Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes (Review)

McDonald SJ, Middleton P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Susan J McDonald[1], Philippa Middleton[2]

[1]Midwifery Professorial Unit, La Trobe University/Mercy Hospital for Women, Heidelberg, Australia. [2]ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia

Contact address: Susan J McDonald, Midwifery Professorial Unit, La Trobe University/Mercy Hospital for Women, Level 4, Room 4.071, 163 Studley Road, Heidelberg, Victoria, 3084, Australia. s.mcdonald@latrobe.edu.au. smcdonald3@mercy.com.au. (Editorial group: Cochrane Pregnancy and Childbirth Group.)

Cochrane Database of Systematic Reviews, Issue 1, 2009 (Status in this issue: *Unchanged, commented*)

DOI: 10.1002/14651858.CD004074.pub2
This version first published online: 23 April 2008 in Issue 2, 2008.
Last assessed as up-to-date: 30 December 2007. (Help document - Dates and Statuses explained)

This record should be cited as: McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD004074. DOI: 10.1002/14651858.CD004074.pub2.

ABSTRACT

Background

Policies for timing of cord clamping vary, with early cord clamping generally carried out in the first 60 seconds after birth, whereas later cord clamping usually involves clamping the umbilical cord greater than one minute after the birth or when cord pulsation has ceased.

Objectives

To determine the effects of different policies of timing of cord clamping at delivery of the placenta on maternal and neonatal outcomes.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (December 2007).

Selection criteria

Randomised controlled trials comparing early and late cord clamping.

Data collection and analysis

Two review authors independently assessed trial eligibility and quality and extracted data.

Main results

We included 11 trials of 2989 mothers and their babies. No significant differences between early and late cord clamping were seen for postpartum haemorrhage or severe postpartum haemorrhage in any of the five trials (2236 women) which measured this outcome (relative risk (RR) for postpartum haemorrhage 500 mls or more 1.22, 95% confidence interval (CI) 0.96 to 1.55). For neonatal outcomes, our review showed both benefits and harms for late cord clamping. Following birth, there was a significant increase in infants needing phototherapy for jaundice (RR 0.59, 95% CI 0.38 to 0.92; five trials of 1762 infants) in the late compared with early clamping group. This was accompanied by significant increases in newborn haemoglobin levels in the late cord clamping group compared with early cord clamping (weighted mean difference 2.17 g/dL; 95% CI 0.28 to 4.06; three trials of 671 infants), although this effect did not persist past six months. Infant ferritin levels remained higher in the late clamping group than the early clamping group at six months.

Authors' conclusions

One definition of active management includes directions to administer an uterotonic with birth of the anterior shoulder of the baby and to clamp the umbilical cord within 30-60 seconds of birth of the baby (which is not always feasible in practice). In this review delaying clamping of the cord for at least two to three minutes seems not to increase the risk of postpartum haemorrhage. In addition, late cord clamping can be advantageous for the infant by improving iron status which may be of clinical value particularly in infants where access to good nutrition is poor, although delaying clamping increases the risk of jaundice requiring phototherapy.

PLAIN LANGUAGE SUMMARY

Effect of timing of umbilical cord clamping at birth of term infants on mother and baby outcomes

At the time of birth, the infant is still attached to the mother via the umbilical cord, which is part of the placenta. The infant is usually separated from the placenta by clamping the cord. The timing of this clamping is one part of the third stage of labour (the time from birth until delivery of the placenta) which can vary according to clinical policy and practice. Early cord clamping is believed to lead to a reduced risk of bleeding after birth (postpartum haemorrhage). This review of 11 trials showed no significant difference in postpartum haemorrhage rates when early and late cord clamping were compared. For neonatal outcomes it is important to weigh the growing evidence that delayed cord clamping confers improved iron status in infants up to six months after birth, with a possible additional risk of jaundice that requires phototherapy.

BACKGROUND

At the time of birth, the infant is still attached to the mother via the umbilical cord, which is part of the placenta. The infant is usually separated from the placenta by putting the umbilical cord between two clamps. One clamp is placed close to the infant's navel and the second is placed further along the umbilical cord; then the cord is cut between the two clamps. This takes place during the third stage of labour, which is that period of time from birth of the infant until delivery of the placenta.

