DELAYED CORD CLAMPING FOR THE REDUCTION OF INTRAVENTRICULAR HAEMORRHAGE IN LOW BIRTH WEIGHT INFANTS: A SYSTEMATIC REVIEW

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

Intraventricular haemorrhage is associated with neurological morbidity and mortality in low birth weight infants. In spite of improvements in treatment to reduce the incidence of the haemorrhage, the condition continues to remain a major cause of long term morbidity in low birth weight infants. The evidence from the literature has shown that low birth weight infants might benefit from delayed cord clamping particularly in reducing the risk of intraventricular haemorrhage and its neurological consequences.

The primary objective of this review was to assess the effects of delayed versus early cord clamping on intraventricular haemorrhage amongst low birth weight infants. The secondary objectives were to evaluate the effects of delayed versus early cord clamping on the Apgar scores, hyperbilirubinaemia and polycythaemia in infants.

The following electronic databases were searched: CINAHL, MEDLINE (searched via PubMed) and Cochrane Central Register of Controlled Trials (CENTRAL). Other information was gathered from the reference lists of retrieved articles and relevant experts. The selection criteria entailed all randomised controlled trials comparing delayed versus early cord clamping following birth in infants with low birth weight. Two reviewers independently extracted the data and assessed the quality of the trials. Disagreements on studies for inclusion were resolved by discussion with the third reviewer.

The review included five randomised controlled trials with 215 participants. The risk of intraventricular haemorrhage was significantly reduced in the delayed compared with early cord clamping (RR0.52, 95% CI 0.33 to 0.82, P=0.005). No statistically significant difference was shown between delayed versus early cord clamping for the risk of hyperbilirubinaemia (RR O.48, 95% CI -0.43 to 1.39, P=0.30). There

was no data available for other comparisons: Polycythaemia and Apgar scores.

There is growing evidence that delayed cord clamping might benefit low birth weight infants. In the included studies, delayed cord clamping for at least 30 seconds appear to have a potential in reducing the risk of intraventricular haemorrhage. The results of this review should however be interpreted with caution due to a limited number of studies with the absence of clinically important secondary outcomes in the included trials. Further research is required on large scale randomised controlled trials.

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OPSOMMING

Intraventrikulêre bloeding word geassosieer met neurologiese morbiditeit en mortaliteit in suigelinge met ’n lae geboortegewig. Ten spyte van die verbetering in die behandeling om die gevalle van bloeding te verminder, duur die toestand voort as ’n belangrike oorsaak van langtermyn morbiditeit in lae gewig geboortes. Bewyse uit die literatuur toon dat suigelinge met ’n lae geboortegewig voordeel mag trek uit vertraagde afklemming, veral deur die vermindering van die risiko van intraventrikulêre bloeding en die neurologiese gevolge daarvan.

Die primêre doelwit van hierdie navorsing was om die effek van vertraagde, versus vroeë afklemming op intraventrikulêre bloeding onder suigelinge met ’n lae geboortegewig te bepaal. Die sekondêre doelwit is om die effekte van vertraagde, versus vroeë afklemming op die Apgar uitslae, hiperbilirubinaemia en polisitaemia by suigelinge te evalueer.

Die volgende elektroniese databasisse is nagegaan: CINAHL, MEDLINE (soektog via PubMed); Cochrane Central Register of Controlled Trials (CENTRAL). Ander inligting is verkry uit die bronnelyste van nagevorsde artikels en van relevante deskundiges. Die seleksie kriteria behels alle ewekansige beheerde toetsing, insluitende toekomstige studies wat vertraagde, versus vroeë afklemming vergelyk by suigelinge met ’n lae geboortegewig. Twee resensente het onafhanklik data geneem en die kwalititeit van die toetse bepaal. Verskille oor insluiting van navorsing, is met ’n derde resensent deur middel van bespreking opgelos.

Die navorsing het vyf ewekansige beheerde steekproewe met 215 deelnemers ingesluit. Die risiko van intraventrikulêre bloeding is beduidend verminder in die vertraagde gevalle, in teenstelling met vroeë afklemming (RR0.52, 95% CI 0.33 tot 0.82, P=0.005). Geen

statistiese beduidende verskil is bewys tussen vertraagde teenoor vroeë afklemming ten opsigte van hiperbilirubinaemia nie (RR 0.48, 95% CI – 0.43 tot 1.39, P=0.30). Daar was geen data beskikbaar vir ander vergelykings nie: Polisytaemia en Apgar uitslae.

Daar is groeiende bewyse dat vertraagde afklemming lae geboortegewig suigelinge mag beïnvloed. Dit wil in die ingeslote studies voor kom dat vertraagde afklemming van ten minste 30 sekondes die potensiaal het om die risiko van intraventrikulêre bloeding te verminder. Die uitslae van hierdie beskouing sal nietemin met omsigtigheid geïnterpreteer moet word, weens die beperkte aantal studies met die afwesigheid van klinies belangrike sekondêre uitkomste in die ingeslote proewe. Verdere navorsing word benodig op grootskaalse ewekansige beheerde proewe.

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LIST OF ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CBF	Cerebral blood flow
C/S	Caesarean section
CT	Computed tomography
DCC	Delayed cord clamping
ECC	Early cord clamping
ELBW	Extremely low birth weight
FIGO	International Federation of Gynaecology and Obstetrics
G	Grams
ITT	Intention to treat analysis
ICM	International Confederation of Midwives
IVH	Intraventricular haemorrhage
KH	Kim Harper
KS	Kelebogile Seloka
LBW	Low birth weight
LOS	Late onset sepsis
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
OS	Oswell Khondowe
P	P-Value
PaCO2	Partial pressure of carbon dioxide
PaO2	Partial pressure of oxygen
PRCT	Packed red cell transfusion

PROM	Premature rupture of membranes
RBC	Red blood cells
RevMan	Review manager
ROP	Retinopathy of prematurity
RR	Risk ratio
RCT	Randomised controlled trial
SMD	Standardised mean difference
SNE	Suspected necrotising enterocolitis
VLBW	Very low birth weight
WHO	World Health Organisation
WMD	Weighted mean difference

CHAPTER 1: SCIENTIFIC FOUNDATION OF STUDY

1.1 INTRODUCTION: BACKGROUND AND RATIONALE

Clamping and cutting of the umbilical cord during birth is by far the oldest and most common interventions in humans (Hutton & Hassan, 2007:1241). Despite this, optimal cord clamping time remains controversial (Van Rheenen, 2011:127).

There has been concerns that umbilical cords are clamped too soon, depriving the neonate of blood that has a vital role in delivering oxygen to body tissues (Mercer & Skovgaard, 2002:56). There are no formal practice guidelines on cord clamping, but most practitioners in developed countries clamp and cut the cord immediately after birth (Hutton & Hassan, 2007:1241), while the practice in developing countries varies widely (Van Rheenen & Brabin, 2006:137).

There is no consensus about the definition of delayed and early cord clamping (Farrar, Tuffnell, Airey & Duley, 2010:23), therefore studies evaluating active management of the third stage of labour use a variety of definitions (Abalos, 2010). In this review, early cord clamping (ECC) refers to clamping of the cord within 30 seconds, while delayed cord clamping (DCC) means clamping done from 30 seconds and beyond, as stated in a Cochrane review (Rabe, Reynolds & Diaz-Rosello, 2004:2).

Mercer, Vohr, Erickson-Owens, Padbury and Oh (2010:11), state that a brief delay in cord clamping during birth leads to about 10 to 15 ml/kg of additional whole cord blood for the very low birth weight (VLBW) infant without placing the baby at increased risk. Studies found no risk of hyperbilirubinaemia, respiratory distress, the need for intensive care or increased length of stay in a hospital when clamping was delayed (Mercer et al., 2010:11). In a randomised controlled trial, it was found that delayed cord clamping significantly reduced intraventricular haemorrhage amongst low birth weight infants when compared to early cord clamping (Mercer, Vohr, McGrath, Padbury, Wallach, & Oh, 2006:1235).

Intraventricular haemorrhage is usually associated with neurological morbidity and mortality in low birth weight infants (Weintraub, Solovechick, Reichman,

Rothschild, Walsman, Davkin et al., 2001:13). The incidence of IVH is about 15-25% in infants delivered at less than 32 weeks of gestation and decrease with advancing gestational age (Riskin, Riskin-Mashiah, Bader, Kulgeman, Lerner-Geva, Boyko et al., 2008:21). In developing countries with higher overall perinatal and neonatal morbidity and mortality linked to neurological problems, the contribution of IVH to these higher rates have not been well defined, primarily because of the paucity of data (Ajayi & Nzeh, 2003:164). In South Africa, a trial conducted at Baragwanath Hospital to determine the prevalence of intraventricular haemorrhage among very low birth weight infants found that, 53% of newborns with weight less than 1500g and 52% of infants born at less than 35 weeks gestation had periventricular intraventricular haemorrhage (Sandler, 1994:26).

Even though there may be good reasons to practice DCC, it is very important to consider certain situations where this may not apply; for instance, in cases of foetal distress and infants with hydrops (Blackburn, 2007:247). According to Weeks (2007:313), there have been concerns that DCC may lead to an increased risk of hyperbilirubinaemia and polycythaemia. However, there have been no randomised controlled trials showing the risk of these harmful effects on the newborn (Cernadas, Carroli, Pellegrini, Otaño, Ferrira, Ricci et al., 2006:779). In a randomised controlled trial, polycythaemia and hyperbilirubinaemia experienced by neonates with DCC was found benign not requiring treatment by partial exchange transfusion or total exchange transfusion (Kulgeman, Borenstein-Levin, Riskin, Christyakov, Ohel, Gohen et al., 2007:307). There were no significant differences found between a DCC and ECC group when serum bilirubin levels were assessed in a study by Mercer et al., (2006:1235). Previous studies considered DCC safe and feasible in neonates (Mercer, McGrath, Hensman, Silver & Oh, 2003:466; Mercer et al., 2006:1235; Kulgeman et al., 2007:307).

1.2 DESCRIPTION OF THE CONDITION

Intraventricular haemorrhage (IVH) is an important cause of severe cognitive and motor neurological impairment in low birth weight infants (Linder, Haskin, Levit, Klinger, Prince, Naor et al., 2003:590). In spite of improvements in the assistance and treatment of low birth weight infants (Dani, Bertini, Pezzati, Poggi, Guerrini, Martano, et al., 2005:1529), intraventricular haemorrhage continues to remain a

major cause of long term morbidity in low birth weight neonates (Kumar, Nair, Pai, Gazal, Da Costa & Al Khusaiby, 2003:551).

Intraventricular haemorrhage originates in the germinal matrix, a very highly vascularised structure more susceptible region to IVH (Vural, Yilmaz, Illikkan, Erginoz & Perk, 2007:341). This periventricular region is selectively vulnerable to haemorrhage in low birth weight infants in the first 48 hours of life (Ballahb, 2010:1). A mild degree of haemorrhage may be asymptomatic or associated with seizure-like events, changes in muscle tone and apnoea (Merenstein & Gardner, 2006:807), while complications involve periventricular leucomalacia and post-haemorrhagic hydrocephalus (Keefe, Kafil-Hussain, Flitcroft & Lanigan, 2001:357).

1.3 DESCRIPTION OF THE INTERVENTION

The optimal timing of cord clamping of the umbilical cord in low birth weight infants at birth is the subject of continuing debate (Rabe, Reynolds & Diaz-Rossello, 2008:138). Cord clamping forms part of active management of the third stage of labour in addition to the use of uterotonics and controlled cord traction but the effects of umbilical cord clamping are unclear (Farrar et al., 2010:23).

