSL= Active management of third stage of labour

ANC= Antenatal clinic

DCC = delayed cord clamping;

ECC = early cord clamping

HB= Haemoglobin

HCT= Haematocrit

HIV= Human immunodeficiency virus

ICC = immediate cord clamping

KDHS= Kenya Demographic and health survey

KNH= Kenyatta National Hospital

LCC= late cord clamping

MCV= Mean corpuscular volume

PCV= Packed cell volume

PPH = Postpartum haemorrhage

RCOG= Royal college of Obstetricians and gynaecology.

RCT = randomized controlled trial

Rh= Rhesus factor

VDRL= Venereal Disease Research Laboratory test

WHO= World Health Organization

DEFINITIONS AND OPERATIONAL TERMS

- **Anaemia:** Hb concentration more than two standard deviations (SD) below the mean of similarly aged infants from an iron-supplemented reference population

- **Anaemia in pregnancy:** defined as Hb < 11 g/dl. (RCOG)

- **AMTSL:** Active management of third stage of labour.

- **Delayed cord clamping (Late cord clamping)**: clamping the umbilical cord > 120 seconds after birth. (RCOG)

- **Early cord clamping/ Immediate cord clamping:** Clamping of the umbilical cord within 30 seconds of birth. (RCOG)

- **Fetal anaemia:** Central venous haemoglobin < 13 g/dL or capillary haemoglobin < 14.5 g/dL in infant. (AAP)

- **Low risk pregnancy:** Refers to a woman aged 18-39, with no previous diagnosis of essential hypertension, renal disease, collagen-vascular disease, liver disease, cardiovascular disease, placenta previa, multiple gestation, intrauterine growth retardation, smoking, pregnancy-induced hypertension, premature rupture of membranes, or other previously documented condition that poses a high risk of poor pregnancy outcome.

- **Neonatal Haematocrit:** Range of normal between 45-65% (AAP)

- **Placental transfusion**: The transfer of residual placental blood to the baby during the first few minutes of age.

- **Polycythaemia:** Haematocrit levels above 65% (AAP)

- **Term infant:** Greater than 37 weeks gestation to 42 weeks gestation (RCOG)

LIST OF FIGURES AND TABLES

ABSTRACT

Background: The umbilical cord is usually clamped immediately after birth. There is no sound evidence to support this approach, which might deprive the newborn of benefits such as an increase in iron storage during the neonatal period. The negative effects of this are more profound in lower socioeconomic groups.

Objective: To determine the effect of timing of umbilical cord clamping on haemoglobin and haematocrit level of term newborns.

Methodology: This was to be a randomized controlled trial that included 96 mother-neonate pairs at term who met the selection criteria, 48 in the delayed cord clamping group (>120seconds) and 48 in the immediate cord-clamping group (<30 seconds).

Setting: Kenyatta National Hospital, Labour ward, Nairobi, Kenya.

Populations: Full term newborns undergoing spontaneous vertex delivery of low risk pregnancy mothers.

Variables:

Primary dependent variables the infants' venous haemoglobin and haematocrit value measured between 6-24 hours after birth.

Secondary dependent variables included early respiratory distress symptoms, neonatal jaundice that necessitated for phototherapy and polycythemia.

Independent variables: Socio-demographic and medical characteristics of the mothers.

Analysis plan: Levels of haemoglobin and haematocrit of newborn infants following delayed umbilical cord clamping were compared to those of newborns who undergo immediate cord clamping using unpaired students T- test and a P value <0.05 (<0.025 at interim analysis) for significance. Multiple linear regressions were done to analyze maternal characteristics as confounding factors to neonatal haemoglobin and haematocrit values.

Results: The mean haemoglobin level in the DCC group was 17.19g/dL and 15.63g/dL in the ICC group, a mean difference of 1.56g/dL. The mean haematocrit levels in the DCC and ICC groups were 53.44% and 47.63% respectively, a mean difference of 5.81%. A statistically significant difference in both Hb and Hct (P value <0.001). There was no significance of maternal characteristics on neonatal Hb and Hct values. Haemoglobin in neonates that underwent DCC did not depend on the mother's haemoglobin, however among the neonates that underwent ICC, the haemoglobin level appeared to increase gradually with increase in the mother's haemoglobin, and thus ICC is more detrimental in a population that suffers from anaemia.

Conclusion: DCC is an easy procedure that can be incorporated into AMSTL as it leads to increased levels of Hb and Hct levels in the neonates and thus reducing complications that occur secondary to anemia in early childhood, especially in resource limited settings.

CHAPTER 1. INTRODUCTION

The optimal time for cord clamping has been under debate for decades. There are advocates for both immediate and delayed clamping, those that support Immediate cord clamping (ICC), report that delayed cord clamping (DCC) can be physiologically distressing to the infant's circulation and increase the risks of polycythaemia and jaundice(1,2). Another recommendation for ICC was to facilitate active management of third stage of labour (AMTSL) where analysis of arterial blood samples immediately after birth was carried out(3).

Observational studies carried out in Sub-Saharan Africa note ICC is commonly used in health care facilities, while the developed world is adopting DCC (Figure 1)(4). Advocates for DCC argue that it is the natural way of terminating delivery. Moreover studies done after 1997 that included a 2-month follow up of babies who underwent DCC support the finding that large transfusion to the newborn could prevent iron deficiency anaemia, this has important health implications especially in low-income countries with high prevalence of anaemia such as Kenya(5–7).

The effects of early onset anaemia have a far-reaching negative effect on the overall health of a child. Young children are at a higher risk of iron deficiency because of high iron requirements due to rapid tissue growth in the first year of life during which period their body weight and blood volume nearly triple, and the circulating haemoglobin mass approximately doubles(7).
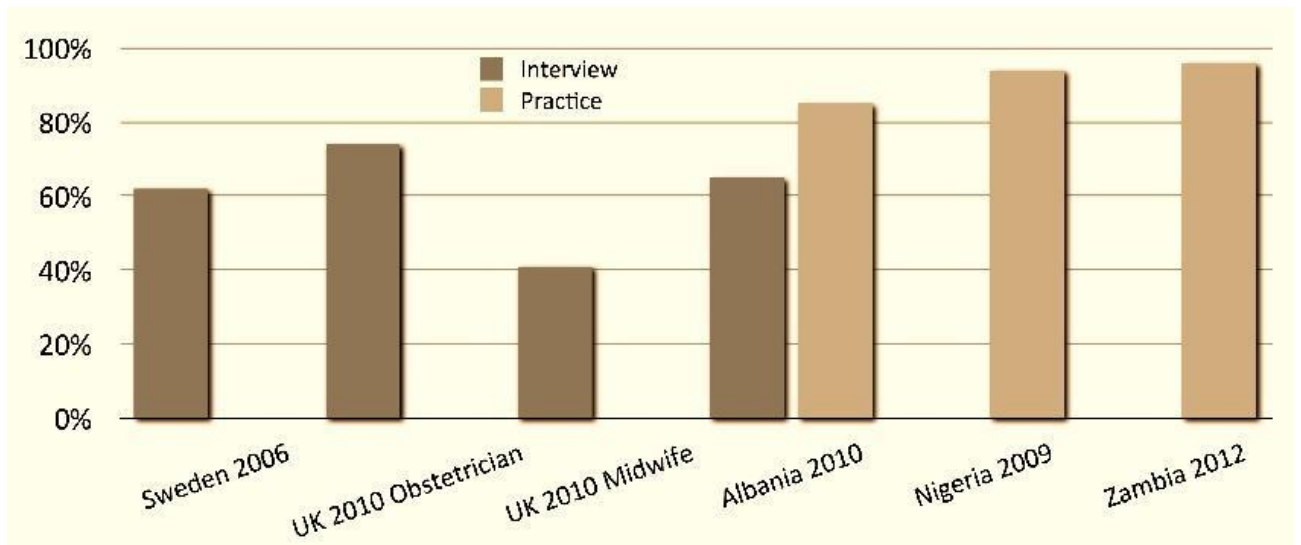
Figure 1: Reported practice of Immediate cord clamping, by interview or observed practices.

LITERATURE REVIEW

One of the goals of neonatal critical care is to deliver adequate oxygen to meet tissue demand. Increasing fetal haemoglobin by placental transfusion is an extremely effective method of enhancing arterial oxygen content, increasing cardiac output and improving oxygen delivery(1,8).

DCC is one way of increasing transfer of red blood cells to the newborn, which interprets as an increase in the oxygen carrying capacity(9).