Active management and expectant management of the third stage of labour

There are two contrasting approaches to managing the third stage of labour: active management and expectant or physiological management. A comparison of these approaches is the subject of a separate Cochrane review (Prendiville 2000).

Expectant management is a non-interventionist approach, which involves waiting for signs of placental separation and allowing the placenta to deliver spontaneously or aided by gravity, maternal effort or nipple stimulation. This strategy is popular in some northern European countries, in some units in the United States and Canada and in some low-income countries (McDonald 1996), although active management is becoming more common in lower income countries. Active management usually involves the clinician intervening in the process through three interrelated processes: the administration of a prophylactic uterotonic drug; cord clamping and cutting; and controlled traction of the umbilical cord. An injection of an uterotonic drug, an agent that stimulates the uterus to contract, is given as a precautionary measure, aimed at reduction in the risk of postpartum haemorrhage. This injection is usually given to the mother at about the same time as the infant's shoulders are born. There are several different types of uterotonic drugs that may be given and the relative advantages and disadvantages of these different drugs are the subject of separate reviews (see Cotter 2001 (oxytocin); Gülmezoglu 2007 (prostaglandins and misoprostol); McDonald 2004 (ergometrine-oxytocin and oxytocin)). In an active management strategy the umbilical cord is usually clamped shortly following birth of the infant, although there can be substantial variation in the application of policies for active management.

Active management is widely practised in high-income countries, although relative timing of each individual component of the strategy varies. Most maternity units in Australia and the United Kingdom administer the uterotonic prior to placental delivery, whereas some units in the United States (Brucker 2001) and Canada (Baskett 1992) advocate withholding uterotonic administration until after the placenta is delivered. A recent survey of active management policies in Europe showed considerable differences, including the timing of cord clamping, with eight countries clamping the cord immediately in 66% to 90% of units, and five countries mostly waiting until the cord stopped pulsating (Winter 2007).

A major reason for practising active management is its association with reduced risk of postpartum haemorrhage (PPH), the major complication of the third stage of labour (Prendiville 2000). The usual definition of PPH is that given by the World Health Organization (WHO): blood loss of equal to or more than 500 mls from the genital tract during the first 24 hours postpartum (WHO 1990; WHO 2000). Stricter definitions of 600 ml (Beischer 1986) and 1000 ml (Burchell 1980) have been suggested although the assessment of blood loss is often significantly underestimated and is based on a clinical estimation of blood loss (Kwast 1991; WHO 1998a). The 500 ml limit is intended to be a warning and blood loss up to 1000 ml in healthy women may still be considered physiological, not necessitating treatment other than uterotonics. In low-income countries, where the prevalence of severe anaemia is high, a 500 ml blood loss can be life threatening for many women (WHO 1996). PPH is the most common fatal complication of pregnancy and childbirth in the world (UNICEF 2002; WHO 2007) and is a major contributor to the conservatively estimated 500,000 maternal deaths occurring throughout the world annually (Adamson 1996; UNICEF 2002; WHO 1990; WHO 2005). Whilst the majority of maternal deaths (99%) occur in low-income countries (WHO 2002), the risk of PPH haemorrhage should not be underestimated for any birth (McDonald 2003). Effects on maternal morbidity are less well documented, but are likely to include interrelated outcomes such as anaemia and fatigue (Patterson 1994). Complications that can arise from major blood loss include shock, the widespread formation of blood clots in the microcirculation, renal failure, liver failure and adult respiratory distress syndrome (Bonnar 2000).

Although active management leads to reduced risk of PPH, it is important to establish which components of the strategy lead to this reduced risk. It can be difficult to adhere to an active management strategy. For instance, in one definition of the strategy, the uterotonic drug is given at the time of the birth of the anterior shoulder of the infant, whereas it is often given after birth of the infant. This may be due to the number of staff available in the room at the time of birth and unexpected occurrences such as malpresentation (for example, a breech presentation) or shoulder dystocia (difficulty in delivering the infant's shoulders, McDonald 1996). Furthermore, some women have preferences for expectant management (McDonald 2003). Thus, it is important to examine the relative importance of each component of an active management strategy.