Delayed cord clamping (DCC) refers to clamping done from 30 seconds and beyond (Rabe, Reynolds & Diaz-Rosello, 2004:2). A delay in cord clamping allows time for a transfer of the foetal blood in the placenta to the newborn (McDonald & Middleton, 2008:3). The volume and the duration of placental transfusion might be influenced by certain factors, other than timing of cord clamping, such as whether a uterotonic drug is administered before clamping; gravity, due to position of the infant relative to the level of placenta and the method of delivery such as vaginal versus caesarean section (Bimbashi et al., 2010:1; Hutchton, 2008:112; Rabe et al., 2004:2; Van Rheenen, 2007:603). For instance, Fraser et al., (2006:500) state that the use of uterotonics may increase placental transfusion as the effect of the drug can precipitate a strong uterine contraction.

1.4 HOW DELAYED CORD CLAMPING MIGHT WORK

In low birth weight infants, a brief delay in cord clamping leads to about 10 to 15 ml/kg of additional cord blood without placing the newborn at increased risk (Mercer et al., 2010:11). Thus, a delay in cord clamping facilitates transition from the foetal to the neonatal circulation due to an increased blood volume at birth (Airey, Farrar & Duley, 2010:3). The potential benefits of delayed cord clamping have been identified and they involve less intraventricular haemorrhaging, less need for blood transfusion, improvement in the blood pressure and cerebral oxygenation in infants (Mercer et al., 2003: 465; Baezinger, Stolkin, Keel, Von Siebenthal, Fauchere, Kundu et al., 2007:455). The additional blood volume received as a result of DCC would help to decrease neonatal morbidity by providing more blood volume and improving cardiovascular stability in the newborn (Mercer et al., 2006:1235).

1.5 WHY IS IT IMPORTANT TO DO THIS REVIEW?

The infants with low birth weight are highly susceptible to neurologically related problems including cranial haemorrhage. Previous studies conducted on the subject area have suggested that cord clamping might have an impact on the newborn. Consequently the researcher found the importance of conducting a research on umbilical cord clamping. The results of this review may in turn help to guide birth attendants on the best intervention and hence reduce the morbidity associated with cord clamping such as intraventricular haemorrhage. In addition, expectant women may find this trial useful when making birth plans.

1.6 PROBLEM STATEMENT

According to the literature against the background, delayed cord clamping has been shown to have a major health impact in low birth weight infants, particularly in reducing the risk of intraventricular haemorrhage among this vulnerable population of neonates. The need was identified to conduct a study comparing delayed and early cord clamping in infants with low birth weight in order to determine the best intervention which may help to reduce the incidence of intraventricular haemorrhage.

1.7 AIM

The aim of this review was to evaluate the effectiveness of delayed versus early cord clamping for the reduction of intraventricular haemorrhage in low birth weight infants.

1.8 OBJECTIVES

An objective is a concrete, measurable end towards which effort or ambition is directed (Brink, Van Der Walt & Van Rensburg, 2006:79). Research objectives are therefore known as clear, concise, declarative statements that are written in the present tense (Brink et al., 2006:79). The objectives for this review are as follows:

1. To compare the effects of delayed and early cord clamping on intraventricular haemorrhage amongst newborns with low birth weight.
2. To compare the Apgar scores in infants exposed to delayed versus early cord clamping.
3. To assess the risk of hyperbilirubinaemia and to identify reported cases of polycythaemia between infants with delayed versus early cord clamping.

1.9 HYPOTHESIS

A hypothesis is defined as a set of assumptions expressed in a logical manner about the observable phenomena (Brink et al., 2006:81; Freshwater & Maslin-Prothero, 2005:291). It is hypothesised that delayed cord clamping reduces the risk of intraventricular haemorrhage amongst low birth weight infants as compared to early cord clamping.

1.10 ETHICAL CONSIDERATION

The protocol for this review was approved by the Ethics Committee at Stellenbosch University (N11/03/091; 23/03/2011; See appendix 7.1). There were no actual human subjects involved in this review but rather, the data was obtained from only published peer reviewed articles for which ethical approval was granted.

1.11 DISSEMINATION OF RESULTS

A thesis was compiled and a copy sent to Stellenbosch University. The results will be presented at various health facilities, conferences and published in accredited journals.

1.12 STUDY LAYOUT

Chapter 1: Introduction; Scientific foundation of study

This section contains the introduction of the research and the rationale about the review.

Chapter 2: Literature review

Chapter 2 provides the reader with an in-depth knowledge about the topic.

Chapter 3: Research methodology

This chapter presents the research methodology used in the review.

Chapter 4: Results

The findings, data synthesis, interpretation and presentation of the results in the form of tables and figures are contained in this section.

Chapter 5: Discussion

In chapter 5 there is a conclusion and recommendations that are put forward, based on the main findings of the study.

1.13 OPERATIONAL DEFINITIONS

Allocation Concealment

In randomised controlled trials, the situation where the participant's assignment to the treatment or control group is not known to the investigator is known as allocation concealment (Rothstein, Sutton & Borenstein, 2005:347).

Anaemia

Anaemia is defined as either a haemoglobin concentration < 10g/dL or haematocrit level <46% and iron deficiency anaemia (defined as a haemoglobin concentration <11g/dL and ferritin concentration <10µg/L) (Hutton & Hassan, 2007: 1242).

Bias

A systematic error or deviation from the truth, in results or inferences (Higgins & Altman, 2008: 8.7).

Cochrane Collaboration

The Cochrane collaboration is an international network that aims to prepare, maintain and disseminate high-quality systematic reviews based on randomised controlled trials (RCTs) and when RCTs are not available, the best available evidence from other sources (Glasziou, Irwig, Bain & Colditz, 2001:118).

Continuous Data

This refers to data where each individual's outcome is a measurement of a numerical quantity (Higgins & Green, 2006:101).

Dichotomous Data

This is data where each individual's outcomes are one of only two possible categorical responses (Higgins & Green, 2006:101).

Heterogeneity

This is a reference to the researcher's attempt to obtain subjects with a wide variety of characteristics to reduce the risk of bias in studies not using random sampling (Burns & Grove, 2001:799).

Hyperbilirubinaemia

This refers to a raised level of bilirubin in the blood (Freshwater & Maslin-Prothero, 2005:313).

Intraventricular Haemorrhage

This refers to the medical terminology for bleeding into the ventricles of the brain (Whitelaw, People, Cherian, Evans & Thoresen, 2003:759).

Low Birth Weight Infants

Low birth weight (LBW) infants are those babies born weighing less than 2500g (<2500g); these are further subdivided into Very Low Birth Weight (VLBW): with a weight of less than 1500g (<1500g) and Extremely Low Birth Weight (ELBW): with birth weight less than 1000g (<1000g) (Farmer, Donders & Warschausky, 2006:62).

Meta-analysis

The statistical combination of results from two or more separate studies (Higgins & Green, 2006:97).

Risk Ratio

The Risk Ratio (RR) is defined as the probability of an event in the treatment group divided by the probability of an event in the control group (Sutton, Abrams, Jones, Sheldon & Song, 2000:23).

Placental Transfusion

The flow of blood from the placenta and cord to the baby at birth (Bimbashi, Ndoni, Dokle & Duley, 2010:1).

Polycythaemia

Polycythaemia is the condition in which an increased red blood cell mass, along with the shortened life span of these cells found in all newborns, results in an increased bilirubin load (with a central venous haematocrit value above 65) (Merenstein & Gardner, 2006:551).

Precision

Precision is a measure of the likelihood of chance effects leading to random errors (Higgins & Green, 2006:79).

Randomised Controlled Trial

An experimental comparison study in which participants are allocated to treatment / intervention or control / placebo groups using a random mechanism. Participants have an equal chance of being allocated to an intervention / or control group and, therefore, allocation bias is minimised and virtually eliminated in very large studies (Glasziou et al., 2001:124).

Systematic Review

Refers to a review of clinical literature in a particular field that has set explicit tests to determine whether an item of research is valuable enough to be included in an overview of the area (Freshwater & Maslin-Prothero, 2005:589).

1.14 CONCLUSION

Chapter 1 gives a brief introduction of the review. Some of the important aspects mentioned in this chapter involve the background of the research, the rationale, and the ethical considerations. The next chapter is a literature review about this review.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

A literature review is regarded as an organised written presentation of what has been published on a topic by scholars (Brink et al., 2006:67). A thorough examination of publications on the topic is vital to develop an understanding of a given area, to limit the scope of the study and to convey the importance of studying the topic (Brink et al., 2006:67). This section provides detailed information on important aspects of this review, such as cord clamping, intraventricular haemorrhage and low birth weight infants.

2.2 NEONATAL PHYSIOLOGY

2.2.1 Transitional events

The birth processes, as well as the transition from intra-uterine to extra-uterine life, are stressful events and demand considerable and effective physiological adaptations by the newborn in order to ensure survival (Fraser, Cooper & Nolte, 2006:693). There are three major changes that take place at birth; firstly, the fluid in the alveoli is reabsorbed, allowing diffusion of air into the surrounding blood vessels; secondly, because the umbilical arteries and vein are clamped, the low-resistance placental circuit is removed and systemic blood pressure increases; and thirdly, there is a reduced pulmonary vascular resistance as a result of mechanical distension of the alveoli and a rise in oxygen content in the alveoli (Merenstein & Gardner, 2006:80). Failure to make a normal transition to extra-uterine life may be a consequence of obstetric anaesthesia or analgesia, neonatal illness, or stress such as perinatal asphyxia and its sequelae (Merenstein & Gardner, 2006: 84).

According to Blackburn (2007:247), the main transitional event for the baby is the removal of the placental circulation with clamping of the umbilical cord. The author continues to state that timing of umbilical cord clamping influences the amount of placental transfusion and subsequent plasma and red blood cell (RBC) volume of the neonate.

At term, the total feto-placental volume is estimated to be about 120ml/kg of foetal weight (Rabe et al., 2004:2). Allowing 3 minutes delay in cord clamping result in a huge foetal blood volume of the ratio 4:1 (Van Rheenen & Brabin, 2004:3). In low birth weight infants, a brief delay in cord clamping leads to about 10 to 15 ml/kg of additional cord blood without placing the newborn at increased risk (Mercer et al., 2010:11). Early clamping of the cord (within 5 to 10 seconds of birth), compared with delayed clamping, results in a decrease to the infant of 20 to 40 ml of blood per kilogram of body weight (Hutton & Hassan, 2007:1241). Figure 1 illustrates the distribution of blood in the feto-placental compartment depending on the timing of cord clamping.

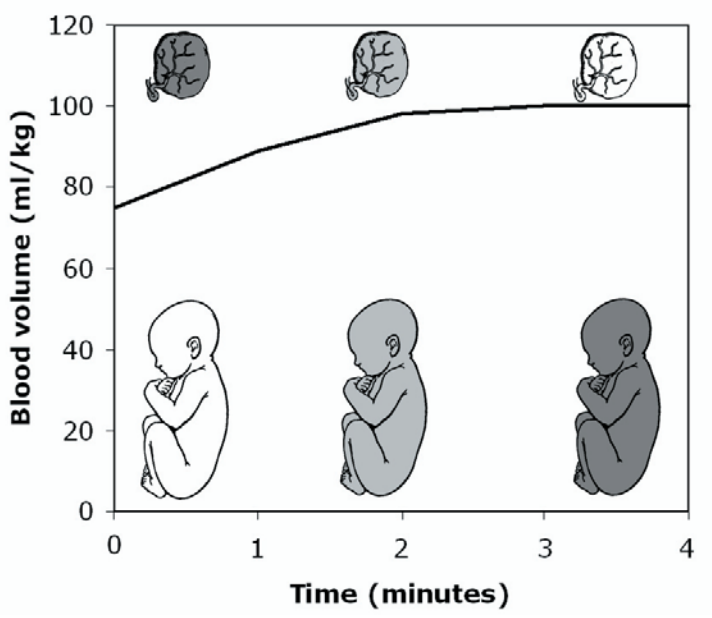


Figure 1: Distribution of blood in the feto-placental compartment depending on timing of cord clamping (Adapted from Van Rheenen, 2007: 603).