In some studies, it was observed that delayed cord clamping could contribute to preventing iron-deficiency anaemia in the first year of life(10–12).
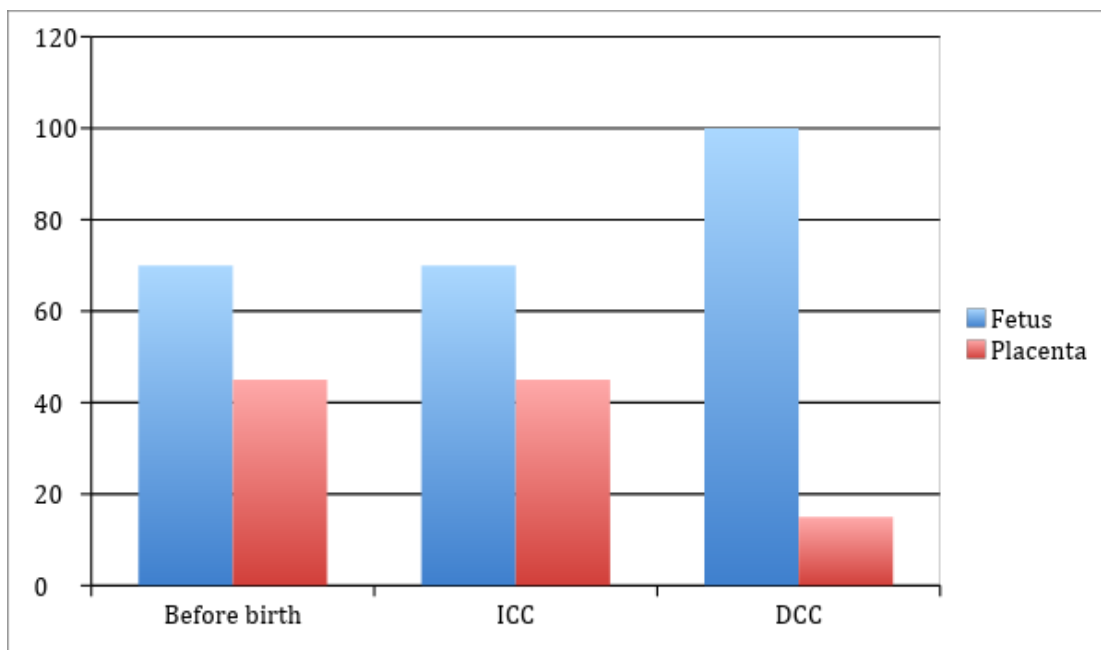
Figure 2: Distribution of blood volume (mls) in placenta (Red) and fetus (Blue) before and after birth.(13)

A recent systematic review confirms this benefit of delayed cord clamping(14). It's based on the fact that after birth the newborn is delivered with a placental transfusion of 80 mL of blood at 1 minute and 100 mL at 2 minutes after birth(Figure 2) (15). For

a 3kg infant with a packed cell volume (PCV) of approximately 0.50 at birth, this amounts to an additional 45 mg of iron added to iron stores.

Theoretically this amount of iron should be sufficient to meet the requirements of an infant for more than 3 months. Previous trials indicated that DCC prevents a steep decline in Hb concentration at 2–3 months of age, especially in infants born to anemic mothers(15,16).

Similar well-conducted observational studies found that DCC is associated with improved cardiopulmonary adaptation after birth, better cutaneous perfusion and higher skin temperature, increased renal blood flow and more urine output, and increased blood flow to the brain and gut(17).

Older physiologic studies of human newborns supported animal studies that showed the newborn responds with a profound bradycardia if ICC occurs before the first breath is taken(18).

Conversely, some observational studies suggest that delayed umbilical cord clamping puts newborns at higher risk of suffering from polycythaemia, respiratory distress symptoms, hyperbilirubinaemia, and other neonatal disorders(19). However, there have been no randomized, controlled trials showing the risk of these harmful effects on the newborn(20–22).

Some studies have shown no increase in the incidence of postpartum haemorrhage from delayed umbilical cord clamping. However, this remains a theoretic concern because blood flow through the spiral arteries and veins in a term uterus is approximately 600 mL/min. Concerns regarding maternal risks become particularly relevant in special circumstances in which the benefits of DCC need to be balanced with the timely resuscitation of the woman e.g., in cases of haemorrhage from placenta previa or placental abruption after delivery of an infant(23).

A study carried out in Kenya looking into the prevalence of anemia in the rural population estimated prevalence of anaemia in children at 28.8% with those less than one year being 2 times more susceptible to anaemia as compared to their older counterparts(24)(25).

Thus far, improving iron status via interventions during gestation and early infancy have proven to be a challenge because maternal supplemental iron is not likely to have a strong effect on breast milk iron concentration(26).

Direct supplementation of infants has poor compliance coupled with the risk of accidental poisoning, impaired absorption of other micronutrients and may worsen outcome of infectious disease(15,16,27).

Furthermore anaemia is directly linked to increased infant mortality, as it is associated with diarrheal and respiratory diseases. Another important reason for addressing iron deficiency anaemia during the neonatal period is it's relation to neurodevelopment. Iron deficiency anaemia has been associated with cognitive delays and long-term behavioral deficits(28,29).

Given the high percentage of those affected in the developing world, with its financial constraints, implementation of cost effective intervention such as DCC will be a sustainable measure in addressing the scourge(30,31).

Moreover in traditional African home deliveries the umbilical cord is cut after placental descent into the vagina, Hospital deliveries however, especially in resource poor settings, immediate cord clamping (ICC) is the routine standard of care, due to lack of information about benefits of DCC, concerns about the practice and low human resource within public hospitals. In 2014 the nurse to patient ratio in public health facilities in Kenya ranged between 1.2-0.08 per 1,000(32).

CONCEPTUAL FRAMEWORK

SOCIODEMOGRAPHIC FACTORS
Age
Education level
Employment
Socioeconomic status

CLINICAL FACTORS
Obstetric history
Maternal Comorbidities
Fetal factors

ANTENATAL HISTORY
Attendance
Hb levels in pregnancy
Iron supplementation
Infections in pregnancy

ICC GROUP
ICC /AMTSL
Cord blood collected > 6 hours

DCC GROUP
DCC/AMTSL
Cord blood collected >6 hours

MATERNAL OUTCOMES
PPH
Maternal sepsis
NEONATAL OUTCOMES
Neonatal Hb and Hct
Polycythaemia
Early respiratory distress symptoms
Hypothermia

CONCEPTUAL FRAMEWORK NARRATIVE

Factors such as age, education level and socio economic status have a direct effect on the patient's health seeking behavior during pregnancy, attendance of antenatal care as well accessing the hospital at time of delivery.

Maternal co-morbidities as well as fetal complications will have an influence on ICC/DCC or exclusion from the study.

DCC is recommended compared to ICC, currently home deliveries tend towards DCC whereas those accessing highest attainable healthcare in the country (KNH) are undergoing ICC as per an observational study done at the same facility.

Theoretically undermining the iron status of the neonate and exposing them to complications that come with anaemia at an early age.

The study seeks to compare the neonatal hemoglobin and haematocrit status between the two groups, and further analyze any connection with other socio-demographic factors.

PROBLEM STATEMENT

According to current literature, delayed cord clamping has been shown to have a positive health impact on neonates in averting risk of anemia in early life, the current practice in our setting is immediate cord clamping with no literature to support this. Midwives stated the low midwife-patient ratio as the cause of hastening cord clamping. A need was identified to conduct a study comparing the effect of cord clamping on neonatal haemoglobin, haematocrit values and assessing for any adverse outcomes to aid in educating and creating guidelines for standard practice.

JUSTIFICATION

Anaemia has a high morbidity and particularly affects young children and pregnant women(33).

At the present time, both immediate and late clamping procedures are standard practices with some obstetrical textbooks recommending immediate clamping while others propose delayed clamping(15,34). Finally, others give no clear recommendation for either immediate or delayed clamping, citing a lack of sufficient evidence(35,36). In our delivery center there is no specific guideline for the time of cord clamping, to date. A recent unpublished study done in Kenyatta National Hospital averaged the cord-clamping time to 20 seconds.

The cause of ICC in our set up may be attributed to a poor nurse patient ratio as well as high patient turnover with the advent of free maternity care. The nurses in most cases have to fast track delivery. If there is no significant difference in Hb and Haematocrit levels between infants who undergo ICC as compared to DCC, it would support current practice, or support ICC in situations of high patient turnover and poor nurse patient ratio.

DCC on the other hand is a cost effective intervention that is thought to allow for a placental transfusion of up to 30% of the total fetal–placental blood volume. This transfusion includes many types of pluripotent stem cells that may have significant long-term value for the child. These additional volumes can supply extra iron amounting to 40-50mg/kg(14).

When DCC occurs at 2 minutes after the birth or later, benefits include a 47% reduction in the risk of iron-deficiency

anaemia(16,17,28)(11,12,16)(10,11,15)(9,10,14) and a 33% reduction in the risk of having deficient iron stores at 2 to 3 months of age(16,17,28,38).

Some of the theoretical concerns from different studies are that DCC may have adverse neonatal effects with increased risk of respiratory symptoms, polycythaemia, hyperbilirubinaemia and need for phototherapy(14,15,18,21,39).

Most studies have been done in the developed world and Asia subcontinent,
The study seeks to replicate similar or better outcomes of Hb levels among a population with higher incidence of anaemia.

The study is to inform if there is a difference in haemoglobin and haematocrit level of term infants in women who undergo either ICC or DCC. This can then be used to formulate policy guidelines on the appropriate timing of cord clamping during delivery in our setting.

NULL HYPOTHESIS

There is no difference in neonatal haemoglobin and haematocrit status of term infants of women who undergo DCC compared to ICC.

ALTERNATIVE HYPOTHESIS

There is a difference in neonatal haemoglobin and haematocrit status of term infants of women who undergo DCC compared with ICC

OBJECTIVES

BROAD:

To evaluate the effect of umbilical cord clamp timing on term infant's haemoglobin, haematocrit levels, development of respiratory distress, neonatal jaundice and polycythemia born at Kenyatta National Hospital, Kenya.

<u>SPECIFIC:</u>

Between term infants undergoing ICC or DCC;

1. To compare the cord blood haemoglobin and haematocrit levels

2. To compare proportion of infants who develop respiratory distress in the first 6 hours.

3. To compare development of neonatal jaundice at day 3 and 7 of life.

4. To compare neonates who develop polycythaemia.

CHAPTER 2. METHODOLOGY

STUDY DESIGN:

This was a randomized control trial (Parallel-group 1:1 randomization) comparing delayed cord clamping (DCC) with immediate cord clamping (ICC) and its effects on neonatal Hb, Hct, development of neonatal respiratory distress, neonatal jaundice and polycythemia.