Early cord clamping as part of active management

In an active management strategy the umbilical cord is usually clamped shortly following birth of the infant. This is generally carried out in the first 30 seconds after birth, regardless of whether

the cord pulsation has ceased (McDonald 2003). The infant may be placed on the mother's abdomen, put to the breast or be more closely examined on a warmed cot if resuscitation is required. Once the placenta is felt to have separated from the wall of the uterus, downward traction may be applied to the remaining length of the umbilical cord to assist delivery of the placenta. Controlled cord traction is believed to reduce blood loss, shorten the third stage of labour and therefore minimise the time during which the mother is at risk from haemorrhage (McDonald 2003).

Arguments against early cord clamping include the reduction in the amount of placental transfusion and thus forgo any associated benefits of extra blood volume. Early cord clamping may increase the likelihood of feto-maternal transfusion (the amount of blood that is forced back across the placental barrier into the maternal circulation), as a larger volume of blood remains in the placenta. This would have been considered a potential issue prior to the introduction of Rh D immunoglobulin prophylaxis, since early clamping of the cord was considered to increase the risk. However, little work appears to have been undertaken since findings from small non-randomised studies (Lapido 1972) suggested there may be a reduction in feto-maternal transfusion if cord clamping was delayed (Smith 2006). Early clamping has also been associated with some higher risks for the pre-term infant. This topic is the subject of a Cochrane systematic review (Rabe 2004), which is currently being updated, and a non-Cochrane systematic review (Rabe 2008).

Delayed cord clamping

Late cord clamping, or delayed clamping, a physiological approach, involves clamping the umbilical cord when cord pulsation has ceased. However, definitions of what constitutes early and late cord clamping vary (Prendiville 1989). If the cord is not clamped, the umbilical circulation usually ceases when the umbilical arteries close and the cord stops pulsating.

Delaying clamping allows time for a transfer of the fetal blood in the placenta to the infant at the time of birth. This placental transfusion can provide the infant with an additional 30% more blood volume and up to 60% more red blood cells (McDonald 2003; Mercer 2001; Mercer 2006). The amount of blood returned to the infant depends on when the cord is clamped and at what level the infant is held (above or below the mother's abdomen) prior to clamping (Yao 1974).

The suggested neonatal benefits associated with this increased placental transfusion include higher haemoglobin levels (Prendiville 1989), additional iron stores and less anaemia later in infancy (Chaparro 2006; WHO 1998b), higher red blood cell flow to vital organs, better cardiopulmonary adaptation, and increased duration of early breastfeeding (Mercer 2001; Mercer 2006). There is growing evidence that delaying cord clamping confers improved iron status in infants up to six months post birth (Chaparro 2006; Mercer 2006; van Rheenen 2004).

Delayed cord clamping has been linked to an increase in the incidence of jaundice (Prendiville 1989) which, in severe cases, could have longer term effects on the health and development of the infant. In addition, early cord clamping has been associated with a reduction in the length of the third stage of labour. One of the aims of active management is to reduce the length of the third stage because the longer the placenta remains undelivered, the greater is the likelihood of maternal bleeding (Inch 1985). A delay in time before clamping the umbilical cord in healthy term infants appears be less crucial as the cord ceases pulsation within the first two minutes of birth in the majority of cases (McDonald 2003).

Rationale for this review

The World Health Organization has recently updated its guidelines on preventing postpartum haemorrhage (WHO 2007) and the International Confederation of Midwives and the International Federation of Gynaecology and Obstetrics also updated its statement on postpartum haemorrhage in 2006 (ICM/FIGO 2006). While both statements refer to benefits of delaying cord clamping, evidence has still been unclear as to whether one timing of cord clamping policy is preferable to another. This review seeks to explore this issue further. Since evidence suggests that the effects of early versus late cord clamping may differ in pre-term and term infants, these are the subjects of separate reviews (see Rabe 2004 (Cochrane review); Rabe 2008 (non-Cochrane systematic review) for reviews of delayed cord clamping in pre-term infants). This review will concentrate on the effect of early versus late cord clamping on maternal and neonatal outcomes.