The volume and the duration of placental transfusion might be influenced by certain factors, other than timing of cord clamping, such as whether a uterotonic drug is administered before clamping; gravity, due to position of the infant relative to the level of placenta and the method of delivery such as vaginal versus caesarean section (Bimbashi et al., 2010:1; Hutchton, 2008:112; Rabe et al., 2004:2; Van Rheenen, 2007:603). For instance, Fraser et al., (2006:500) state that the use of uterotonics may increase placental transfusion as the effect of the drug can precipitate a strong uterine contraction. An infant held 50-60 cm above the placenta will receive none of the blood from the placenta; at 10 cm above or below the level of placenta the infant will receive most of the blood within 3

minutes of birth, while placing the infant 40 cm below the placenta, blood flow will hasten to almost completion within 1 minute (Van Rheenen, 2007: 603).

The timing of umbilical cord clamping and the magnitude of placental transfusion have physiological and clinical effects on various body systems (Blackburn, 2007:247). Numerous authors have clearly demonstrated the significance of these changes in infants and there have been concerns raised that cords are being clamped too early, depriving the newborn of blood that has a crucial role in opening the lungs, increasing pulmonary perfusion, enhancing lung fluid clearance and improving oxygen delivery to the baby's tissues (Mercer & Skovgaard, 2002:56). Delayed cord clamping has therefore, been shown to facilitate transition from the foetal to the neonatal circulation due to an increased blood volume at birth (Airey et al., 2010:3). Early cord clamping interferes with placental transfusion, which results in a decrease in blood volume at birth (Kulgeman et al., 2007:307).

2.3 THE EFFECTS OF DELAYED AND EARLY CORD CLAMPING ON INFANTS

The potential benefits of delayed cord clamping have been identified and they involve less intraventricular haemorrhage, less need for blood transfusion, improvement in the blood pressure and cerebral oxygenation in low birth weight neonates (Mercer et al., 2003:465; Baezinger et al., 2007:455). There is a concern that delayed cord clamping could result in polycythaemia and hyperbilirubinaemia (Ultee, van der Deure, Swart, Lasham & van der Baar, 2008:20).

Blackburn (2007:248), notes that it is vital to keep in mind that there are some situations in which it is advisable to perform early cord clamping. For instance, infants with hydrops are already overloaded with fluid and may not tolerate additional volume; during foetal distress there is also a greater than normal transfer of blood from the placenta to the foetus prior to delivery; infants at risk for polycythaemia, such as infants of diabetic mothers or severely growth restricted infants, severely asphyxiated infants, and in cases where resuscitative efforts need to be initiated without delay, early cord clamping may be warranted (Rabe et al., 2004:2; Blackburn, 2007:248).

2.4 ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOUR AND CORD CLAMPING

During the third stage of labour, which is from the birth of the baby to delivery of the placenta, women may be at risk of major haemorrhage, particularly if the uterus does not retract adequately or the placenta partially separates (Matar, Almarie, Alsabbagh, Jawoosh, Almerie, Abdulsalam & Duley, 2010:1). Active management of the third stage of labour is a package of care which aims to shorten the duration of the third stage of labour in order to minimise the risk of post-partum haemorrhage (Maughan, Heim & Galazka, 2006:1025). According to Bimbashi et al., (2010:1) traditionally, active management was defined as the administration of a prophylactic uterotonic drug, immediate clamping of the umbilical cord and cord traction. Early cord clamping has been associated with depriving the infant of the additional blood transfusion (Cernadas et al., 2006:779). Although the evidence is not yet conclusive on timing of cord clamping, several international agencies such as the World Health Organisation (WHO), the International Confederation of Midwives (ICM) and the International Federation of Gynaecology and Obstetrics (FIGO) now recommend deferring cord clamping for three minutes (Bimbashi et al., 2010:1).

2.5 INTRAVENTRICULAR HAEMORRHAGE IN THE NEONATE

2.5.1 Definition

Haemorrhage into the ventricles of the brain is one of the most complicated forms of intracranial haemorrhage in low birth weight infants (Whitelaw et al., 2003:759). A mild degree of haemorrhage may be asymptomatic or associated with seizure-like events, changes in muscle tone and apnoea (Merenstein & Gardner, 2006:807) while an extensive bleeding often presents as a catastrophic event on the second or third day of life and there is usually a preceding history of severe hypoxia related to foetal distress, asphyxia or apnoea (Harrison, Keet & Shore, 2001:164). The signs involve shock, pallor, abnormal eye movements, hypotonia and bulging fontanelle (Harrison et al., 2001:164). The important neurological complications associated with IVH are periventricular leucomalacia and post-haemorrhagic hydrocephalus (Keefe et al., 2001:357).

2.5.2 Incidence

In developed countries, IVH (of all grades in general) have a current rate of about 20% in very low birth weight (VLBW) infants while the few studies from developing countries have reported figures ranging from 50% both in South Africa and Hong Kong, to almost 100% in Malaysia (Ajayi & Nzeh, 2003:165). Intraventricular haemorrhage (IVH) is an important cause of severe cognitive and motor neurological impairment (Linder et al., 2003:590) and continues to remain a major cause of long term morbidity in low birth weight (LBW) infants (Kumar et al., 2003: 551). According to Farmer et al. (2006:62), babies born with LBW have a 6-8% incidence of these major handicaps; VLBW babies have a 14-17% incidence, whereas infants of extremely low birth weight (ELBW) have a 20-25% incidence. The prevalence of IVH increases progressively with decreasing gestational age, for instance, from 1.6% at 38-43 weeks up to 50% at 24-30 weeks of gestation (Keefe et al., 2001:357). Thus, IVH continues to be a major problem in premature infants in modern neonatal intensive care units (NICU) worldwide, particularly in newborns with extremely low birth weight (Ballabh, 2010:1).

2.5.3 Grades of intraventricular haemorrhage

IVH is graded (I-IV), according to the amount of blood in the ventricles and the degree of extension, with grades III and IV being regarded severe (Farmer et al., 2006:65). Grade IV involves intracerebral involvement or other parenchymal lesions and is thought to not be on a continuum, reflecting periventricular haemorrhagic infarction (Farmer et al., 2006:65). The three grades of germinal matrix-IVH using ultrasonographic scanning to identify the presence and extent of blood in the germinal matrix and lateral ventricles are shown in Table 1.

Table 1: Grading of severity of germinal matrix-intraventricular haemorrhage by ultrasound scanning (Adapted from Merenstein, 2006:802)

SEVERITY	DESCRIPTION
Grade I	Germinal matrix haemorrhage with no or minimal intraventricular haemorrhage (10% of ventricular area on parasagittal view)
Grade II	Intraventricular haemorrhage (10%-50% of ventricular area on parasagittal view)
Grade III	Intraventricular haemorrhage (greater than 50% of ventricular area on parasagittal view; usually distends lateral ventricle)

2.5.4 Neonatal risk factors in the pathogenesis of intraventricular haemorrhage

The pathogenesis of intraventricular haemorrhage is multifactorial and is primarily ascribed to: i) inherent fragility of the germinal matrix vasculature, ii) disturbance in the cerebral blood flow (CBF), and iii) platelet and coagulation disorders (Ballabh, 2010:1). Several factors, including underlying infection, chorioamnionitis, maternal hypertensive disorders such as eclampsia, vaginal delivery, spontaneous premature uterine contraction, premature rupture of membranes (PROM) and other factors predispose to the development of IVH (Riskin, Riskin-Mashiah, Bader, Kulgeman, Lerner-Geva & Boyko et al., 2008:26). These risk factors seem to induce IVH primarily by disturbing the CBF (Ballabh, 2010:1). The neonatal risk factors in the pathogenesis of intraventricular haemorrhage are illustrated in Table 2.

Table 2: Neonatal risk factors in the pathogenesis of IVH (Ballabh, 2010: 3)

Major pathogenic mechanism	Putative mechanism	Risk factors
1. Disturbance in Cerebral Blood Flow (CBF).	Fluctuation in CBF	Hypoxia, hypercarbia, severe acidosis, asynchrony between infants and ventilator breathe, severe respiratory distress syndrome (RDS), patent ductus arteriosus, frequent suctioning of the airway and rapid infusion of $NaHCO_3$
	High cerebral venous pressure	Pneumothorax, high ventilator pressure, prolonged labour and vaginal delivery
	Abnormal blood pressure	Hypotension, hypertension, sepsis or dehydration
	Pressure-passive circulation	Extreme prematurity and low birth weight (< 1000g) or Clinically unstable resulting from (respiratory compromise, sepsis, or other reasons)
2. Inherent fragility of the germinal matrix vasculature	Might be worsened by an inflammatory injury to the blood-brain barrier	Hypoxic ischaemic insult and sepsis
3. Platelet and coagulation disturbances	Haemostatic failure.	Thrombocytopaenia and disseminated intravascular coagulopathy

2.5.5 Diagnostic tests

These tests are done because there are no clinical signs that are specific for IVH, the diagnosis is invariably made by non-invasive cranial imaging (Fanaroff & Martin, 2002: 883).

2.5.5.1 Cranial Ultrasound

Ultrasonography is considered the most reliable and safest technique for diagnosis of IVH (Avery, Fletcher & MacDonald, 1999:459). The main advantage of ultrasound when compared with other imaging techniques is its portability, which permits evaluation at the infant's bedside (Fanaroff & Martin, 2002:883).

2.5.5.2 Other tests

Computed Tomography [CT] (Fanaroff & Martin, 2002:883) and Magnetic Resonance Imaging [MRI] (McCrea & Ment, 2006:1) are some of the tools which could be used for diagnosis. However, ultrasonography is the most recommended since it does not use any radiation as well as the fact that the infant does not need to be transported (Merenstein & Gardner 2006:805).

2.5.6 Interventions in the prevention and management of intraventricular haemorrhage

In developing countries, where well equipped neonatal intensive care units (NICU) are inadequate, the prevention of prematurity (Vural et al., 2007:341), improvements in antenatal, labour and delivery and immediate newborn care, such as the provision of basic resuscitation equipments and skills to midwives, may reduce the incidence and the severity of IVH (Ajayi & Nzeh, 2003:164).

In terms of antenatal care, a study was conducted to examine the relationship between grade III and IV intraventricular haemorrhage and antenatal exposure to tocolytic treatment in VLBW premature infants, and it was found that, ritodrine tocolysis was associated with lower incidence of grade III-IV intraventricular haemorrhage, as compared to tocolysis induced by magnesium sulphate or indomethacin (Weintraub et al., 2001:13). Vural et al. (2007:341), notes that maternal corticosteroid administration has also been found to be protective in the development of IVH.

The two primary goals in the management of infants who have sustained IVH are the maintenance of adequate perfusion, pressure and ventilation, and efforts should

be made to maintain normal PaO_2, $PaCO_2$, pH and osmolality (Fanaroff & Martin, 2002:884).

The immediate management of IVH in infants includes stabilization of the cardiovascular system, correction of any bleeding diathesis, if present; careful monitoring of hyperbilirubinaemia and hyperkalaemia (Avery et al., 1999:459). The cranial ultrasounds, careful neurologic examination, and serial measurements of head circumference should be performed to allow early detection of hydrocephalus (Avery et al., 1999:459). If progressive ventricular dilatation is present, intervention with daily serial punctures or drugs that reduce the cerebral spinal fluid (CSF) production such as acetazolamide and furosemide are warranted (Fanaroff & Martin, 2002:884). In a situation where there is rapid, progressive ventricular dilatation or if dilatation progresses despite treatment, surgical ventricular drainage may be considered (Avery et al., 1999:459; Fanaroff & Martin, 2002:884).

2.6 POLYCYTHAEMIA

Polycythaemia is known as a venous haematocrit above 65% (Sankara, Agarwal, Deodari & Paul, 2010:1). It is the condition in which an increased red blood cell mass, along with the shortened life span of these cells found in all newborns, results in a raised level of bilirubin (Merenstein & Gardner, 2006:551). Polycythaemia may be idiopathic or may occur as a result of a maternal-foetal transfusion, chronic in-utero hypoxia or delayed clamping of the cord at the time of delivery, babies who are very small for dates (usually less than 3rd percentile), infants of diabetic mothers, and the recipient twin in the twin-to-twin transfusion syndrome (Sankara et al., 2010:2; Merenstein & Gardner, 2006:551).