STUDY SITE/SETTING:

The study was carried out in The Labour and Postnatal wards (Ward GFA, GFB, and 1A) at The Reproductive Health Unit in Kenyatta National Hospital (KNH). KNH is the country's largest public referral and teaching hospital to the University of Nairobi and Kenya Medical Training College. It receives participants from Nairobi and its environs as well as referrals from all other hospitals in Kenya. It has a bed capacity of 1800 beds and is located 2km southwest of the Nairobi Central Business District (CBD).

It has an average of 1,000 deliveries in a month. These deliveries occur among mothers of varying socioeconomic spheres.

The Initial sample size calculation necessary for comparing proportions proportion p_1 being the estimated proportion of infants with good Hb after delayed cord clamping and p_2 being the estimated proportion of infants with good Hb after immediate cord clamping. (40). However as part of data monitoring an interim analysis of data was carried out at the midpoint.

$$n = (\frac{r+1}{r})\frac{(\overline{p})(1-\overline{p})(Z_\beta + Z_{\alpha/2})^2}{(\mathrm{p}_1 - p_2)^2}$$

ratio of delayed cord clamping : immediate cord clamping (r)	1
Estimated proportion with Good Hb among Delayed CC p_1	88.8%
Estimated reduction in poor outcome	2
Estimated proportion with Good Hb among Immediate CC p_2	77.5%
Power (1-α/2)	95%
Power (1-β)	80%
Sample size per group	87
Adjusting upwards by 10% for incomplete data, sample size per group	96
Total sample size	**192**

STUDY POPULATION

INCLUSION CRITERIA:

1. Women willing to provide consent, delivering at Kenyatta National Hospital are candidates for inclusion in the study. Following the criteria below:

2. Full-term infants (>37 weeks gestation) of singleton pregnancies,

3. Reassuring fetal status,

4. Spontaneous vertex delivery

5. Low risk pregnancies i.e. women aged 18-39, with;

   ● No previous diagnosis of essential hypertension, renal disease, collagen-vascular disease, liver disease, cardiovascular disease,

   ● No placenta previa,

   ● No multiple gestation,

   ● No intrauterine growth restriction,

   ● No history of smoking,

   ● No pregnancy-induced hypertension,

   ● No other previously documented condition that pose a high risk of poor pregnancy outcome.

EXCLUSION CRITERIA:

Women who come in with:

1. Twin pregnancy,

2. History of post-partum haemorrhage (PPH),

3. Medical complications e.g. Pre-eclampsia, diabetes, renal disease, chronically medicated e.g. anticonvulsants, antidepressants, thyroid hormone etc,

4. Abruptio placenta,

5. Caesarean section,

6. Tight nuchal cord necessitating early cutting,

7. Need for neonatal resuscitation

8. Major congenital abnormalities (e.g. neural tube defects).

9. Infants who were preterm or weighed <2500 g,.

<u>INTERVENTION</u>

Written informed consent was obtained following a clear explanation of what the study entails. When delivery was imminent (expected within 10 minutes), the midwife opened a sealed, numbered, opaque envelope containing the treatment allocation. Two interventions for the newborns were immediate umbilical cord clamping (within the first 30 seconds after birth) and delayed umbilical cord clamping (greater than 120 seconds after birth). The cord-clamping technique used in the 2 groups was similar. Use of sterile delivery packs that were ready packed with plastic clamp and cutter. The first clamp was placed 5-7.5 cm away from the baby, the second about 5 cm away from the first with the cutter. Timing was done using a stopwatch and was started at the point of delivery of baby's feet and end at the point of clamping.

ICC was done within 30 seconds of birth and apgar scoring of newborn at 1, 5 and 10-minute mark. Milking of the cord was not done.10iu of oxytocin was administered intramuscularly as is the standard procedure in active management of third stage and after confirmation of no second fetus. The newborn was reevaluated for development of respiratory symptoms before transfer to the ward i.e. within the first 6 hours of life. Continuous pad monitoring of the mother was done as well to rule out development of PPH.

For DCC all infants were placed between the legs of the mother (approximately 10 cm below the vaginal introitus), dried and wrapped in a warm towel. The infants remained in this position until the cord was clamped. Apgar scoring was also done at 1, 5 and 10-minute mark. 10iu of intramuscular oxytocin was administered to the mothers immediately after cord clamping and confirmation of no second fetus. The newborn was reevaluated for development of respiratory symptoms before transfer to the ward i.e. within the first 6 hours of life. Continuous pad monitoring of the mother was done as well to rule out development of PPH.

Newborns without spontaneous breathing during the first 10 seconds of life, with major congenital malformations diagnosed at birth, with estimated neonatal birth weight in the10th percentile, and/or with tight nuchal cord were subjected to early cord clamping based on need for resuscitation, regardless of the assigned intervention.

Blood sample collection was done between 6-24 hours of birth into an edta-microtainer. In case blood was drawn for any other reason, the testing was done on the first sample collected from the baby. The log available in the labor ward had details of patient's location if transferred to a different ward.

A follow up telephone call was made to participants on day 3 and 7 postpartum to follow on any neonatal complications that may have developed. A clear definition of neonatal sepsis and jaundice was explained to the mothers including yellowness of eyes, refusal to breast-feed, excessive irritability, increased body temperatures, reduced urinary output and umbilical discharge.

DATA COLLECTION AND MANAGEMENT

RANDOMIZATION

The statistician used block randomization; in equal blocks of 16 until the total sample size was achieved. For allocation concealment, the randomization instructions were given to the investigator and research assistants in sequentially numbered, opaque, sealed identical envelopes with unpredictable allocation code.

Randomization occurred when delivery was imminent, reason being, the caesarian section rate in Kenyatta National hospital stands at nearly 40% this translates to a loss of almost half of the potential participants, as the study included only those who deliver via spontaneous vertex delivery

RECRUITMENT

Patient files identified the potential participants i.e. participants in active labour (4-6cm dilatation) and fulfilling the inclusion criteria (women aged 18-39, with no previous diagnosis of chronic disease, complications of pregnancy or other previously documented condition that pose a high risk of poor pregnancy outcome) at the time of admission to the labour ward, in KNH.

CONSENTING

The principal investigator or research assistant briefed the participants on the study and verbal consent was given following this. Written informed consent was obtained following a clear explanation of what the study entailed. The details of the study were also laid out in the consent form. This process was free from coercion and was explicitly voluntary.

A log was available in Labour ward, whomever obtained consent (the investigator or any of the research assistants) from the participants, observed the intervention and collected samples were required to sign the book at every point.

The investigator or research assistant countersigned the consent form. A copy of the signed consent form was given to the participant. All consenting participants who meet the inclusion criteria were allowed to progress in labor until the second stage when they were randomized into the two different intervention groups.

BLINDING

Although study staff did not inform the mothers of their assignment, the nature of the intervention made it impossible to blind them. If an already randomized mother became ineligible, the assigned allocation code was not re-used. The principal investigator or either one of the research assistants monitored the delivery procedure, and were therefore not blinded to treatment assigned, however they were blinded to the results of neonatal haemoglobin and haematocrit levels.

The laboratory staff that performed analyses of the blood samples were blinded to the infants allocation group.

VARIABLES
- Primary dependent variables; the infants' venous haemoglobin and haematocrit value will be measured between 6-24 hours after birth.
- Secondary dependent variables: neonatal anaemia, polycythaemia, early respiratory symptoms and need for phototherapy.

- <u>Independent variables:</u> Maternal Socio-demographic and medical characteristics.

<u>Maternal data</u>

Some of the obstetric and medical information was collected from maternal health care records taken at the time of admission to antenatal care these included reported illness, medication, parity, blood group, Rhesus factor status, and Hb value. After giving birth, the estimated maternal postpartum blood loss was recorded by the midwife within two hours after delivery. After 3rd and 4th stage of labour, mothers were interviewed further to complete the questionnaire.

<u>Neonatal data</u>

The research assistants measured the time from complete delivery of the baby to the first clamp on the umbilical cord with a stopwatch. The infant was assessed at 1 and 6 hour mark by the midwife, who recorded if the baby had been breastfed and the presence of respiratory symptoms, i.e. respiratory rate above 60, presence of nostril flaring, grunting or intercostal recession.

<u>Blood samples</u>

All neonatal blood samples were collected using a 25-gauge needle from the umbilical vein, amounting 0.5mls. It was transferred to the laboratory and analysed for 'complete blood count': Hb, Hct, MCV, MCHC (mean cell haemoglobin concentration.) Blood was collected in EDTA tubes (BD microtainers)

Blood samples were stored for a maximum of 1 hour in room temperature and then transported to the hospital's laboratory where analyses were performed. Complete blood counts were analysed using the automated haematology analyser

As part of data monitoring, analysis was done at the midpoint and the statistician alerted the principal investigator of any overt differences in the two groups. The study was halted due to evidence of significant statistical advantage of DCC over ICC, to avoid denying the ICC group an advantageous intervention.

DATA ANALYSIS

As part of data monitoring, analysis was done at the midpoint and the statistician alerted the principal investigator of any overt differences in the two groups. The study was halted due to evidence of significant statistical advantage of DCC over ICC, to avoid denying the ICC group an advantageous intervention.

Data was exported to Stata for analysis. For descriptive statistics, differences in proportions for categorical variables were compared using a t-test, while differences in means were compared using chi squared (X^2) test. Mean, standard deviation and 95% confidence interval were used for continuous variables.