OBJECTIVES

The objective of this review was to determine the maternal and neonatal effects of different policies for the timing of cord clamping in the third stage of labour.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised comparisons of different strategies for the timing of umbilical cord clamping of term infants during the third stage of labour for inclusion. We excluded quasi-randomised studies.

Types of participants

Women who:

1. have given birth to a term infant (equal to or greater than 37 completed weeks' gestation); and
2. have been involved in a birth where clamping of the umbilical cord is applied.

Exclusions:

1. Women who have given birth to a pre-term infant (less than 37 weeks' gestation; as these are the subject of separate reviews, see Rabe 2004 (Cochrane review); Rabe 2008 (non-Cochrane systematic review).
2. Breech presentation.
3. Multiple pregnancies.

Exclusions 2 and 3 were due to the lack of control over the timing of cord clamping in these conditions.

Types of interventions

1. Early cord clamping, defined as application of a clamp to the umbilical cord within 60 seconds of the birth of the infant.
2. Later (delayed) cord clamping, defined as application of a clamp to the umbilical cord greater than one minute after birth or when cord pulsation has ceased.

Types of outcome measures

The outcome measures chosen in this review were based on those factors that were likely to be seen as clinically relevant in terms of an outcome changing clinical practice, as well as what factors would be most likely to advantage or disadvantage a woman's recovery from childbirth and the wellbeing of her infant.

Maternal outcomes

1. Postpartum haemorrhage (PPH, clinically estimated blood loss of 500 mls to 999 mls)
2. Severe PPH (blood loss of 1000 mls or greater)
3. Mean blood loss (ml)
4. Maternal haemoglobin concentration (after birth and longer term)
5. Maternal ferritin levels (after birth and longer term)
6. Need for blood transfusion
7. Need for manual removal of the placenta
8. Length of the third stage of labour
9. Need for therapeutic uterotonics

Neonatal and infant outcomes

1. Apgar score less than seven at five minutes
2. Admission to special care nursery (SCN) or neonatal intensive care unit (NICU)
3. Respiratory distress
4. Jaundice requiring phototherapy
5. Clinical jaundice
6. Polycythaemia (haematocrit greater than 65%)
7. Infant haemoglobin levels (at birth and longer term)
8. Infant ferritin levels (at birth and longer term)
9. Exclusive breastfeeding

Cord measures

Cord haemoglobin levels

In future versions of this review, we will seek for and include mortality for the baby and longer term outcomes such as neonatal and child neurodevelopment.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (December 2007).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

At least two review authors independently assessed the full text of potential studies for the appropriateness of inclusion and methodological quality.

Data extraction and management

Review authors performed data extraction separately and double checked data for discrepancies. Careful assessment and data extraction of the McDonald 1996 trial was made independently by three people not involved with this trial (J Abbott, S Higgins and P Middleton). We undertook thorough discussions between review authors (S McDonald and P Middleton) about the appropriateness of all other studies for inclusion. We contacted individual investigators if we required clarification before deciding if a trial met the inclusion criteria.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). Methods used for generation of the randomisation sequence were described for each trial.

1. Selection bias (randomisation and allocation concealment)

We assessed selection bias as follows:
A. adequate concealment of allocation: such as telephone randomisation, consecutively numbered, sealed opaque envelopes;
B. unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach.
We excluded quasi-randomised trials.

2. Attrition bias (loss of participants, for example, withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up by describing loss of participants and recording reasons for losses where available.

3. Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:
A. blinding of participants (yes/no/unclear);
B. blinding of caregiver (yes/no/unclear);
C. blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2003). We used fixed-effect analysis for combining data in the absence of significant heterogeneity and when trials were sufficiently similar. If heterogeneity was found this was explored by sensitivity analysis followed by random effects analysis if required.

Dichotomous data

For dichotomous data, we used relative risks with 95% confidence intervals.