2.7 HYPERBILIRUBINAEMIA

Hyperbilirubinaemia is described as an excessive level of accumulated bilirubin in the blood and is characterised by jaundice or icterus, a yellowish discoloration of the skin and other organs (Wong, Hockenberry, Wilson, Winkelstein & Kline, 2003:303). Hyperbilirubinaemia is common in the neonate and usually temporary and benign (Jones, 2011:19). However, in extreme cases, it can indicate a pathologic state (Wong et al., 2003:303).

Hyperbilirubinaemia in a newborn becomes apparent at 85 to 120 mmol/l (1 mg/dl of bilirubin = [17mmol/l] (Coovadia & Wittenberg, 2002:135). The measurements for bilirubin need to be interpreted based on the infant's age in hours at the time of measurement and allow classification of bilirubin levels into high risk, high intermediate risk, low intermediate risk and low risk zones (Mishra, Argawal, Deorari & Paul, 2007:12).

The risk factors for hyperbilirubinaemia in the newborn include isoimmunisation (primarily Rh) and ABO blood group incompatibility, ethnic variation and geographic location (Wong et al., 2003:310). The complications associated with the condition involve bilirubin encephalopathy and kernicterus (Merenstein & Gardner, 2006:564).

2.7.1 Treatment of hyperbilirubinaemia

Phototherapy and exchange transfusions are widely used in the treatment of hyperbilirubinaemia and the treatment is aimed at preventing the complications of acute bilirubin encephalopathy [the acute manifestations of bilirubin toxicity seen in the first few weeks of life] and kernicterus [the chronic and permanent clinical sequelae of bilirubin toxicity] (Merenstein & Gardner, 2006: 556). Table 3 indicates the guidelines for the management of hyperbilirubinaemia.

Table 3: Guidelines for the management of hyperbilirubinaemia (Coovadia & Wittenberg, 2002:138)

Serum Bilirubin Mmol/l	<24 hrs		24-48hrs		49-72hrs		>72hrs	
	<2500g	>2500g	<2500g	>2500g	<2500g	>2500g	<2500g	>2500g
<85								
85-150	Phototherapy if haemolysis							
170-240	Exchange if haemolysis		< < < < < < < < < phototherapy > > > > > > > > >					

250-320	< < < < < Exchange > > > > >	< < < < < Phototherapy > > > > >
>=340	< < < < < < < < < < < < < < < Exchange > > > > > > > > > > > > > > >	

2.8 APGAR SCORE

Apgar score is defined as the numerical expression of a newborn infant's well-being and ability to survive; it consists of the sum of points from zero to ten, based on five signs ranked in order of importance, with assessments being at one minute and five minutes after birth (Freshwater, & Maslin-Prothero, 2005:46). The five items to determine the baby's Apgar score comprise of the heart rate, respiratory effort, muscle tone, reflex irritability and colour (European Perinatal Health Report, 2008:133).

2.9 CONCLUSION

Recently there has been emerging evidence from various studies which indicate that infants with low birth weight can benefit from delayed cord clamping, particularly in reducing the risk of IVH and its neurological consequences. Intraventricular haemorrhage has been identified as a major complication amongst low birth weight infants and the interventions to manage the disorder within this vulnerable population remain complex. The evidence is not yet conclusive on timing of the umbilical cord clamping. Further research is required to come up with strategies that can be implemented to reduce the incidence of IVH in low birth weight infants.

CHAPTER 3: RESEARCH METHODS

3.1 INTRODUCTION

This section of a research report describes how the study was conducted and it usually includes the study design, treatment (if appropriate), study sample, setting, instruments, methods of measurement and data collection process (Burns & Grove, 2007:47).

3.2 AIM

The aim of this review was to evaluate the effectiveness of delayed versus early cord clamping for the reduction of intraventricular haemorrhage in low birth weight infants.

3.3 OBJECTIVES

3.3.1 Primary objective

1. To compare the effects of delayed versus early cord clamping on intraventricular haemorrhage amongst newborns with low birth weight.

3.3.2 Secondary objectives

1. To compare the Apgar scores in infants exposed to delayed versus early cord clamping.
2. To assess the risk of hyperbilirubinaemia and to identify reported cases of polycythaemia between infants with delayed versus early cord clamping.

3.4 HYPOTHESIS

It is hypothesised that delayed cord clamping reduces the risk of intraventricular haemorrhage amongst low birth weight infants as compared to early cord clamping.

3.5 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

3.5.1 Types of studies

Randomised Controlled Trials (RCTs) either blinded or unmasked.

3.5.2 Types of participants

Infants with low birth weight (<2500g), born either vaginally or through caesarean section regardless of gestational age.

3.5.3 Types of interventions

- Delayed versus early cord clamping (DCC is the intervention while ECC the control group)
- DCC should be defined as from 30 seconds or beyond, while the time range for ECC should be clamping of the cord in less than 30 seconds after birth.
- Various birth practices based on the position of the newborn in relation to the level of the placenta, milking of the cord towards the infant or the use of uterotonics in mothers during birth were considered for inclusion.

3.5.4 Types of outcome measures

The outcome measures for this review are outlined below:

a). Primary outcome measure

- Intraventricular haemorrhage of all grades (i, ii, iii and iv) - (Cranial Ultrasound)

b). Secondary outcome measures

- Apgar score > 7 from the 5^{th} minute and/or beyond.
- The risk of Hyperbilirubinaemia- (Maximum serum bilirubin mg/dl).
- Reported cases of polycythaemia as defined by trial authors.

3.6 EXCLUSION

- Trials that included women with multiple pregnancies.

- Studies that did not mention at least one of the outcomes of interest for this review.
- Non- randomised studies including observational or cohort studies
- Timing of cord clamping not the same as that pre-specified in a protocol of this review.
- Failure to locate potential articles.

3.7 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

3.7.1 Electronic search strategy

An extensive search was done to identify relevant studies for this review. The data was searched from PubMED (inception to March 2011), COCHRANE Register of controlled trials (inception to March 2011) and CINAHL from inception to March 2011. The search was conducted between January 2011 to March 2011.

The following Medical Subject Headings (MeSH terms) were used to obtain the relevant studies: Delayed cord clamping, early cord clamping, infants, newborns, neonates, cord clamping, low birth weight infants, intraventricular haemorrhage, Apgar score, polycythaemia and randomised controlled trials.

The search strategy for PubMed was as follows:
(cord clamp*) AND (delayed OR early) AND (newborn OR neonate); (cord clamp*) AND (delayed OR early) AND newborn* AND Apgar score or Polycythaemia or hyperbilirubinaemia; Delayed cord clamping AND intraventricular (haemorrhage OR hemorrhage)) AND (low birth weight) (infant OR newborn OR neonate)) AND randomised controlled trials AND cord clamping.

The search strategy for CINAHL was as follows:
(cord clamp*) AND (delayed OR early) AND (newborn OR neonate); (cord clamp*) AND (delayed OR early) AND newborn* AND Apgar score or Polycythaemia or hyperbilirubinaemia; Delayed cord clamping AND intraventricular (haemorrhage OR hemorrhage)) AND (low birth weight) (infant OR newborn OR neonate)) AND randomised controlled trials AND cord clamping.

The following search strategy was used to search COCHRANE register of controlled trials:

#1 Delayed cord clamping*
#2 Early cord clamping
#3 Intraventricular haemorrhage*
#4 Infants*
#5 Newborn or neonate*
#6 Apgar score
#7 Polycythaemia
#8 Hyperbilirubinaemia
#9 Controlled trials
#10 Randomised controlled trials
#11 Cord clamping
#12 Low birth weight
#13 (# 1 and #3) and #9
#14 Cord clamp
#15 ((# 10 or # 9) and #1
#16 (#12 and #4) and #11)

3.7.2 Searching other resources

The reference lists and links from identified articles were retrieved to identify additional reports. Several articles related to the review were obtained from the experts in the field of paediatrics, obstetrics and nursing (see appendix 7.6). Relevant Conference proceedings were not found during the search.

3.8 DATA COLLECTION AND ANALYSIS

3.8.1 Selection of studies

The two assessors KS and OK screened the titles searched. The titles that were irrelevant were not retrieved and those that were found relevant identified. The abstracts were then retrieved for potential eligible articles in the review. Full texts were retrieved for further evaluation and for closer examination. The assessors determined whether the studies met the criteria or were not eligible for inclusion. A

standardised data extraction form from the Cochrane collaboration which was first modified to suit this review was used to assess potential studies for inclusion (see appendix 7.3). Any disagreements were resolved through discussion with the third reviewer KH.

3.8.2 Data extraction and management

A template of data extraction form from the Cochrane collaboration was obtained and modified in order to suit this review (see appendix 7.3). The form included data such as the citation of the report, type of study, trial characteristics, study design used, outcome measures and characteristics of participants.

The two independent reviewers OK and KS extracted the data. The data was double checked for accuracy and entered in the review manager (RevMan 5.1, 2011) for analysis. Discrepancies were resolved through discussion and when necessary the third reviewer, KH was consulted for an opinion.

3.8.3 Assessment of risk of bias in included studies

The studies that met inclusion criteria were assessed for methodological quality based on a standard tool for assessing risk of bias from the Cochrane collaboration. The guidelines were obtained from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2008). The review authors made a judgement about the risk of bias from each of the six domains in the tool namely: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting and other sources of bias. The reviewers' judgements involved answering a certain question for each entry. In all cases, an answer 'low risk of bias', 'high risk of bias' or 'unclear' (unknown risk of bias) were indicated depending on a judgement by assessors. The following domains were addressed and presented in figures 4.1 and 4.2.

1. Sequence generation (Selection bias): Sequence generation was assessed as 'Low risk', 'High risk' or 'UNCLEAR' as follows:

Low risk of bias- e.g. using computer random number generator; shuffling cards or envelopes.

High risk- e.g. sequence generated by date of birth or clinic record number.
Unclear risk- insufficient information to permit either ‘High risk’ or ‘Low risk’.

2. Allocation concealment (Selection bias): Allocation concealment was assessed as ‘Low risk’, ‘High risk’ or ‘UNCLEAR’ as follows:
Low risk of bias- e.g. sequentially numbered opaque sealed envelopes.
High risk- e.g. envelopes unsealed or non-opaque; alternation or rotation.
Unclear risk- insufficient information to permit either ‘Low risk’ or ‘High risk.’

3. Blinding (Performance and detection bias): Blinding was assessed as ‘Low risk’, ‘High risk’ or ‘UNCLEAR’ as follows:
Low risk of bias- e.g. blinding of key study personnel.
High risk of bias- e.g. the outcome or outcome measurements likely to be influenced by lack of blinding.
Unclear risk- e.g. insufficient information to permit either ‘Low risk’ or ‘High risk’.
Blinding of participants and personnel was assessed separately from blinding of outcome assessors.

4. Incomplete outcome data (Attrition bias): Incomplete outcome data was assessed as ‘Low risk’, ‘High risk’ or ‘UNCLEAR’ as follows:
Low risk of bias- e.g. no missing outcome data; missing data has been imputed using appropriate methods.
High risk of bias- e.g. reason for missing outcome data likely to be related to the outcome or attrition rate more than 15% .
Unclear risk- e.g. insufficient information to permit either ‘Low risk’ or ‘High risk’.

5. Selective outcome reporting: Incomplete outcome data was assessed as ‘Low risk’, ‘High risk’ or ‘UNCLEAR’ as follows:
Low risk of bias- e.g. the study protocols available and all pre-specified (primary and secondary) outcomes that are of interest in the study have been reported in the pre-specified way.
High risk of bias- e.g. the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Unclear risk- e.g. insufficient information to permit either ‘Low risk’ or ‘High risk.’