Multiple linear regressions were done to evaluate the effect of the maternal characteristics on neonatal haemoglobin and haematocrit levels.

ETHICAL CONSIDERATIONS

Permission was sought from the Kenyatta Hospital- University of Nairobi Ethics and Research Committee (KNH-UON ERC) to collect and analyze the data as part of the

Thesis Dissertation. Authorization was obtained from KNH administration.

The recruitment process was free from coercion and was explicitly voluntary. No personal identifiers were employed for participants. A code was assigned to each, for purposes of identification. The key, linking the participant to the identifying code was stored separately from the research data, in a password-protected database. This was accessible only to the statistician.

CHAPTER 3. RESULTS

The trial profile was as below:

MOTHERS ASSESSED FOR ELIGIBILITY BEFORE DELIVERY AND RANDOMIZED (n=116)

CONTROLS EARLY CLAMPING <30 SEC (n=58)
DELAYED CORD CLAMPING >120 SEC (n=58)

Excluded ⌞SEP⌟
1. *Birth weight <2500 g*
2. *Major congenital Abnormalities*
3. *Unexpected twin*
4. *Tight nuchal cord*
5. *Need for resuscitation*

Excluded ⌞SEP⌟
1. *Birth weight <2500 g*
2. *Major congenital Abnormalities*
3. *Unexpected twin*
4. *Tight nuchal cord*
5. *Need for resuscitation*

REFUSED FURTHER PARTICIPATION (n=0)

REFUSED FURTHER PARTICIPATION (n=0)

RECEIVED INTERVENTION (n=48)
RECEIVED INTERVENTION (n=48)

ANALYZED (n=48)
ANALYZED (n=48)
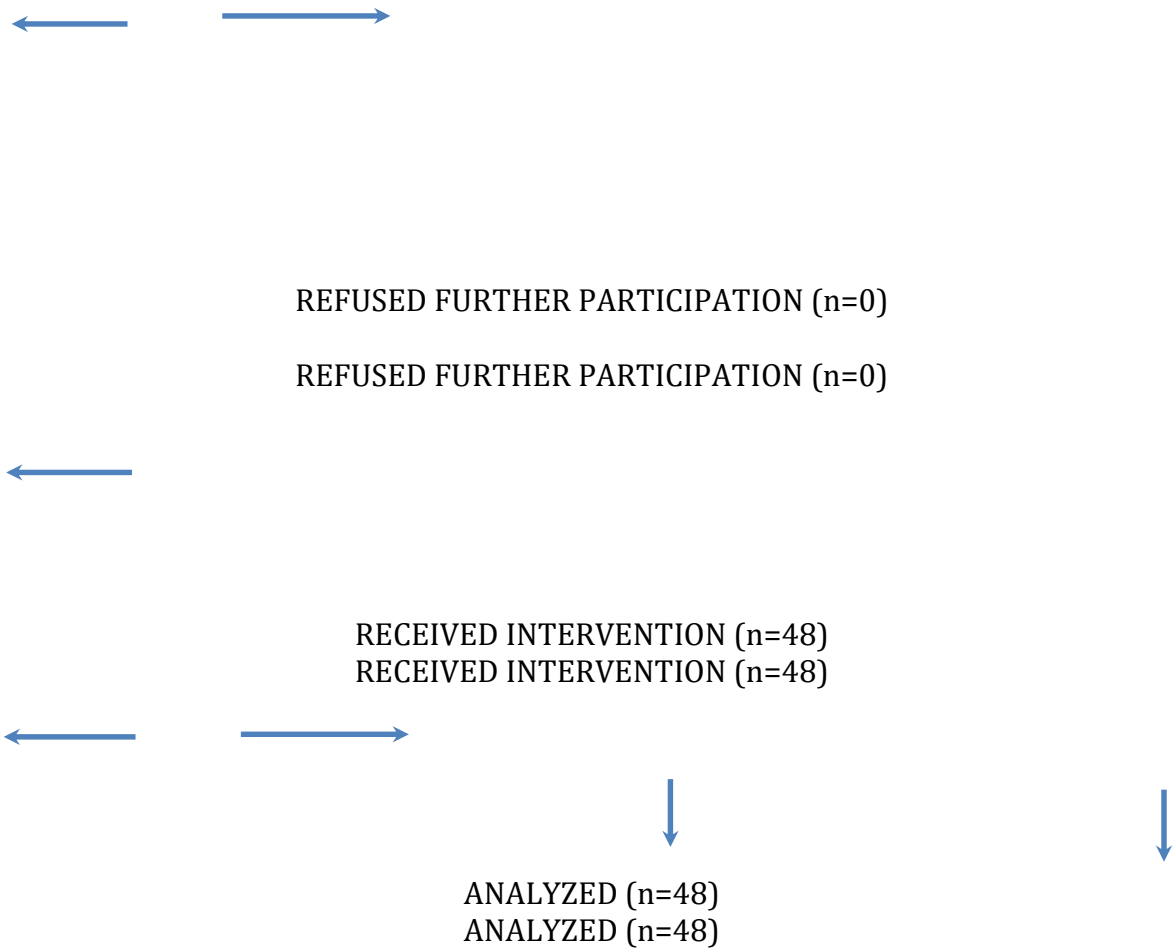
An interim analysis done using information obtained from the first 96 mother-neonate pairs in the study; each arm comprising 48 pairs.

There was no statistical difference in the maternal socio-demographic characteristics between the two groups.(figure 3, table 2 and 3) and thus randomization was effective.

DESCRIPTIVE CHARACTERISTICS
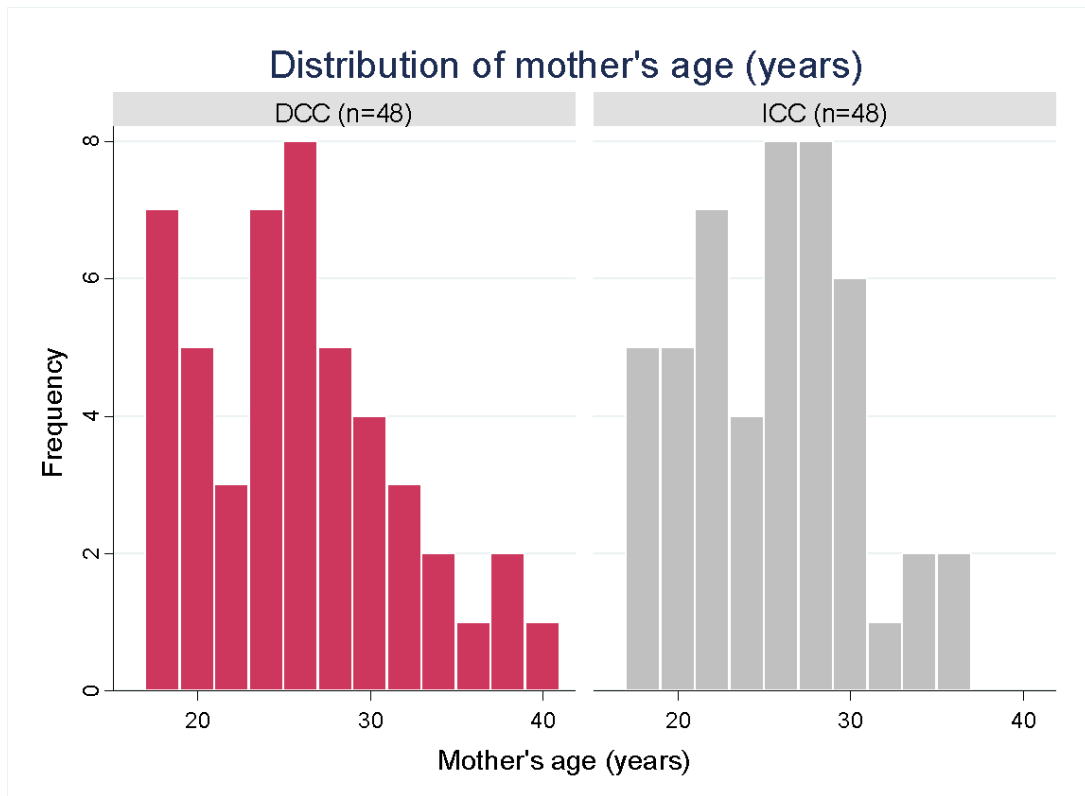
Figure 3: Distribution of mothers' age by group (DCC/ICC)

Seventy five percent of the mothers in both arms were younger than 30 years.

Table 1: Socio-demographic characteristics of the mothers

VARIABLE	CATEGORY	ICC n (%)	DCC n (%)
	Married	38 (79.2)	38 (79.2)
Marital status	Single	9 (18.8)	9 (18.8)
	Widowed	1 (2.1)	1 (2.1)
	Primary	14 (29.2)	11 (22.9)
Education level	Secondary	21 (43.8)	21 (43.8)
	Tertiary	13 (27.1)	16 (33.3)
	Formal employment (salary)	10 (20.8)	9 (18.8)
Employment status	Self employed	9 (18.8)	12 (25.0)
	Unemployed	29 (60.4)	27 (56.3)

The distribution of mother's age, marital status, educational level, employment status was similar between the two groups as seen in table 1. More than 70% of the mothers had attained at least secondary level education.