Continuous data

For continuous data, we used the weighted mean difference with 95% confidence intervals.

Dealing with missing data

We analysed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomised, and there was sufficient information in the trial report, we attempted to restore them to the correct group.

Assessment of heterogeneity

We used the I^2 statistic to test for statistical heterogeneity. We explored high levels of heterogeneity among the trials (exceeding 50%).

Subgroup analyses

It was stated in the protocol for this review that subgroup analyses would be considered on the basis of:
1. whether uterotonics (oxytocic drugs used to stimulate the uterus to contract) were used as part of the third stage management;
2. whether the infant was held above or below the abdomen prior to cord clamping;
3. the extent of control for selection bias.
The uterotonic subgroup was presented as part of the analysis structure.
There was insufficient information or variation to present subgroup analyses by placement of infant (however this was noted in the 'Characteristics of included studies' table) or selection bias.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Participants

Participants generally were healthy pregnant women expected to give birth vaginally. However, in Gupta 2002, the women were anaemic and the van Rheenen 2007 trial was conducted in a malaria-endemic area. Cernadas 2006 included some women who gave birth by caesarean section.

Settings

Studies were conducted in Argentina, Australia, Canada, India (two studies), Libya, Mexico, UK, USA (two studies) and Zambia.

Interventions

Timing of cord clamping

While the timing of early clamping was relatively consistent between studies at less than one minute (mostly within 15 seconds of birth), the timing of late clamping was quite variable:

- one minute in one arm of Cernadas 2006 and Saigal 1972, with the latter holding the baby 30 cm below the perineum;
- two minutes in Chaparro 2006;
- three minutes in another arm of Cernadas 2006; and Oxford Midwives 1991; Spears 1966;
- when the cord stopped pulsing in Emhamed 2004; Nelson 1980 and van Rheenen 2007;
- when the cord stopped pulsing, or five minutes, in McDonald 1996;
- after placental descent in Geethanath 1997 (baby placed 10 cms below the vaginal introitus) and Gupta 2002 (baby placed below the level of the mother's abdomen).

The one-minute and three-minute arms of Cernadas 2006 were combined to give data for late cord clamping; as were the one-minute and five-minute arms in Saigal 1972.

Use and timing of uterotonic

McDonald 1996 used a factorial design with four arms, randomising not only by early and late cord clamping but also by whether uterotonics were administered early or late. Early uterotonic administration involved administration at the time of birth of the anterior shoulder of the baby; late uterotonic administration was after the birth of the baby (literally) and if the cord clamping allocation was early, then it was allocated to be after the cord was clamped (ie not within 30 seconds). The uterotonic used was intramuscular oxytocin 10 IU.

van Rheenen 2007 also used intramuscular oxytocin, but this was administered after clamping of the cord and no dosage was recorded.

In the Oxford Midwives 1991 trial, uterotonic was given at the time of birth of the anterior shoulder of baby in both arms; in Emhamed 2004 it was given when the cord was clamped and in Saigal 1972 it was given after the cord was clamped.

The remaining six trials did not specify either use or timing of any uterotonic (Cernadas 2006; Chaparro 2006; Geethanath 1997; Gupta 2002; Nelson 1980; Spears 1966)

See table of 'Characteristics of included studies' for further details of the included trials.

Studies which involved pre-term infants were excluded since this review focuses on term infants (see Rabe 2004 (Cochrane review); Rabe 2008 (non-Cochrane systematic review) for reviews focusing on pre-term infants).

Risk of bias in included studies

Allocation concealment

Five trials (Cernadas 2006; Chaparro 2006; McDonald 1996; Oxford Midwives 1991; van Rheenen 2007) all had adequate allocation concealment in the form of sequentially numbered sealed opaque envelopes. The remaining trials had unclear allocation concealment - opaque envelope systems (Emhamed 2004; Geethanath 1997; Gupta 2002) - and not specified (Nelson 1980; Saigal 1972; Spears 1966).

Blinding

The nature of the intervention precluded blinding of women and caregivers. However at least some form of blinding of outcome assessment was reported in three trials (Cernadas 2006; McDonald 1996; van Rheenen 2007).