6. Other potential threats (bias): Other potential threats were assessed as 'Low risk', 'High risk' or 'UNCLEAR' as follows:
Low risk of bias- e.g. the study appears to be free of other risks of bias.
High risk of bias- e.g. study had potential source of bias related to the specific study design or other problems.
Unclear risk- e.g. insufficient information to permit either 'Low risk' or 'High risk.'

3.8.4 Measures of treatment effect

The effect measure of treatment for dichotomous data was presented as summary risk ratio (RR) with a 95% confidence interval (CI). For continuous data, a weighted mean difference (WMD) was used when outcome measurements across studies were made on the same scale. The standard mean difference (SMD) would have been used to combine data where studies measured the same outcome but used different methods.

The fixed effect analysis was used for combining data. There was no substantial heterogeneity observed in the meta-analysis. A fixed effect meta-analysis is performed if it is assumed that each study is estimating exactly the same quantity (Higgins & Green, 2006:127).

3.8.5 Unit of analysis issues

All randomised controlled trials with subjects randomised to either a control or a treatment group.

3.8.6 Dealing with missing data

To deal with missing data, attempts were made to contact trial authors. Where the information could not be obtained, the studies with an attrition rate of more than 15% and which were likely to affect the overall quality of the results were to be excluded from the meta-analysis.

In the meta-analysis, an intention to treat (ITT) analysis was performed if in the original articles, participants were not analysed in the group to which they were

randomised. With available data the participants were restored in the group to which they were allocated, in spite of whether or not they received the allocated intervention.

3.8.7 Assessment of heterogeneity

To assess statistical heterogeneity in each meta-analysis, a chi² and I² were used. Heterogeneity was considered substantial when I² was greater than 30% or when in the chi² there was a low p-value (less than 0.10). If there was significant heterogeneity, a possible cause (for example, the differences in study participants or intervention) was to be explored by a subgroup analysis. In the analysis, a fixed effect model was used with a 95% confidence due to insignificant heterogeneity between studies when the data was pooled.

3.8.8 Assessment of reporting biases

When reporting bias was suspected, the trial authors were contacted asking them to provide missing outcome data. If this was not possible, and the missing data were thought to introduce serious bias, the impact of including such studies in the overall assessment of results was explored by a sensitivity analysis.

3.8.9 Data synthesis

The data was entered in review manager software (RevMan 5.1, 2011) for analysis and checked for accuracy. The fixed effect model was used for all meta-analysis. For dichotomous data the risk ratio (RR) with a 95% confidence interval was calculated. For continuous data, a weighted mean difference (WMD) was used when outcome measurements across studies were made on the same scale. For trials that used different methods to measure the same outcome, standard mean difference (SMD) would have been used. A p-value less than 0.05 (<0.05) was considered significant in the meta-analysis.

3.8.10 Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned on the following:

1. Very low birth weight (<1500g).
2. Extremely low birth weight infants (<1000g).

A subgroup analysis could not be performed due to lack of data on the above outcomes.

3.8.11 Sensitivity analysis

A sensitivity analysis was performed by including two studies with adequate sequence generation, allocation concealment and an attrition rate below 15% (Mercer 2003; Mercer 2006). There were no differences in the overall direction of the findings. Funnel plots could not be done due to few included studies.

Funnel plots are not useful if the number of trials is less than ten (Higgins & Green, 2006:214).

3.9 ETHICAL CONSIDERATION

The protocol was first sent through an Ethics Committee at the University of Stellenbosch for approval before the research was conducted. The review was exempted from ethical review since it does not involve any actual human participants but only relies on peer reviewed published studies. However, permission was granted to proceed with the research (N11/03/091; 23/03/2011; See appendix 7.1)

3.10 DISSEMINATION OF RESULTS

A thesis was finally compiled and submitted at the University of Stellenbosch. The results will be presented in various health facilities, conferences and published in accredited journals.

3.11 CONCLUSION

This chapter discussed steps followed and methods used to conduct the review.

CHAPTER 4: RESULTS

4.1 INTRODUCTION

Data analysis is conducted to reduce, organise and give meaning to the data (Burns & Grove, 2007:41). According to Brink et al., 2006:171), the most powerful tool available to the researcher in analysing quantitative data is statistics; statistical methods enable the researcher to manipulate, evaluate, interpret and communicate quantitative data.

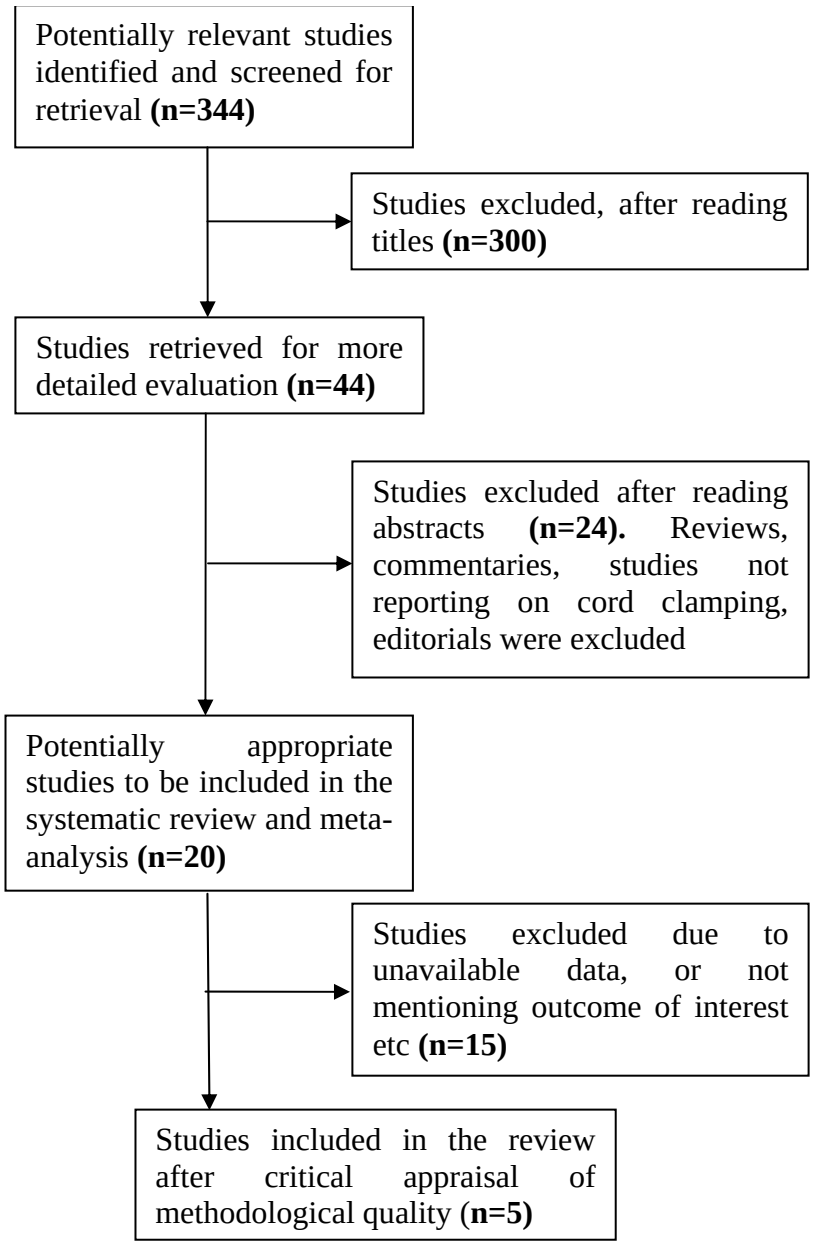
4.2 DESCRIPTION OF STUDIES

See: characteristics of studies; characteristics of included studies (appendix 7.5) and characteristics of excluded studies (appendix 7.2).

4.2.1 Results of the search

A search was done from PubMed, CINAHL, and COCHRANE Register of Controlled Trials (CENTRAL) and other sources such as reference lists which provided additional information. Potentially relevant citations were identified and screened for retrieval (n=344). Irrelevant studies (n=300) were then excluded after reading titles. A total of (n=44) studies were retrieved for further evaluation. Studies that did not report on cord clamping, the reviews, editorials, duplicates and comments (n=24) were excluded after reading the abstracts. The full texts of studies with the potential for inclusion in the review were retrieved for closer examination (n=20). A total of (n=15) studies were then excluded due to some reasons such as none of outcome of interest not being reported, study designs, or unavailable data (see appendix 7.2 for reasons of exclusion). Studies included in the review were (n=5) in total after critical appraisal of methodological quality. The included studies were published between the years 1988-2006. A flow diagram below in figure 2 illustrates the study selection process.

Figure 2: A flow diagram of study selection process



4.2.2 Included studies

This section outlines the included studies in table 4 and describes the characteristics of included trials.

Table 4: Studies included in this review

Study ID	Citation
Hofmeyr, 1988	Hofmeyr, G.J., Bolton, K.D., Bowen, D.C. & Govan, J.J. 1988. Periventricular / Intraventricular haemorrhage and umbilical cord clamping: Findings and hypothesis, *South African Medical Journal*, 73:104-106.

Mercer, 2003	Mercer, J.S., McGrath, M.M., Hensman, A., Silver, H. & Oh, W. 2003. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: A pilot randomized controlled trial. *Journal of Perinatology*, 23:466-472.
Mercer, 2006	Mercer, J.S., Vohr, B.R., McGrath, M.M., Padbury, J.F., Wallach, M. & Oh, W. 2006. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular haemorrhage and late-onset sepsis: A randomized, controlled trial. *Pediatrics*, 117:1235-1242.
Oh, 2011	Oh, W., Fanaroff, A.A., Carlo, W.A., Donovan, E.F., McDonald, S.A. & Poole, W.K. 2011. Effects of delayed cord clamping in very-low-birth-weight infants. *Journal of Perinatology*, 31:68-71.
Rabe, 2000	Rabe, H., Wacker, A., Hülskamp, G., Hönig-Franz, I., Schulze-Everding, A., Cirkel, U., Louwen, F., Witteler, R. & Schneider, H.P.G.2000. A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. *European Journal of Pediatrics*, 159:775-777.

The characteristics of included studies are discussed below according to the; study design used, participants, outcomes, sample size and settings where the trials were conducted. See appendix 7.5 for a summary of characteristics of included studies.

4.2.2.1 Study Design

All the included studies were randomised controlled trials (Hofmeyr 1988; Mercer 2003; Mercer 2006; Oh, 2011; Rabe, 2000). Another study was a pilot prospective randomised controlled trial (Mercer, 2003). The study was considered for inclusion due to the methodological quality identified by the reviewers and for being published in accredited journals.

4.2.2.2 Participants

The 5 trials which were all conducted as single-centre studies recruited pregnant women with singleton pregnancies with gestational ages between 24 and 34 weeks. The infants' weights for the infants across studies were less than 2500g.

4.2.2.3 Sample size and settings

The total number of participants combined from all the included studies was 215 infants. The studies were relatively small in general with sample sizes between 72 and 32 in individual studies. The trials were conducted in three different countries including USA (Mercer, 2003; Mercer, 2006; Oh, 2011), Germany (Rabe, 2000) and South Africa (Hofmeyr, 1988).

4.2.2.4 Outcome measures

The primary outcome of interest for this review (intraventricular haemorrhage) was reported in all the studies. All trials reported on Apgar score while two trials reported on hyperbilirubinaemia (Mercer 2003; Mercer 2006). No data was available on polycythaemia from the included studies.