Table 2: Obstetric characteristics of the neonate's mothers

VARIABLE	CATEGORY	ICC n (%)	DCC n (%)
Parity	Primigravida	28 (58.3)	28 (58.3)
	Multigravida	20 (41.7)	20 (41.7)
ANC attendance	Yes	48 (100)	48 (100)
Facility attended	KNH	5 (10.4)	5 (10.4)
	Other	43 (89.6)	43 (89.6)
Number of visits	<4 visits	26 (54.2)	31 (64.6)
	≥ 4 visits	22 (45.8)	17 (35.4)
Blood group	A	12 (25.0)	11 (22.9)
	B	13 (27.1)	14 (29.2)
	AB	1 (2.1)	1 (2.1)
	O	22 (45.8)	22 (45.8)
Rhesus factor	Negative	6 (12.5)	4 (8.3)
	Positive	42 (87.5)	44 (91.7)
VRDL results	Negative	48 (100)	48 (100)
HIV status	Negative	48 (100)	48 (100)
Iron supplements	Yes	36 (75.0)	39 (81.3)
	No	12 (25.0)	9 (18.7)

The obstetric characteristics i.e. Parity, ANC attendance, blood group, HIV status,

iron supplementation were similarly distributed between the two groups (table 2)

NEONATES' CHARACTERISTICS AT BIRTH

Table 3: Neonates' gender and APGAR score distribution by group

VARIABLE	CATEGORY	ICC n (%)	DCC n (%)
Sex	Female	19 (39.6)	22 (45.8)
	Male	29 (60.4)	26 (54.2)
Apgar score at 5 minutes	8	3 (6.3)	-
	9	17 (35.4)	19 (39.6)
	10	28 (58.3)	29 (60.4)

The neonatal characteristics i.e. sex, apgar score, birth weight, length and head circumference in both groups were similarly distributed (Table 3 and 4)

Table 4: Neonates characteristics at birth by group

Variable	Group	Median	IQR	Min	Max	Pearson Chi2	P-value
Gestation age	DCC	39	38-40	37	42	**0.168**	**0.682**
at delivery	ICC	39	37-41	37	41		
Birth weight	DCC	3100	2825-3400	2000	3800	**2.050**	**0.152**
(grams)	ICC	3000	2700-3200	2000	3800		
Birth length	DCC	54	48-56	46	62	**0.375**	**0.540**
	ICC	52	49-58	26	63		

Head circumference	DCC	32	30-34	24	38	**2.263**	**0.133**
	ICC	30	28-33	24	37		
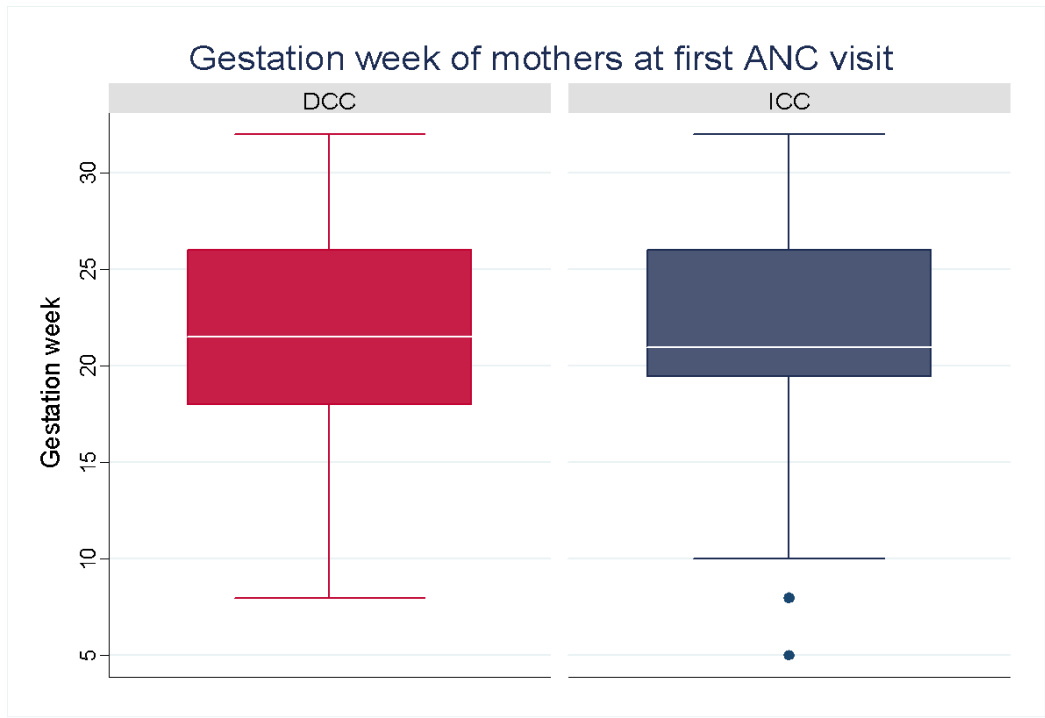
Figure 4: Mother's gestation age (week) at first ANC visit

Most of the first time ANC visits occurred in the second trimester. 75% of the mothers attended their first ANC session at 18 weeks gestation.

Figure 5: Distribution of Neonatal haemoglobin by group (DCC/ICC)

Figure 7 shows the distribution of haemoglobin level in neonates in the DCC and ICC groups. The confidence interval of Hb level was 16.87g/dl to 17.50g/dl in the DCC group and between 15.27g/dl to 15.98 g/dl in the ICC group. Fifty percent of the neonates who underwent DCC had less than 17.45g/dl whereas among the neonates that underwent ICC, 50% had less than 15.6g/dl
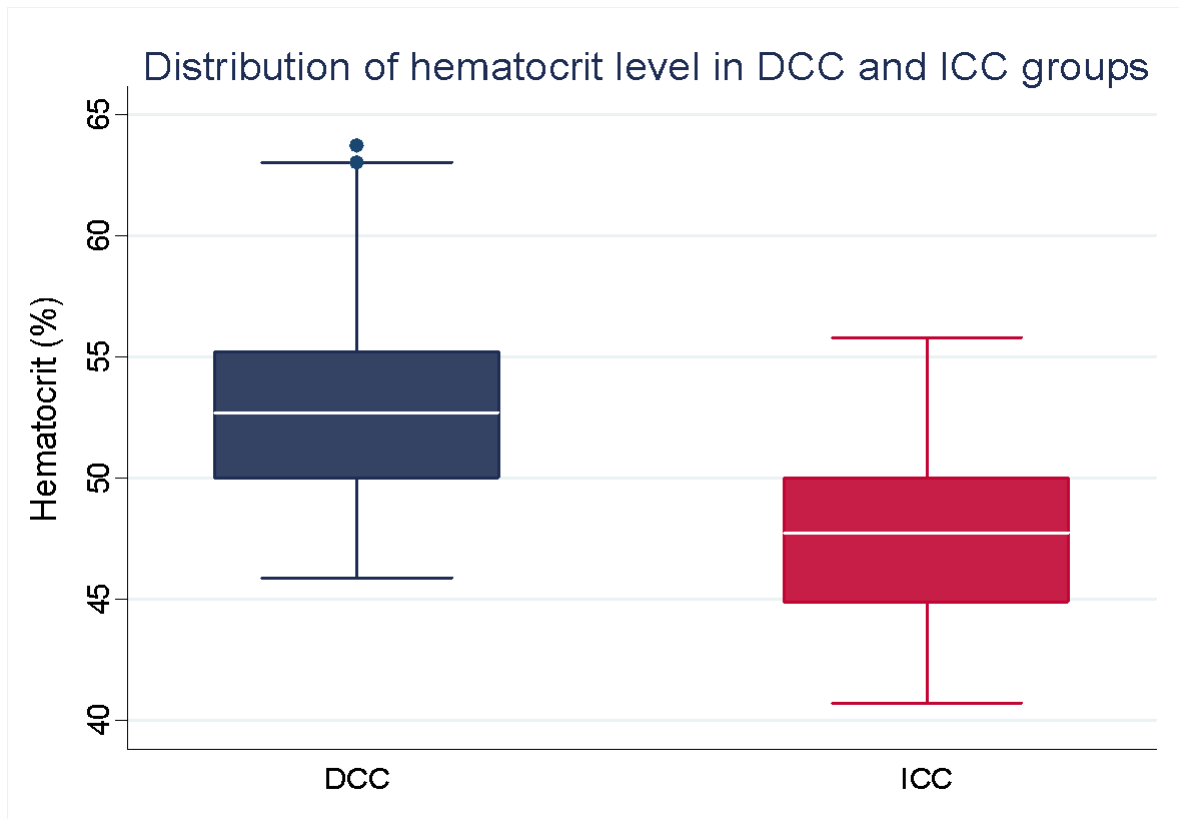
Figure 6: Distribution of UC haematocrit level by group (DCC/ICC)