Losses to follow up

Losses to follow up were generally low (when reported). Chaparro 2006 had 29% of participants lost to follow-up at six months and van Rheenen 2007 had lost about 33% of participants (including post-randomisation exclusions) by six months.

Effects of interventions

We included 11 trials involving a total of 2989 women and infant pairs.

Results are presented by whether uterotonics were given before or after cord clamping, or whether it was not stated whether a uterotonic was used.

Maternal outcomes

Postpartum haemorrhage ≥ 500 mls

(four trials - Cernadas 2006; McDonald 1996; Oxford Midwives 1991; van Rheenen 2007: 1878 women)

The timing of cord clamping was not shown to be of any statistical significance with regard to postpartum haemorrhage of 500 mls or more (RR 1.22, 95% CI 0.96 to 1.55).

Severe postpartum haemorrhage ≥ 1000 mls

(four trials - Cernadas 2006; Chaparro 2006; McDonald 1996; van Rheenen 2007: 1684 women)

No significant differences between early and late cord clamping groups were seen for the outcome of severe postpartum haemorrhage (RR 0.84, 95% CI 0.48 to 1.49).

Mean blood loss

No significant differences in mean blood loss between early and late cord clamping were seen in McDonald 1996 (weighted mean difference (WMD) 6.36 mls; 95% confidence interval (CI) -34.94 to 47.66; 963 women).

Maternal postpartum haemoglobin

(three trials - Geethanath 1997; Gupta 2002; McDonald 1996: 1128 women)

Maternal haemoglobin values were similar between the early and late cord clamping groups (WMD -0.12 g/dL; 95% CI -0.30 to 0.06) at 24 to 72 hours after birth.

Need for blood transfusion

In McDonald 1996, there were no statistically significant differences in need for blood transfusion between the early and late cord clamping groups (RR 0.79, 95% CI 0.20 to 3.15; 963 women).

Need for manual removal of placenta

(two trials - McDonald 1996; Oxford Midwives 1991: 1515 women)

No clear difference was seen between the early and late cord clamping groups for manual removal of placenta (RR 1.59, 95% CI 0.78 to 3.26).

Length of third stage of labour

In McDonald 1996, neither instances of third stage greater than 30, nor 60 minutes, were significantly different between the early and late cord clamping groups (963 women).

Therapeutic uterotonics

McDonald 1996 showed no significant differences in need for therapeutic administration of uterotonics between the early and late cord clamping groups (RR 0.94, 95% CI 0.74 to 1.20; 963 women).

Maternal ferritin levels at birth

In Geethanath 1997, maternal ferritin levels at birth were significantly higher in the early clamping group than the late clamping group (WMD 9.10 ug/L; 95% CI 7.86 to 10.34; 107 women).

Neonatal outcomes

Apgar score

Apgar score less than seven at five minutes did not show significant differences between the early and late cord clamping groups in McDonald 1996 and Spears 1966 (RR 1.23, 95% CI 0.73 to 2.07; 1342 neonates).

Admission to special care baby nursery (SCN) or neonatal intensive care unit (NICU)

(three trials - Cernadas 2006; McDonald 1996; Nelson 1980: 1293 infants)

None of the early versus late cord clamping comparisons showed statistically significant differences for SCN or NICU admission (RR 1.03, 95% CI 0.56 to 1.90).

Respiratory distress

(four trials - McDonald 1996; Nelson 1980; Saigal 1972; Spears 1966: 1387 infants)

The number of infants admitted to any level of NICU (1, 2 or 3) for respiratory distress was similar between the early and late cord clamping groups (RR 1.01, 95% CI 0.18 to 5.75; 3 trials of 1008 infants).
In Spears 1966 similar numbers of infants showed signs of respiratory distress (RR 1.11, 95% CI 0.65 to 1.89; 379 infants).