4.2.2.5 Interventions

The infants were delivered either vaginally or through caesarean section (C/S) in the trials. The outcome data for infants delivered by caesarean section were not reported separately from those born vaginally across the studies. In all studies included, delayed cord clamping (DCC) occurred 30 seconds after birth or beyond while early cord clamping (ECC) was done within 30 seconds (Hofmeyr, 1988; Mercer, 2003; Mercer, 2006; Oh, 2011; Rabe, 2000). However, in one study the timing of ECC was not specified but defined as clamping of cord immediately after birth (Hofmeyr, 1988). In the majority of the studies, DCC lasted for 45 seconds while ECC occurred within 10 seconds.

The level of the infant in relation to the placenta was the same in the majority of studies (Mercer, 2003; Mercer, 2006; Oh, 2011; Rabe, 2000). The infant was placed below the placenta or the birth canal at birth or below the level of the incision at birth. The use of uterotonics was reported in two studies. In one study (Mercer, 2003), uterotonics were only administered after cord clamping while in the other trial (Rabe, 2000) the uterotonics were administered during birth (after delivery of the first shoulder) before cord clamping to enhance placento-foetal transfusion by uterine contraction (confounding factor).

The use of prophylaxis (confounding factor) for intraventricular haemorrhage was reported in two studies (Hofmeyr, 1988; Mercer, 2006). Indomethacin was administered within the first 24 hours of birth to all infants born between 24 and 27 weeks as a prophylaxis for IVH (Mercer, 2006). In the other study (Hofmeyr, 1988) in which participants were randomised to three arms (2 groups of DCC and 1 group of ECC), a prophylaxis Ergometrine was administered at delivery in the other arm of DCC. From the results reported, there was no 'strong' evidence on the incidence of IVH between the participants with or without Ergometrine due to one trial and as a result, the data from the two arms of DCC were analysed together.

4.3 EXCLUDED STUDIES

A total of 39 studies were excluded after retrieving full texts. Articles, duplicates, editorials, comments, reviews or studies that were irrelevant were discarded (n=25). The following articles (n=15) were excluded after further evaluation and assessment for possible inclusion due to the following reasons: Absence of outcome of interest (n=2) (Aladangy, 2006; Baezinger, 2007), infants with birth weight more than 2500g (n=5) (Cerdanas, 2006; Oh, 1967; Saigal, 1972; Shohat, 1984; Yao, 1971), the study included multiple pregnancies n=1 (Grajeda, 1997), data not available n=1 (Hofmeyr, 1993), timing of cord clamping varied with that of the protocol for this review n=2 (Ibrahim, 2000; Kinmond, 1993), there was no comparison between delayed and early cord clamping n=2 (Linder, 2003; Ramamurthy, 1981), a study reported on toddlers n=1 (Mercer, 2010), participants defined in terms of gestational age with no birth weight provided n=1 (Strauss, 2008). See reasons for excluded studies in appendix 7.2.

4.4 RISK OF BIAS IN INCLUDED STUDIES

To assess the risk of bias, the reviewers used the Cochrane handbook of systematic reviews (Higgins & Altman, 2008). The third assessor KH was consulted for any discrepancies that could not be resolved.

In the included studies, 2 trials were considered having low risk of bias in the main aspects of sequence generation, allocation concealment and completeness of data

collection (Mercer, 2003; Mercer, 2006), this being the criteria for the overall quality for sensitivity analysis. One study was considered at high risk of bias for sequence generation (Oh, 2011). The other study was assessed to be unclear for both sequence generation and allocation concealment although completeness of data, blinding and selective reporting seemed acceptable (Hofmeyr, 1988). One study was considered as unclear for sequence generation (Rabe, 2000). All the included studies were assessed as having unclear for other bias due to the unknown risk of bias. Figures 4.1 and 4.2 indicate assessors' judgements about included studies. See also appendix 7.4 for reasons of judgement given for each study.

A risk of bias graph in figure 3 presents the proportion of studies of the judgement by assessors. A risk of bias summary in figure 4 illustrates all the judgements in a cross-tabulation for each study.

Figure 3: Methodological quality graphs: judgements about each methodological quality item presented as percentages across all included studies.

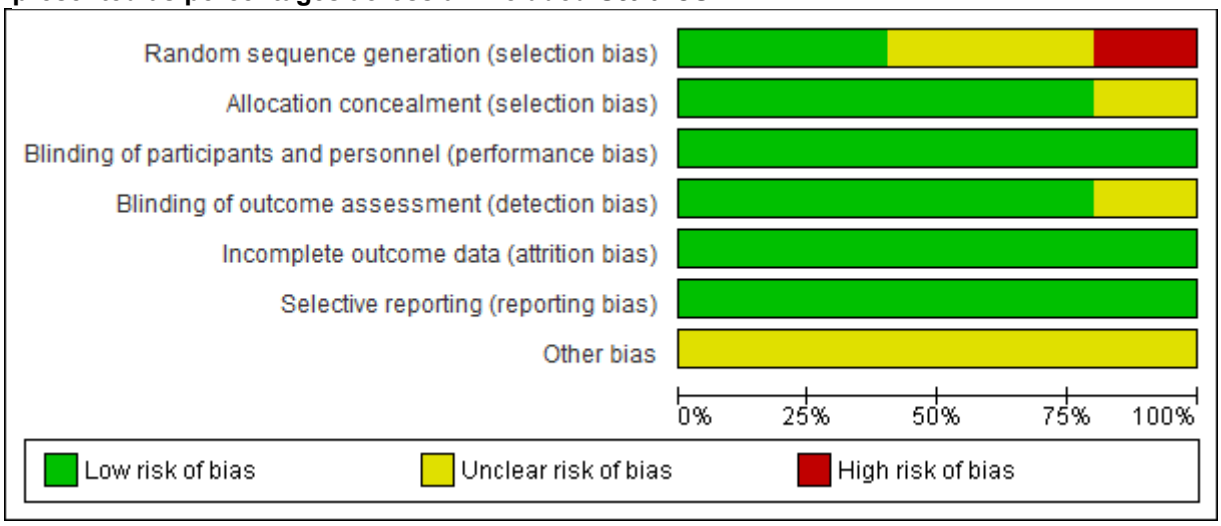
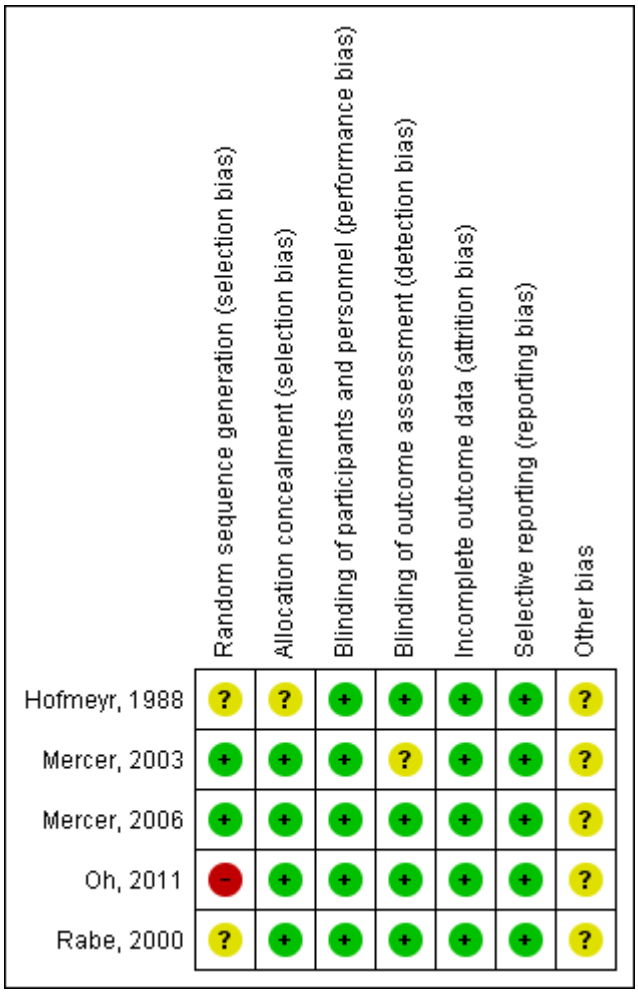


Figure 4: Methodological quality summary: judgements by review authors about each methodological quality item for each included study



4.5 EFFECTS OF INTERVENTION

4.5.1 Comparison 1: The effects of delayed cord clamping compared to early cord clamping on Intraventricular haemorrhage

4.5.1.1 Outcome: Intraventricular haemorrhage of all grades

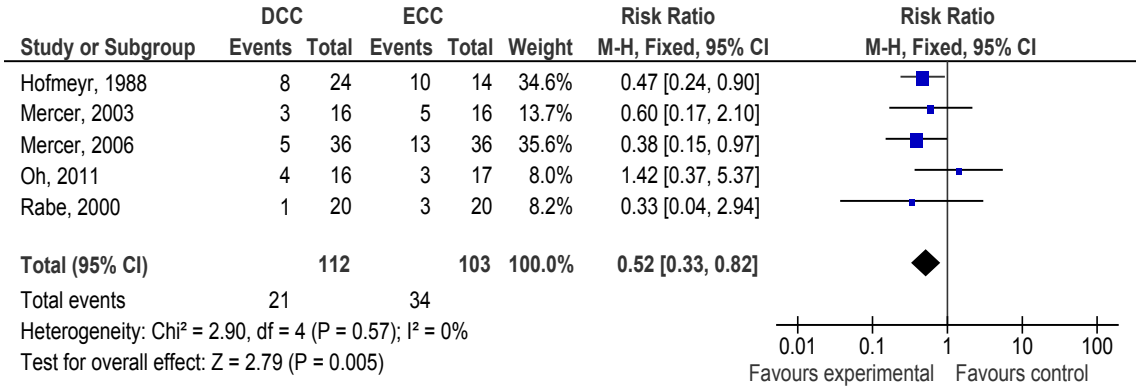


Figure 5: The effect of delayed cord clamping compared to early cord clamping on intraventricular haemorrhage

In figure 5, the results on the effects of intraventricular haemorrhage was pooled from five studies (n=215). The risk of intraventricular haemorrhage among infants was significantly reduced in the delayed cord clamping group (DCC) as compared to early cord clamping (ECC) (RR 0.52, 95% CI 0.33 to 0.82, I^2= 0, P= 0.005). There was no statistical heterogeneity observed (I^2= 0, P value 0.57 for chi^2).

4.5.2 Comparison 2: Risk of hyperbilirubinaemia among infants with delayed cord clamping compared (DCC) to early cord clamping (ECC).

4.5.2.1 Outcome: Maximum serum bilirubin (mg/dL).

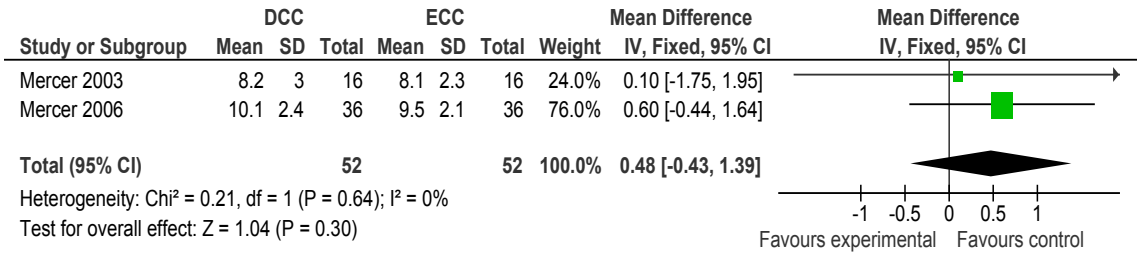


Figure 6: The risk of hyperbilirubinaemia among infants with delayed cord clamping (DCC) compared to early cord clamping (ECC)

The data aggregated from two studies (n=104) did not show any increased risk of hyperbilirubinamia associated with delayed cord clamping after birth. The results

for serum bilirubin levels in delayed versus early cord clamping indicated the following (RR 0.48, 95% CI -0.43 to 1.39, P= 0.30). There was no evidence of substantial heterogeneity across studies (I^2=0%, P=0.64 for chi^2).