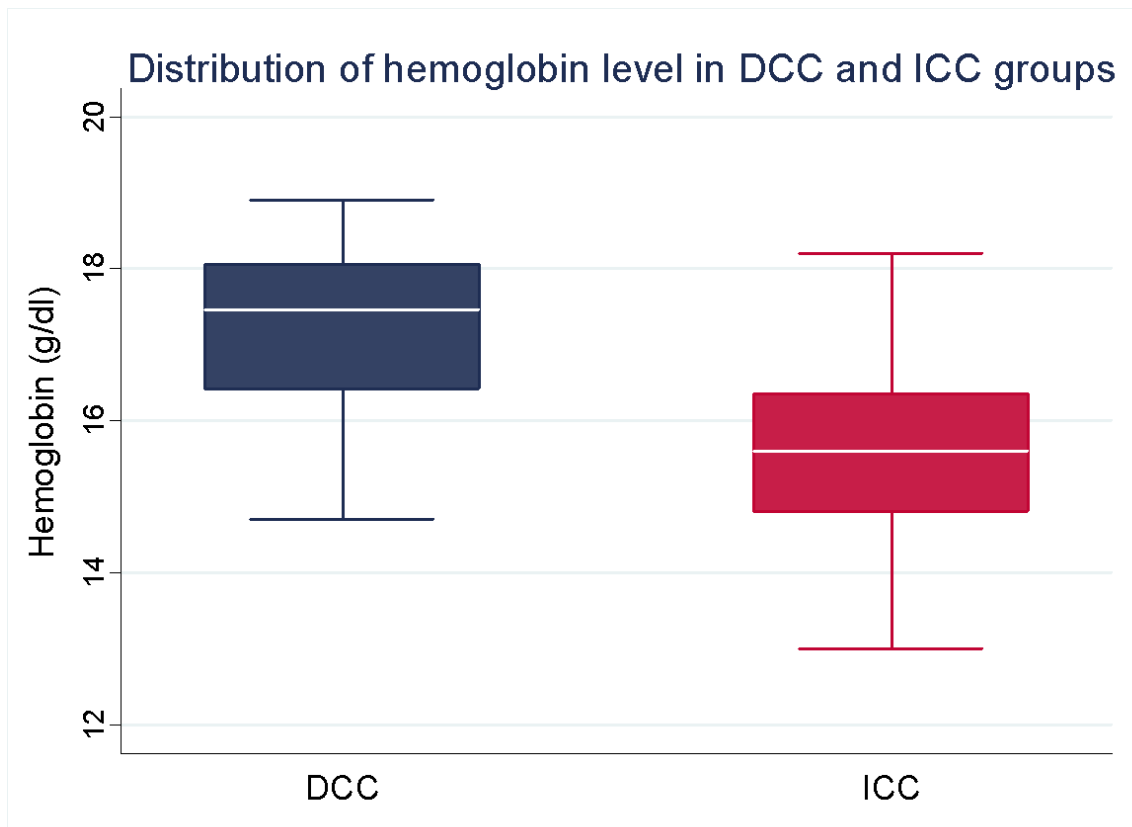Figure 8 shows the distribution of haematocrit level in neonates in the DCC and ICC groups. The confidence level of haematocrit was 52.03% to 54.85% with a median of 52.7% in the DCC group and from 46.48% to 48.75% in the ICC group with a median of 47.6.

Table 6: Comparison of Haemoglobin and haematocrit distribution between DCC and ICC groups

Variable	Group	Mean	SD	[95% CI]	t-statistic	P-value
UC Haemoglobin	DCC	17.19 (g/dl)	1.07 (g/dl)	[16.87; 17.50]	6.666	<0.001
	ICC	15.63 (g/dl)	1.22 (g/dl)	[15.27; 15.98]		
UC Haematocrit	DCC	53.44 %	4.85 %	[52.03; 54.85]	6.432	<0.001

| | ICC | 47.63 % | 3.96 % | [46.48; 48.78] | | 38 |

Two-sample independent t-tests were done to compare the means of haemoglobin and haematocrit between the DCC and ICC groups. Both tests showed that there was a highly statistically significant difference in the haemoglobin level (p<0.001) and haematocrit level (p<0.001) between neonates who underwent DCC and ICC (table 6).

SECONDARY RESULTS

Respiratory distress syndrome was noted in three neonate all in the ICC group. All three were discharged from newborn unit within 24 hours of admission.

None of the neonates during day 3 and 7 follow up developed jaundice requiring phototherapy.

None of the neonates had a haematocrit level above 65%, therefore no diagnosis of polycythaemia was made.

CHAPTER 4: DISCUSSION

The sample size calculation was 192, however as part of data safety and monitoring, an interim analysis was done at the midpoint i.e. 96 participants. The study was to be halted if there was evidence of significant statistical advantage in either group, to avoid denying the corresponding group an advantageous intervention. The O'Brien Fleming design was used in the interim analysis, a p value of < 0.025 was significant.

PRIMARY OUTCOME

The study found that delaying clamping of the umbilical cord in term infants born of low risk mothers had significant effects on measured indicators of iron status haemoglobin and haematocrit. The analysis of this study showed a significant difference in the values of neonatal haemoglobin and haematocrit levels between the two groups. The average haemoglobin in DCC group was 17.19g/dL while in the ICC group it was 15.63g/dL. The average haematocrit level was 53.4 in the DCC group and 47.6 in the ICC group (Table 5). Similar findings were reported in studies conducted by Chaparro, Andersson, McDonald and Van rheenen (8-11).

Though many RCTs show no adverse effects of DCC, ICC is still being practiced in Kenya, as noted at the highest level of care hospital in the country- Kenyatta National Hospital. An observational study done in the labor ward showed the average cord clamping time to be 20 seconds as of 2016.

The study also showed that among the neonates that underwent ICC, the haemoglobin level appeared to increase gradually with increase in the mother's haemoglobin. In our population that has high rates of anaemia among antenatal mothers; standing at 36.2% this is significant in that the infants of anemic mothers

are more prone to have low Hb and Hct from the onset if ICC is practiced, this effect was not noted in DCC(30)(41).

Similar studies done in Guatemala, Peru and Zambia not only showed higher haemoglobin and haematocrit levels six hours after birth but also the sustained effect of late clamping such as increased ferritin levels at 4 months of age (7)(42)(43). Our study however did not follow up the participants to analyze any further advantages of DCC. DCC has been documented to lead to 47% reduction in the risk of anaemia and a 33% reduction in the risk of having deficient iron stores at ages two to three months(9). This is of particular importance for developing countries in which anaemia during infancy and childhood is highly prevalent(16).

SECONDARY OUTCOMES

The three infants who were diagnosed to have respiratory distress were all in the ICC group and were admitted to the newborn unit, they were all discharged within 24 hours, and this is against the expectation that respiratory distress would be an outcome of the DCC group. There was follow up of all neonates to assess development of neonatal jaundice, by day 7 there was no noted jaundice that necessitated phototherapy and this corresponded to other RCTs. (7, 9, 11, 18)

It has been postulated that delayed cord clamping may increase the risk of neonatal polycythaemia and respiratory symptoms but we did not find any group differences in these outcomes, which is also consistent with Cochrane meta-analysis (10, 13).

Maternal outcomes were similar in both groups; there was no development of PPH secondary to either intervention. A similar study by Clausen found no increased risk in PPH with delayed cord clamping(44). This was thought to be one of the arguments for ICC as there was need to administer oxytocin, the study supports DCC as oxytocin can be administered 3 minutes post-delivery with no adverse outcome(15).

These findings support incorporation of DCC protocol as part of AMTSL as per current WHO protocol(45).

The main limitation of the study is it only recruited low risk deliveries by healthy mothers from a well-nourished population. The findings may not be reproducible to term infants with various perinatal risk factors such as maternal diabetes or intrauterine growth restriction.   Haemoglobin and haematocrit are also indirect measures of iron status and as such further evaluations such as ferritin would show a definitive benefit of DCC.

CONCLUSION

The study concludes that delayed cord clamping resulted in improved Hb and Hct thus reducing the prevalence of neonatal anaemia at birth without increasing the rate of respiratory symptoms or need for phototherapy. This effect is clinically relevant and should lead to a change in practice. Further studies are needed to explore long term health effects of delayed and early cord clamping.

RECOMMENDATIONS

It is vital to inform policy makers both at a facility and national level on the importance of in cooperating DCC as an easy and safe measure of reducing anaemia in the neonatal population as well as undertaking the education of midwives on the benefits of the practice.

Follow up study to review neonatal haemoglobin and haematocrit levels after one month of life.

CHAPTER 5: REFERENCES

1. Linderkamp O. Placental transfusion: determinants and effects. Clin Perinatol. 1982 Oct;9(3):559–92.

2. Saigal S, Usher RH. Symptomatic neonatal plethora. Biol Neonate. 1977;32(1–2):62–72.

3. Jelin AC, Kuppermann M, Erickson K, Clyman R, Schulkin J. Obstetricians' attitudes and beliefs regarding umbilical cord clamping. J Matern Fetal Neonatal Med. 2014 Sep 1;27(14):1457–61.

4. Boere I, Smit M, Roest AAW, Lopriore E, Lith JMM van, Pas AB te. Current Practice of Cord Clamping in The Netherlands: A Questionnaire Study. Neonatology. 2015;107(1):50–5.

5. Yeluri SK. Prevalence of anemia and its etiology: a study in a semi urban area. Pediatr Rev Int J Pediatr Res [Internet]. 2016 Apr 30 [cited 2017 Mar 22];3(04). Available from: http://medresearch.in/index.php/IJPR/article/view/730

6. Macro ICF. Kenya health and demographic survey 2014. Data Downloaded Httpwww Meas Com [Internet]. 2011 [cited 2017 Mar 22]; Available from: http://cmidwivesc.org/documents/publications/pfs_32.pdf

7. De Benoist B, World Health Organization, Centers for Disease Control and Prevention (U.S.). Worldwide prevalence of anaemia 1993-2005 of WHO Global Database of anaemia [Internet]. Geneva: World Health Organization; 2008 [cited 2015 Apr 23]. Available from: http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf

8. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. J Perinatol. 2017 Feb;37(2):105–11.

9. Yao A, Hirvensalo M, Lind J. PLACENTAL TRANSFUSION-RATE AND UTERINE CONTRACTION. The Lancet. 1968 Feb 24;291(7539):380–3.

10. Gyorkos TW, Maheu-Giroux M, Blouin B, Creed-Kanashiro H, Casapía M, Aguilar E, et al. A hospital policy change toward delayed cord clamping is effective in improving hemoglobin levels and anemia status of 8-month-old Peruvian infants. J Trop Pediatr. 2012 Dec;58(6):435–40.