Jaundice requiring phototherapy

(five trials - Emhamed 2004; McDonald 1996; Nelson 1980; Oxford Midwives 1991; van Rheenen 2007: 1762 infants)
Significantly fewer infants in the early cord clamping group required phototherapy for jaundice than in the late cord clamping group (RR 0.59, 95% CI 0.38 to 0.92). This equates to 3% of infants in the early clamping group and 5% in the late clamping group, a risk difference of 2% (95% CI -0.04 to 0.00).

Clinical jaundice

(five trials - Cernadas 2006; Emhamed 2004; McDonald 1996; Nelson 1980; Oxford Midwives 1991: 1828 infants)

The difference between early and late cord clamping for clinical jaundice did not reach statistical significance (RR 0.84, 95% CI 0.66 to 1.07).

Polycythaemia

(three trials - Cernadas 2006; Emhamed 2004; van Rheenen 2007: 463 infants)
No difference between the early and late cord clamping groups was detected for polycythaemia (RR 0.39, 95% CI 0.12 to 1.27).

Cord haemoglobin (g/dL)

(four trials - Emhamed 2004; Geethanath 1997; Gupta 2002: Saigal 1972: 314 infants)

The early cord clamping group showed higher levels of cord haemoglobin than did the late clamping group (WMD 0.42 g/dL; 95% CI 0.03 to 0.80).

Newborn haemoglobin (g/dL)

(three trials - Cernadas 2006; Chaparro 2006; Saigal 1972: 671 infants)

There were significantly lower infant haemoglobin levels at birth in the early clamping group compared with the late clamping group (WMD -2.17; 95% CI -4.06 to -0.28; random effects model). This outcome showed very high heterogeneity between trials (I^2 96.5%).

Infant haemoglobin (g/dL)

- *at 24-48 hours*

In Emhamed 2004 and Cernadas 2006, the early cord clamping groups showed significantly lower infant haemoglobin levels 24 hours after birth than the late clamping groups (WMD -1.34 g/dL; 95% CI -1.88 to -0.88; 382 infants).

- *2 to 4 months*

(three trials - Geethanath 1997; Gupta 2002; van Rheenen 2007: 256 infants)

While one trial (Gupta 2002) reported a significantly favourable effect on infant haemoglobin from late cord clamping, no difference between early and late clamping was seen for all three trials combined (WMD -0.30 g/dL; 95% CI -1.25 to 0.65). This discrepancy manifested as extremely high statistical heterogeneity (I^2 = 88%).

- *at four months (haemoglobin > 2 SDs below 10.3 g/dL)*

In van Rheenen 2007, infant anaemia at four months did not reach a statistically significant difference between early and late clamping (RR 1.84, 95% CI 0.96 to 3.54; 91 infants).

- *six months*

(two trials - Chaparro 2006; van Rheenen 2007: 447 infants)
No difference in infant haemoglobin at six months between early and late clamping (WMD 0.03 g/dL; 95% CI -0.17 to 0.23) was seen. Nor was a significant difference seen when measured by

haemoglobin < 11.7 g/dL (Chaparro 2006) or haemoglobin > 2 SDs below 10.5 g/dL (van Rheenen 2007).

Haematocrit

- *at six hours (haematocrit < 45%)*

When measured as a haematocrit threshold greater than 45%, fewer infants in the late clamping group had anaemia compared with the early clamping group (RR 16.18, 95% CI 2.05 to 127.37; Cernadas 2006; 272 infants).

- *at 24 to 48 hours (haematocrit < 45%)*

This difference in favour of late clamping persisted at 24 to 48 hours (RR 6.03, 95% CI 2.27 to 16.07; Cernadas 2006; 268 infants).

Infant ferritin

- *at three months (ug/L)*

In one trial of 107 infants (Geethanath 1997), infant ferritin levels were significantly higher in the late clamping group compared with early clamping (WMD 17.90 ug/L; 95% CI 16.59 to 19.21) at three months.

- *at six months (ug/L)*

Ferritin levels were significantly higher in the late clamping group compared with early clamping (WMD 11.80 ug/L; 95% CI 4.07 to 19.53; Chaparro 2006; 315 infants).