4.5.3 Comparison 3: To compare the Apgar scores in infants exposed to delayed versus early cord clamping

Outcome: Apgar score > 7 from the 5th minute and beyond

The data from included studies was not presented in a manner that would have allowed a meta- analysis on this outcome. In one study (Hofmeyr, 1988) the Apgar score evaluated was less than 7 (<7). The rest of other studies did not specify the Apgar scores according to the inclusion criteria of this review. Therefore a meta-analysis was not possible for Apgar score since one study reported on this outcome.

4.5.4 Comparison 4: To evaluate reported cases of polycythaemia by comparing infants with delayed and early cord clamping

None of the included studies assessed this comparison.

4.6 CONCLUSION

This chapter explicitly described the analysis for this review. The next chapter covers a conclusion and summary of the main results.

CHAPTER 5: DISCUSSION

5.1 SUMMARY OF MAIN RESULTS

5.1.1 Primary outcome

The statistical evidence from this review shows a reduced risk of intraventricular haemorrhage if cord clamping is delayed for at least 30 to 45 seconds in low birth weight infants (RR 0.52, 95% CI 0.33 to 0.82, I^2= 0%, P= 0.005). This effect may be related to an improvement in the circulating blood volume, and better control of blood pressure, secondary to greater placental transfusion if the umbilical cord is not clamped quickly (Rabe et al., 2004:3). These results are consistent with previous trials (Mercer, et al 2006:1241, Hofmeyr et al., 1988:104) and a review conducted in low birth weight infants (Rabe, Reynolds & Diaz-Rossello, 2007:3). The results should however, be interpreted with caution due to limited number of studies with small sample sizes studies.

5.1.2 Secondary outcomes

In terms of the secondary outcomes for this review, it was difficult to analyse since there was insufficient data to be pooled. The only measurement that could be meta-analysed was hyperbilirubinaemia. The adverse effect of hyperbilirubinaemia was assessed depending on the availability of information from selected studies as stated in the protocol. The only data that was provided was the maximum level of bilirubin from two studies (Mercer, 2003:470; Mercer, 2006:1239). The results of the meta-analysis revealed no statistical significant difference between the levels of serum bilirubin between delayed versus early cord clamping (RR 0.48, 95% CI -0.43 to 1.39, I^2= 0%, P= 0.30, I^2=0). The heterogeneity was not significant in the meta-analysis. However, though the studies had small sample size, the results of this outcome were consistent with previous studies that evaluated the risk of hyperbilirubinaemia when delayed cord clamping was compared with early cord clamping (Ultee et al., 2008;20: Strauss et al., 2008:658)

The studies that evaluated the Apgar score did not present the data in a manner that would have allowed an analysis on this outcome. The results from all included trials have indicated no significant difference when delayed was compared to early

cord clamping on Apgar scores (Hofmeyr 1988; Mercer 2003; Mercer 2006; Oh, 2011; Rabe, 2000). There was no data available on the other outcome polycythaemia.

5.1.3 Limitations of the study

The ability of this review to make firm conclusions on the findings and provide adequate evidence to guide future practice was limited by few studies and differences in terms of birth practices.

5.1.3.1 Different birth practices (Confounding factors)

The timing of cord clamping and the level of the infant in relation to the placenta was relatively similar in the majority of the studies, while a variation on the other birth practices was noted between the studies. The uterotonics were given at different points between the two studies (Mercer, 2003:467; Rabe, 2000:776) while the rest of other trials did not provide information on these potentially confounding factors. The use of uterotonics and the height of the infant in relation to placenta have been found to precipitate the rate of placental transfusion (Fraser et al., 2006:500).

Two trials used prophylaxis for intraventricular haemorrhage for various reasons. In one study the prophylaxis formed part of the intervention in the other arm of the three groups of study (Hofmeyr, 1988:104) while in the other study (Mercer, 2006:1237) all infants born between 24 and 27 weeks received the drug regardless of the study groups they were allocated to. The other trials did not report on this possible confounding factor.

5.1.3.2 Other limitations

The review comprised of limited number of articles with small sample sizes. The potential bias in the review process consists of limitation to language and search strategies due to time constraints. Further research is warranted to provide adequate evidence that could guide future practices on delayed cord clamping and low birth weight infants.

5.2 OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

The attrition rate was generally low in the studies and where the data was available dropouts or losses were analysed on the intention to treat analysis (ITT). The included studies were small to give a firm conclusion on the applicability of evidence.

5.3 QUALITY OF THE EVIDENCE

The included studies were quality randomised controlled trials (Hofmeyr 1988; Mercer, 2003; Mercer, 2006; Oh, 2011; Rabe, 2000). On assessment of methodological quality, a Cochrane tool was employed. The majority of studies had good quality evidence. A low risk of bias was indicated in the majority of studies for allocation concealment (Mercer, 2003; Mercer 2006; Oh, 2011; Rabe, 2000) and all trials for blinding, incomplete outcome data and selective reporting. Any dropouts in the studies were adequately addressed and therefore attrition bias was low. Efforts were made in most trials to blind assessors of outcomes. The authors adequately reported on the primary and secondary outcomes.

5.4 POTENTIAL BIASES IN THE REVIEW PROCESS

The search for studies was restricted to the English language. The exclusion of other foreign languages could be a source of bias in the review. To minimise biases in the review, the methods from the Cochrane handbook for systematic reviews was used as a guide (Higgins & Green, 2006:). To assess the risk of bias, a standardised data extraction form and the Cochrane collaboration tool were also used in the review. The data was rigorously extracted by two reviewers to identify studies for inclusion and the third assessor was consulted where possible.

5.5 AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

This review is in agreement with the majority of studies that delayed cord clamping may reduce the risk of intraventricular haemorrhage among low birth weight infants when compared to early cord clamping. The studies in agreement with the primary outcome for this study involve randomised controlled trials by Mercer (2006:1241), Hofmeyr (1988:104), Rabe (2000:776) and a Cochrane review titled ‘early versus

delayed cord clamping in preterm infants' by Rabe, Reynolds & Diaz-Rossello (2004:3).

In terms of secondary outcome, (hyperbilirubinaemia) there was no significant difference found between delayed compared to early cord clamping in the analysis of this review. The majority of studies are also consistent with the results that, there is insignificant difference on the above mentioned secondary outcome (Strauss, Mock, Johnson, Cress, Burmeister, Zimmerman et al., 2008:658; Mercer 2003:468; Mercer 2006:1237; Ultee et al., 2008:20). However, in some studies, hyperbilirubinaemia have been found to be increased in the delayed cord clamping group in comparison to those in the early cord clamping and in most cases it was clearly reported to have been benign (Strauss 2008:658; Kulgeman et al., 2007:307).

5.6 AUTHOR'S CONCLUSIONS

5.6.1 Implications for practice

The evidence reported is not yet conclusive on optimum timing of umbilical cord clamping. However the growing evidence from recent studies indicates that this vulnerable population of neonates might benefit from delayed cord clamping.

Overall, this review has identified the potential of delayed cord clamping in reducing the risk of intraventricular haemorrhage in infants. However, due to small sample size of included studies, the results should be interpreted with caution and need confirmation through large scale randomised controlled trials (RCTs).

5.6.2 Implications for research

Further research is warranted on timing of the umbilical cord clamping particularly in developing countries. There is no adequate data on the incidence of intraventricular haemorrhage, including studies on cord clamping on the latter as compared to the developed countries. These additional studies need to assess the incidence of IVH and address important outcomes such as polycythaemia and hyperbilirubinaemia in relation to cord clamping. The trials should also consider the confounding factors such as the prophylaxis for intraventricular haemorrhage and the use of uterotonics during birth.

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7 APPENDICES

Appendix 7.1 Ethical approval

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot • your knowledge partner

23 March 2011 **MAILED**

Miss K Seloka
Department of Nursing
2nd Floor
Teaching Block

Dear Miss Seloka

Delayed cord clamping for the reduction of intraventricular haemorrhage in low birth weight infants: a systematic review.

ETHICS REFERENCE NO: N11/03/091

RE : ETHICAL REVIEW NOT REQUIRED

Thank you for your application. The application is for a systematic review using only data that is available in the public domain therefore the cluster head for Research Ethics has considered this proposal to be exempt from ethical review.

This letter confirms that this project is now registered and you can proceed with the work.

Yours faithfully

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Appendix 7.2 Excluded studies

Citation	Reason for exclusion
Aladangady, N., McHugh, S., Aitchison, T.C., Wardrop, C.A.J. & Holland, B.M. 2006. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. *Pediatrics*, 117:93-98.	Outcomes: Outcomes of interest not reported. The study was mainly about the infant's blood volume.
Baenziger, O., Stolkin, F., Keel, M., Siebenthal, K., Fauchere, J., Kundu, S., Dietz, V., Bucher, H. & Wolf, M. 2007. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: A randomized, controlled trial. *Pediatrics*, 119(3):455-459.	Outcomes: None of the outcomes of interest reported.
Cernadas, J.M.C., Carroli, G., Pellegrini, L., Otaño, L., Ferrira, M., Ricci, C., Casas, O., Giordano, D. & Lardizábal, J. 2006. The effects of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: A randomized, controlled trial. *Pediatrics*, 117:779-786.	Participants: Birth weight more than 2500g.
Grajeda, R., Pérez-Escamilla, R. & Dewey, K.G.1997. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of age. *American Journal of clinical Nutrition*, 65:425-31.	Participants: The study included multiple pregnancies as subjects.
Hofmeyr, G. J., Gobetz, L., Bex, P. J., Griendt, M., Nikodem, C. & Delahunt, T. 1993. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord-clamping. A randomized controlled trial. *Online Journal of Current Clinical Trials*, 110:2002.	Data Unavailable: The librarian was unable to locate the article.

Ibrahim, H.M., Krouskop, R.W., Lewis, D.F. & Dhanireddy, R. 2000. Placental transfusion: Umbilical cord clamping and preterm infants. *Journal of Perinatology*, 20:351-354.	Intervention: Delayed cord clamping done from 20 seconds (within 30 seconds).
Kinmond, S., Aitchison, T.C., Holland, B.M., Jones, J.G., Turner, T.L. & Wardrop, C.A.J. 1993. Umbilical cord clamping and preterm infants: A randomised trial. *British Medical Journal*, 306:172-5.	Intervention: Timing for Delayed cord clamping commences from 20 seconds.
Linder, N., Haskin, O., Levit, O., Klinger, G., Prince, T., Naor, N., Turner, P., Karmazyn, B. & Sirota, L. 2003. Risk factors for intraventricular hemorrhage in very low birth weight premature infants: A retrospective case control study. *Pediatrics*, 111:590-595.	Intervention: The study does not mention delayed or early cord clamping. Study design: A retrospective case-control study
Mercer, J.S., Vohr, B.R., Erickson-Owens, D.A., Padbury, J.F. & Oh. W. 2010. Seven month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping. *Journal of Perinatology*, 30(1):11-16.	Participants: The study report on toddlers.
Oh, W., Wallgren, G., Hanson, J.S. & Lind, J. 1967. The effects of placental transfusion on respiratory mechanics of normal term newborn infants. *Pediatrics*, 40(1):6-12.	Participants: Birth weight for infants was greater than 2500 g.
Ramamurthy, R.S. & Brans, Y.W. 1981. Neonatal polycythemia: I. Criteria for diagnosis and treatment. *Pediatrics*, 68:168.	Intervention: There was no comparison between delayed or early cord clamping.
Saigal, S., O'Neill, A., Surainder, Y., Chua, L. & Usher, R. 1972. Placental transfusion and hyperbilirubinemia in the premature. *Pediatrics*, 49:406-419.	Participants: The study included infants with a birth weight more than 2500 g. Babies weighed

	between 1,020 to 3,250 grams.
Shohat, M., Merlob, P. & Reisner, S.H. 1984. Neonatal polycythemia: I. Early diagnosis and incidence relating to time of sampling. *Pediatrics*, 73:7-10.	Participants: Infants weighed more than 2500 grams. Intervention: Timing of cord clamping was done within 30 seconds in all subjects. There was no comparison in terms of delayed or early clamping.
Strauss, R.G., Mock, D.M., Johnson, K.J., Cress, G.A., Burmeister, L.F., Zimmerman, M.B., Bell, E.F. & Rijhsinghani, A. 2008. A randomized clinical trial comparing immediate vs delayed clamping of the umbilical cord in preterm infants: Short-term clinical and laboratory endpoints. *Transfusion*, 48(4):658-665.	Participants: Participants defined in terms of gestational age only. Birth weight not mentioned.
Yao, A.C., Lind, J. & Vuorenkoski, V. 1971. Expiratory grunting in the late clamped normal neonate. *Pediatrics*, 48:865.	Participants: The participants weighed more than 2500 g.