11. Chaparro CM. Timing of umbilical cord clamping: effect on iron endowment of the newborn and later iron status: Nutrition Reviews©, Vol. 69, No. S1. Nutr Rev. 2011 Nov;69:S30–6.

12. Andersson O, Hellstrom-Westas L, Andersson D, Domellof M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4

months: a randomised controlled trial. BMJ. 2011 Nov 15;343(nov15 1):d7157–d7157.

13. Van Rheenen P, De Moor L, Eschbach S, De Grooth H, Brabin B. Delayed cord clamping and haemoglobin levels in infancy: a randomised controlled trial in term babies: Cord clamping and haemoglobin levels in infancy. Trop Med Int Health. 2007 Mar 27;12(5):603–16.

14. McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2008 [cited 2015 Jan 18]. Available from: http://doi.wiley.com/10.1002/14651858.CD004074.pub2

15. Van Rheenen P, De Moor L, Eschbach S, De Grooth H, Brabin B. Delayed cord clamping and haemoglobin levels in infancy: a randomised controlled trial in term babies: Cord clamping and haemoglobin levels in infancy. Trop Med Int Health. 2007 Mar 27;12(5):603–16.

16. Gyorkos TW, Maheu-Giroux M, Blouin B, Creed-Kanashiro H, Casapía M, Aguilar E, et al. A hospital policy change toward delayed cord clamping is effective in improving hemoglobin levels and anemia status of 8-month-old Peruvian infants. J Trop Pediatr. 2012 Dec;58(6):435–40.

17. Mercer J, Erickson-Owens D. Delayed cord clamping increases infants' iron stores. The Lancet. 2006 Jun;367(9527):1956–8.

18. Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: Systematic review and meta-analysis of controlled trials. JAMA. 2007 Mar 21;297(11):1241–52.

19. Shirvani F, Radfar M, Hashemieh M, Soltanzadeh MH, Khaledi H, Mogadam MA. Effect of timing of umbilical cord clamp on newborns' iron status and its relation to delivery type. Arch Iran Med. 2010;13(5):420–5.

20. Usher R, Shephard M, Lind J. The Blood Volume of the Newborn Infant and Placental Transfusion. Acta Pædiatrica. 1963 Sep 1;52(5):497–512.

21. Saigal S, Usher RH. Symptomatic neonatal plethora. Biol Neonate. 1977;32(1–2):62–72.

22. Saigal S, O'Neill A, Surainder Y, Chua LB, Usher R. Placental transfusion and hyperbilirubinemia in the premature. Pediatrics. 1972 Mar;49(3):406–19.

23. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2012 [cited 2015 Jul 13]. Available from: http://doi.wiley.com/10.1002/14651858.CD003248.pub3

24. Ngesa O, Mwambi H. Prevalence and Risk Factors of Anaemia among Children Aged between 6 Months and 14 Years in Kenya. PLoS ONE. 2014 Nov 25;9(11):e113756.

25. Brabin B. Fetal anaemia in malarious areas: its causes and significance. Ann Trop Paediatr. 1992;12(3):303–10.

26. Status I of M (US) S on N, Pregnancy WG during, Intake I of M (US) S on D, Pregnancy NS during. Nutrition during pregnancy: part I, weight gain: part II, nutrient supplements. Natl Academy Pr; 1990.

27. Ekvall H, Premji Z, Björkman A. Micronutrient and iron supplementation and effective antimalarial treatment synergistically improve childhood anaemia. Trop Med Int Health. 2000;5(10):696–705.

28. Chaparro CM. Timing of umbilical cord clamping: effect on iron endowment of the newborn and later iron status: Nutrition Reviews©, Vol. 69, No. S1. Nutr Rev. 2011 Nov;69:S30–6.

29. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr. 2007 Apr 1;85(4):931–45.

30. van Rheenen PF, Brabin BJ. A practical approach to timing cord clamping in resource poor settings. BMJ. 2006 Nov 4;333(7575):954–8.

31. Lefeber & Voorhoeve 1997). The role of delayed umbilical cord clamping to control infant anaemia in resource-poor settings. Rozenberg Publishers; 2007. 170 p.

32. Wakaba M, Mbindyo P, Ochieng J, Kiriinya R, Todd J, Waudo A, et al. The public sector nursing workforce in Kenya: a county-level analysis. Hum Resour Health. 2014 Jan 27;12:6.

33. van Hensbroek MB, Jonker F, Bates I. Severe acquired anaemia in Africa: new concepts: Review. Br J Haematol. 2011 Sep;154(6):690–5.

34. Enkin M, Keirse M, Neilson J, Crowther C, Duley L, Hodnett E, et al. Guide to Effective Care in Pregnancy and Childbirth. Third Edition. Oxford, New York: Oxford University Press; 2000. 544 p.

35. Moore T, Reiter R, Rebar R, Baker V, eds. Gynecology and Obstetrics: A Longitudinal Approach. New York. Churchill Livingstone; 1998. 689 p.

36. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Books; 1988.

37. McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term in-fants on maternal and neonatal outcomes. Status Date New Search Stud Content Updat Conclus Chang Publ In [Internet]. 2013 [cited 2015 Jan 18];(7). Available from:

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004074.pub3/pdf/standard

38. King TL, Pinger W. Evidence-Based Practice for Intrapartum Care: The Pearls of Midwifery. J Midwifery Womens Health. 2014 Nov;59(6):572–85.

39. Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet Lond Engl. 1969 Oct 25;2(7626):871–3.

40. Wiley: Sampling Techniques, 3rd Edition - William G. Cochran [Internet]. [cited 2017 Apr 2]. Available from: http://www.wiley.com/WileyCDA/WileyTitle/productCd-047116240X.html

41. DR. CAROLYNE NDUHIU, PROF KOIGI KAMAU. PREVALENCE OF ANAEMIA AMONG PREGNANT WOMEN ATTENDING ANTENATAL CLINIC AT MBAGATHI DISTRICT HOSPITAL [Internet]. Available from: http://obsgyn.uonbi.ac.ke/sites/default/files/chs/medschool/obsgyn/DR%20Carolyne%20Wanjiru.pdf

42. Grajeda R, Perez-Escamilla R, Dewey KG. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of age. Am J Clin Nutr. 1997;65(2):425–431.

43. Andersson O, Hellström-Westas L, Andersson D, Domellöf M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ. 2011 Nov 15;343:d7157.

44. Andersson O, Hellström-Westas L, Andersson D, Clausen J, Domellöf M. Effects of delayed compared with early umbilical cord clamping on maternal postpartum hemorrhage and cord blood gas sampling: a randomized trial. Acta Obstet Gynecol Scand. 2013 May;92(5):567–74.

45. WHO | Delayed clamping of the umbilical cord to reduce infant anaemia [Internet]. WHO. [cited 2017 Dec 1]. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/delayed-cord-clamping/en/

CHAPTER 6: APPENDICES

<u>APPENDIX 1: CONSENT</u>

Code number of mother-baby pair:

Date (dd/mm/yy):   _____

<u>Study Title:</u> <u>THE EFFECT OF TIMING OF CORD CLAMPING ON NEONATAL HAEMOGLOBIN AND HAEMOTOCRIT VALUES AT KENYATTA NATIONAL HOSPITAL</u>

<u>Investigator:</u>

Dr. Achieng Aling (MBChB)

Department of Obstetrics and gynecology, University of Nairobi.

Tel Number: 0726-862227

<u>Investigator's Statement:</u>

We are requesting you and your newborn to kindly participate in this research study. The purpose of this consent form is to provide you with the information you will need to help you decide whether to participate in the study. This process is called 'Informed Consent'. Please read this consent information carefully and ask any questions or seek clarification on any matter concerning the study with which you are uncertain. You are free to ask any questions about the study. The investigator will be available to answer any questions that arise during the study and afterwards.

<u>Introduction:</u>

Delayed cord clamping (DCC) improves both the short-term and long-term hematologic status for the newborn and does not have clinically significant adverse effects. The optimal duration of DCC appears to be >120 seconds, unless the cord stops pulsing sooner. In our setup, average cord clamping time is 20 seconds.

Benefits:

Delayed cord-clamping increases the transfer of Haemoglobin and consequently the iron stores of the neonate. This transfusion includes many types of pluripotent stem cells that may have significant long-term value for the child. When DCC occurs at 2 minutes after the birth or later, benefits include a 47% reduction in the risk of iron-deficiency anaemia, which is a common ailment in our country, this also reduces chances of infections.

Risks:

The possible adverse effects of DCC are thought to be secondary to over-perfusion leading to hyper-bilirubinemia and polycythaemia, these have been found to be theoretically and no statistical difference in the population has been documented between DCC and ICC.

Incase a baby requires resuscitation, ICC is considered so as not to delay resuscitative efforts and this will be given priority.

Voluntariness:

The study will be fully voluntary. There will be no financial rewards to you for participating in the study. One is free to participate or withdraw from the study at any point. Refusal to participate will not compromise you or your child's care in any way.

All the information obtained from you will be held in strict confidentiality. Any information that may identify you or your child will not be published or discussed with any unauthorised persons. No specific information regarding you, your child or your family will be released to any person without your written permission. Your research number will be used in place of your names.

Intervention

A structured survey questionnaire will be used to gather your obstetrical and medical details and a venous blood sample will be taken for a full hemogram in the first stage of labour.