Appendix 7.3 Data extraction form

7.3.1. Citation

First author, Year	
Title	
Journal/Conference Proceedings etc	

7.3.2. Study eligibility

7.3.2.1. Type of studies

(Tick √ where appropriate)

RCT/Quasi/Prospective	Yes / No / Unclear
Relevant participants	Yes / No / Unclear
Relevant interventions	Yes / No / Unclear
Relevant outcomes	Yes / No* / Unclear

*** Iissue relates to selective reporting – when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.**

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

7.3.2.2 Participants characteristics

Participant characteristics	
	Further details
Gender	
Gestational age (e.g. born at 30 weeks)	
Birth weight (e.g. > 2500 g)	
Method of delivery	
Other	

7.3.2.3 Trial characteristics

	Further details
Single centre / multicentre	
Country / Countries	
Method of delivery used e.g. caesarean section	
How many infants were randomised?	
How was timing defined in each group?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Trial design	
Number of participants who were analysed	
Other	

7.3.2.4 Types of interventions

Interventions	Tick (√) where appropriate
Delayed versus early cord clamping	
Others	

7.3.2.5 Outcome measures

Outcome	Reported in paper **(Tick √)**
1. Intraventricular haemorrhage	Yes / No
2. hyperbilirubinaemia	Yes / No
3. Polycythaemia	Yes / No
4. Apgar Score	Yes / No

7.3.2.5.1 Continuous data

For continuous data							
Code of paper	Outcomes	Unit of Measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (SD)	n	Mean (SD)	
A etc	Outcome A						
	Outcome B						
	Outcome C						
	Outcome D						
	Outcome E						

7.3.2.5.2 Dichotomous data

For Dichotomous data			
Code of paper	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
A etc	Outcome A		
	Outcome B		
	Outcome C		
	Outcome D		

7.3.3 Methodological quality and risk of bias assessment

Cochrane 'risk of bias' assessment tool

Item	**Author's Judgement (Tick where appropriate)**	**Description**
Random sequence generation (selection bias)	Low risk High risk UNCLEAR	
Allocation concealment (selection bias)	Low risk High risk UNCLEAR	
Blinding of participants and personnel (Performance bias)	Low risk High risk UNCLEAR	
Blinding of outcome assessment (detection bias)	Low risk High risk UNCLEAR	
Incomplete outcome data (attrition bias)	Low risk High risk UNCLEAR	
Selective reporting (reporting bias)	Low risk High risk UNCLEAR	
Other bias	Low risk High risk UNCLEAR	

Intention-to-treat An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.	
All participants entering trial	
15% or fewer excluded	
More than 15% excluded	
Not analysed as 'intention-to-treat'	
Unclear	

Were withdrawals described? Yes ☐ No ☐ not clear ☐

- Discuss if appropriate

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……
……

Appendix 7.4 Methodological assessment of studies

Source: Hofmeyr, 1988; Randomised controlled trial conducted at Johannesburg (Baragwanath hospital), South Africa.

Item	Author's Judgement	Description
Random sequence generation (selection bias)	UNCLEAR	Not reported
Allocation concealment (selection bias)	UNCLEAR	Not described
Blinding of participants and personnel (Performance bias)	Low risk	Outcome assessors blinded from randomisation.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded from randomisation.
Incomplete outcome data (attrition bias)	Low risk	Information on drop outs was reported.
Selective reporting (reporting bias)	Low risk	None identified
Other bias	UNCLEAR	Nil known

Source: Mercer, 2003; A prospective randomised controlled trial conducted at Women and infants' hospital, Rhode Island, USA (October 1998 to March 2001).

Item	Author's Judgement	Description
Random sequence generation (selection bias)	Low risk	Used randomly prepared cards in sealed envelope.
Allocation concealment (selection bias)	Low risk	Used no-transparent envelopes

Blinding of participants and personnel (Performance bias)	Low risk	Personnel reported not blinded.
Blinding of outcome assessment (detection bias)	UNCLEAR	Assessors of outcomes not reported blinded or not.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	None identified
Other bias	UNCLEAR	Nil known

Source: Mercer, 2006; A randomised controlled trial conducted at Women and Infant's Hospital of Rhode Island, USA (August 2003 and December 2004).

Item	Author's Judgement	Description
Random sequence generation (selection bias)	Low risk	Used computer-generated random number system.
Allocation concealment (selection bias)	Low risk	Used cards enclosed in sequenced, opaque envelopes.
Blinding of participants and personnel (Performance bias)	Low risk	Reported no blinding due to the nature of the study.
Blinding of outcome assessment (detection bias)	Low risk	Effort made not to reveal the group allocation in infant's charts.
Incomplete outcome data (attrition bias)	Low risk	Reported cases of protocol violation
Selective reporting	Low risk	None identified

(reporting bias)		
Other bias	UNCLEAR	Nil known

Source: Oh, 2011; Randomised unmasked controlled trial, USA (May 2000 to June 2001).

Item	Author's Judgement	Description
Random sequence generation (selection bias)	High risk	Randomisation stratified by mode of delivery and centre.
Allocation concealment (selection bias)	Low risk	Subjects randomised per phone call.
Blinding of participants and personnel (Performance bias)	Low risk	Study not blinded.
Blinding of outcome assessment (detection bias)	Low risk	Efforts made not to reveal grouping of infants to attending clinicians.
Incomplete outcome data (attrition bias)	Low risk	Data on all outcomes reported.
Selective reporting (reporting bias)	Low risk	None identified
Other bias	UNCLEAR	Nil known

Source: Rabe, 2000; A randomised controlled trial, Germany.

Item	Author's Judgement	Description
Random sequence generation (selection bias)	UNCLEAR	Sequence generation not mentioned
Allocation concealment (selection bias)	Low risk	Used sealed dark envelopes

Blinding of participants and personnel (Performance bias)	Low risk	Efforts to blind the study reported.
Blinding of outcome assessment (detection bias	Low risk	Information about actual cord clamping time recorded separately from infant's notes.
Incomplete outcome data (attrition bias)	Low risk	Information on outcome data reported.
Selective reporting (reporting bias)	Low risk	None identified
Other bias	UNCLEAR	Nil known

Appendix 7.5

Table 4.1 Characteristics of included studies

Source	Country	Study design & Sample size (N=)	Intervention	Participants	Outcomes
Hofmeyr,1988	South Africa	Randomised controlled trial N=38 infants	ECC: cord clamping immediately after birth DCC1: 1 minute after birth DCC2: Clamping after 1 minute and ergometrine given at delivery	Inclusion- Women with singleton cephalic presentation in advanced labour, judged to be less than 35 weeks gestation Exclusion- Women with full term pregnancy, refusal to sign informed consent	Primary: Intraventricular haemorrhage (ultrasonography performed at 6 hours, 72 hours and 24 hours after birth) Secondary: Apgar scores, systolic blood pressure, placental arterial blood gases, neonatal death

Source	Country	Study design & Sample size (N=)	Intervention	Participants	Outcomes
Mercer, 2003	USA	Prospective randomised controlled trial N=32 infants	ECC: Umbilical clamping between 5 and 10 seconds after delivery of the buttocks DCC: Clamping interval ended at 30 45 seconds Infant held approximately10-15 inches either below the mothers introitus or below the level of the incision at caesarean section (C/S)	Inclusion- Women with gestational age between 24 and 31 and 6/7 weeks, singleton pregnancy, the obstetrician agreed to enrolment into the study and when parents have given a written consent Exclusion- Women were excluded if the obstetrician or parents refused consent, if there was intent to withhold or withdraw care or if the women had diagnoses of placenta previa or abruption, or a foetus with major anomaly	Primary: Initial mean blood pressure Secondary: Secondary: Temperature on admission to NICU, initial venous haematocrit, suspected necrotising enterocolitis (SNEC), IVH, transfusions, maximum bilirubin levels and days hospitalised

Source	Country	Study design & Sample size (N=)	Intervention	Participants	Outcomes
Mercer, 2006	USA	Randomised controlled trial N=72 infants	ECC: clamping <10 seconds DCC: 30-45 seconds Infant held approximately10-15 inches either below the mothers introitus or below the level of the incision at caesarean section (C/S)	Inclusion- All women admitted between 24 & 31.6 weeks gestation with preterm labour Exclusion- Obstetrician refusal to participate, major congenital abnormalities or multiple gestations, intent to withhold care, severe maternal illnesses such as placenta abruption or previa	Primary: bronchopulmonary dysplasia (BPD) Secondary: suspected necrotising enterocolitis (SNE), intraventricular haemorrhage (IVH), late-onset sepsis (LOS) and retinopathy of prematurity (ROP) Other outcomes: Apgar scores, temperature, serum bilirubin

Source	Country	Study design & Sample size (N=)	Intervention	Participants	Outcomes
Oh, 2011	USA	Randomised unmasked controlled trial N=33 infants	ECC: occurred <10 seconds after delivery of the infant's presenting part DCC: occurred 30-45 seconds after delivery of the infant's presenting part Infant held approximately 10cm below birth canal or abdomen in case of caesarean section	Inclusion: women with gestational age between 24 0/7 and 27 6/7 weeks singleton pregnancies and admitted for preterm labour, women with approval from the attending obstetrician and informed consent obtained from the infant's parents Exclusion: multiple pregnancies was excluded	Primary: capillary haematocrit at 2, 4, and 6 week of age, amount of blood withdrawn for clinical indications and amount of blood transfused Secondary: Apgar scores at 1 and 5 minutes, hourly mean arterial blood pressures during the first 12 hours Other outcomes: intraventricular haemorrhage (IVH), late-onset sepsis at >3 days of age, NE, BPD and ROP

Source	Country	Study design & Sample size (N=)	Intervention	Participants	Outcomes
Rabe, 2000	Germany	Randomised controlled trial N=40 infants	ECC: clamping at 20 seconds DCC: clamping at 45 seconds Infant held approximately 20 cm below the level of placenta beside the mother	Inclusion: single preterm infants of <33 weeks gestation Exclusion: Infants with Rhesus incompatibility, foetal hydrops, congenital foetal anomalies,Apgar <3 at 0 minute (thus allowing obstetrician to stop DCC if the infant was deteriorating and multiple pregnancy was excluded)	Primary: requirement for packed red cell transfusion (PRCT) Secondary: Apgar scores, requirement for artificial ventilation, temperature on admission, Heart rate at 1, 4 and 24 hours, intraventricular haemorrhage, patent ductus arteriosus, phototherapy and mean duration of phototherapy
Key: BPD= Bronchopulmonary Dysplasia, C/S=Caesarean section, DCC= Delayed Cord Clamping, ECC= Early Cord Clamping, IVH= Intraventricular Haemorrhage, LOS= Late-Onset Sepsis, NE= Necrotising Enterocolitis, NICU= Neonatal Intensive Care Unit, ROP= Retinopathy of Prematurity, SNE= Suspected Necrotising Enterocolitis, PRCT= Packed Red Cell Transfusion.					

Appendix 7.6

Contacted expert for additional literature sources

1. Dr. K. Harper
2. Prof Hofmeyr
3. East London hospital complex midwives