When delivery is imminent, the midwife will open a sealed, numbered, opaque envelope containing the treatment allocation. Two interventions for the newborns will be early umbilical cord clamping (within the first 30 seconds after birth) and delayed umbilical cord clamping (within 2 minutes after birth). The cord-clamping technique used in the 2 groups will be similar. After vaginal birth all infants will be placed between your legs (approximately 10 cm below the vaginal introitus), dried and wrapped in a warm towel. The infants will remain in this position until the cord is clamped. Intramuscular oxytocin will be administered immediately after cord clamping.

Newborns requiring resuscitation will undergo ICC regardless of the assigned intervention.

A follow up telephone call will be made to you two weeks postpartum to follow on any neonatal complications that may have developed.

<u>Problems or Questions:</u>

If you ever have any questions about the study or about the use of the results you can contact the principal investigator, Dr. Achieng Aling by calling 0726-862227

If you have any questions on your rights as a research participant you can contact the Kenyatta National Hospital Ethics and Research Committee (KNH- ESRC) by calling 2726300 Ext. 44355.

Consent Form: Participant's Statement:

I _____having received adequate

information regarding the study research, risks, benefits hereby AGREE /

DISAGREE (Cross out as appropriate) to participate in the study with my child. I

understand that our participation is fully voluntary and that I am free to withdraw at

any time. I have been given adequate opportunity to ask questions and seek

clarification on the study and these have been addressed satisfactorily.

Parents Signature: _____   Date _____

I _____ declare that I have

adequately explained to the above participant, the study procedure, risks, benefits

and given him /her time to ask questions and seek clarification regarding the study. I

have answered all the questions raised to the best of my ability.

Interviewer's Signature   _____   Date _____

_____

APPENDIX 2: INCLUSION AND EXCLUSION SCREENING ENROLLMENT FORM

Date: (dd/mm/yy): _____

Code Number of the Mother-Baby pair: _____

Subject Initials: _____

Inclusion Criteria:

1. Age of mother (years)   ………………………….

2. Parity

3. Gestation >37 weeks at time of presentation

4. Birth plan spontaneous vertex delivery.

5. History of previous antepartum, intrapartum and postpartum complications

Yes   No

If yes,

expound …………………………………………………………………………

…………………………………………………………………………………………

…………………………………………………………………………………………

…………………………………………………………………………………………

..

Exclusion criteria: *If any answer is yes, exclude from enrollment*

1. Twin pregnancy,

2. History of post-partum haemorrhage (PPH),

3. Clinical disease e.g. Pre-eclampsia, diabetes, renal disease,

4. Chronically medicated e.g. anticonvulsants, antidepressants, thyroid hormone etc,

Exclusions that may occur after randomization

5. Placental separation before delivery,

6. Emergency caesarean section,

7. Tight nuchal cord necessitating early cutting,

8. Need for neonatal resuscitation

9. Major congenital abnormalities (e.g. neural tube defects).

10. Infants weighing<2500 g, or with gestational age below 37 weeks.

BASELINE QUESTIONNAIRE

Part I: Socio demographics

Indicate all times using the 24 hour clock, and dates in this format dd/mm/yyyy.

Code number of mother-infant pair: _____   Randomization arm: ___

Date of Signed Informed Consent: dd/mm/yy) ____/_____/_____

Copy given to patient: Yes / No   Mobile Phone Number:_____

1. Age of mother (years)   ……………………………….

2. Marital Status

   Single   □   Widowed   □

   Married   □   Separated   □

   Divorced   □

3. Level of Education

   Primary   □   Secondary □   Tertiary   □

4. Employment status

   Self employed □   Salaried employment □   Unemployed □

Part II: Obstetric History

5. Parity   ………………………

6. Obstetric History

	Date (Year)	Place Home or HF*	GA** at delivery	Mode of Delivery	Maternal Complications	Neonatal Outcome
1						
2						
3						
4						

*HF-Health Facility   GA** Gestational age

7. ANC attendance   Yes □   No   □

8. If yes, facility attended: KNH □   Other facility □

9. Number of visits   …………………………..

10. Date of first visit …./…../……..

11. Gestational age at first visit   (in completed weeks)   ………/40

12. Iron supplementation during pregnancy   Yes □   No □

13. Duration of Iron supplementation…………
14. ANC Profile:

        Haemoglobin……………

        Blood group:…………... Rh: ……………

        VDRL:

        HIV:

Part III: Index Admission

15. Date of Admission   ……/……. /…….

16. Time of admission   ……………….

17. Referral status

    Referred from other facility   □

    Self referred   □

    Booked for delivery at KNH   □

18. Gestational age at delivery (in completed weeks) ……../40

19. Gestational age calculated by Dates   □   Quickening □

                             Ultrasound □   Fundal Height □

                             First clinic visit estimate   □

Part IV: Infant characteristics

20. Gestational age (weeks)………………
21. Time of delivery …………

22. Time from admission to delivery (days)…………….. Or hours (if less than 24 hours)…………..

23. Live birth □   Still birth   □

24. Admitted to NBU   Yes □   No   □

25. If Yes, diagnosis…………………………………

26. Sex of infant: Males   □   Female   □

27. Apgar score at 5 minutes
< 7   □   >7-10   □

28. Birth weight (g)…………………

29. Birth length (cm) ……………………

30. Head circumference (cm)……………..

31. Umbilical cord haemoglobin:

32. Umbilical cord packed cell volume:

Part V: Follow up

MATERNAL COMPLICATIONS

Post-partum haemorrhage Yes   □   No   □

Post-partum anaemia Yes   □   No   □

Post partum sepsis   Yes   □   No   □

NEONATE COMPLICATIONS

Hyperbilirubinaemia   Yes   □   No   □

Polycythaemia   Yes   □   No   □

Neonatal sepsis   Yes   □   No   □

APPENDIX 4: DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan
Study Title: **THE EFFECT OF TIMING OF CORD CLAMPING ON NEONATAL AND HAEMATOCRIT VALUES AT TERM: AN RCT.**
Principal Investigator: Dr Carolyn Achieng' Aling'

MEMBERS
Prof. Wamalwa- Acting chairman Pediatric department, UON.
Prof. James Kiarie- WHO, coordinator Human reproductive health.
Dr. Rose Kosgei- Obstetrician and Epidemiologist
Francis Njiiri- Statistician
Dr. Gwako- Obstetrician

BRIEF STUDY OVERVIEW
Objective: To determine the effects of delayed umbilical cord clamping on haemoglobin and haematocrit level of term newborns.
Methodology: This will be a randomized controlled trial that will include mother-baby pairs at term who meet the selection criteria, 96 newborns will be randomized to delayed umbilical cord clamping (≥120 seconds after delivery as the experimental group) and 96 newborns will be randomized to early umbilical cord clamping (≤30 seconds after delivery as the control group) and their haemoglobin and haematocrit level determined.
OVERSIGHT RESPONSIBILITIES
Oversight of the trial is provided by the DSMB
Given the short duration of data collection, it has been agreed that an interim meeting will not take place if the interim data analysis is significant.
The DSMB members will have a first meeting before study is commenced.
A meeting will be constituted in case of any adverse event and a final meeting on conclusion of the study.
MONITORING PROCEDURES
Dr. Aling will ensure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the ERC-approved research plan.
Study data are accessible at all times for the PI to review. The PI will review study conduct every alternate day. I.e. acquisition of consent, any dropouts, completeness of questionnaire. The PI will review AEs individually real-time and in aggregate on a daily basis.
The PI will ensure all protocol deviations, AEs, and SAEs are reported to the DSMB, ERC and KNH administration according to the applicable regulatory requirements.
COLLECTION AND REPORTING OF SAEs AND AEs
For this study, the following standard AE definitions are used:
Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.
Serious Adverse Event: Any AE that results in any of the following outcomes:
- Death

- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

Mild: An experience that is transient, & requires no special treatment or intervention. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

MANAGEMENT OF RISKS TO SUBJECTS

Expected AEs

Expected AEs associated with the delayed cord clamping include:

MATERNAL- Postpartum haemorrhage (PPH)

NEONATAL- Respiratory symptoms, polycythaemia, hyperbilirubinaemia and need for phototherapy

AE Management

All adverse events will be reported to ERC within 24 hours.

Maternal AE: To prevent PPH, AMTSL with administration of IM oxytocin will be included in all deliveries, labour ward is also equipped with other uterotonics and a theatre incase PPH still occurs.

Midwives in labour ward are well trained to manage PPH.

Neonatal AE: The infant will be assessed at 1 and 6 hour mark by the midwife, who will record if the baby had been breastfed and the presence of respiratory symptoms, i.e. respiratory rate above 60, presence of nostril flaring, grunting or intercostal recession. Mothers will be informed of Jaundice and continuous phone follow ups done post discharge.

DATA ANALYSIS PLANS

The statistician will not be blinded and data monitoring will be continuous, he will alert the principal investigator of any overt differences in the two groups at the mid-point of data collection. The study will be halted if there is evidence of significant statistical advantage in whichever group, to avoid denying the corresponding group an advantageous intervention.

Incase of SAE, a report will be forwarded to ERC and study halted immediately pending clearance.

PLAN FOR DATA MANAGEMENT

Compliance of regulatory documents and study data accuracy and completeness will be maintained through the DSMB.

Confidentiality throughout the trial is maintained by assigning a code to each participant, for purposes of identification. The key, linking the patient to the identifying code will be stored separately from the research data, in a password-protected database. This will only be accessible to the principal investigator.

APPENDIX 5: CALL LOGS OF FOLLOWUP INTERVIEWS:

SERIAL NUMBER	Code number for mother-baby pair:	MOBILE NUMBER/ NEXT OF KIN NUMBER	(Day 3) Date: R= Reached NR= Not reached	(Day 7) Date: R=Reached NR=Not reached
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				