Breastfeeding

No differences in the rate of exclusive breastfeeding between early and late clamping groups were seen for any time period except for one month postpartum:

- at discharge (McDonald 1996; 963 infants);
- at one month (RR 1.10, 95% CI 1.00 to 1.20; Cernadas 2006; 268 infants) in favour of early clamping;
- at two months (Chaparro 2006; 302 infants);
- at three months (Geethanath 1997; Gupta 2002; total of 144 infants);
- at four months (Chaparro 2006; 313 infants);
- at six months (Chaparro 2006; 358 infants).

DISCUSSION

Recent reviews such as Hutton 2007 and van Rheenen 2006 have highlighted beneficial effects from delayed cord clamping compared with early cord clamping, but these reviews did not encompass maternal outcomes (which have been rarely measured in trials of the timing of cord clamping) and only a few of the studies included in this review reported on maternal wellbeing. Women experiencing ill health postpartum may be less able to mother as effectively which ultimately reflects on the health and wellbeing of the newborn infant and family life in general.

The ability of the review to reach conclusive findings and sufficient evidence to guide future practice was limited by differences in variables such as the lengths of timing for both early and late cord clamping, as well as the inconsistent coverage of outcomes between trials. In addition, the use of prophylactic uterotonics was not always well described in the trials.

In this review of nearly 3,000 women and their babies, no differences were seen for PPH or any other maternal outcome (except for maternal ferritin at birth in one trial). However the risk of postpartum haemorrhage may be higher with late administration of uterotonics (Cotter 2001; Oh 2007).

For neonatal outcomes, our review showed both benefits and harms for late cord clamping. There was a significant increase in infants needing phototherapy for jaundice with late cord clamping. This was accompanied by significant increases in haemoglobin levels which were higher with late cord clamping just after birth, although this favourable effect did not persist till six months. Ferritin levels remained higher in the late clamping groups than the early clamping groups at six months. Ferritin levels less than 50 ug/L for infants aged three months are regarded as indicative of deficient iron stores (Hutton 2007) and so the results of the Chaparro 2006 trial are likely to be clinically important (with the late clamping group almost reaching this threshold at six months). This trial also noted that late clamping demonstrated significantly greater effects in the subgroup of women with low ferritin levels at birth; and they also found, in a subgroup of women with high lead levels, that early cord clamping can contribute to higher blood lead concentrations through a decrease in iron status.

The benefits and harms seen for delayed cord clamping are compatible with the same mechanism of an increased amount of red blood cells for the infant. Additional red blood cells can improve the infant's iron stores, but it also has the potential to overload the newborn's metabolism, leading to increased levels of bilirubin and in very severe cases, severe jaundice and later kernicterus (AAP 2004). The potential for harm would need to be weighed up by clinicians in context with the settings in which they work. For instance, if treatment for moderate to severe jaundice was not easily accessible and there was a risk of causing further complications for the infant, late cord clamping may be less optimal. On the other hand, increasing iron stores in infants through delayed cord clamping may be particularly beneficial in resource-poor settings where severe anaemia is common (McDonald 2007).

If late cord clamping in term infants can lead to improved iron stores in infants, it may have long-term benefits but this needs to be confirmed in long-term follow-up studies. In addition, more conclusive answers are needed regarding postpartum haemorrhage and other measures of maternal wellbeing, as well as potential adverse effects on infants such as jaundice requiring photother-

apy. WHO has recently recommended that "the cord should not be clamped earlier than is necessary" and notes that this would normally take around three minutes. They have graded this recommendation as "weak recommendation, low quality evidence" (WHO 2007). Although this review contains some additional data not considered by WHO 2007, this cautious recommendation appears to be appropriate.

AUTHORS' CONCLUSIONS

Implications for practice

A more liberal approach to delaying clamping of the umbilical cord in healthy term infants appears to be warranted, particularly in light of growing evidence that delayed cord clamping may be of benefit in the longer term in promoting better iron stores in infants, as long as access to treatment for jaundice requiring phototherapy is easily accessible.

Implications for research

Future studies should include adequate power and rigour to be able to detect the true advantages and disadvantages of cord clamping on outcomes. Future studies should compare maternal outcomes such as PPH, longer term (6-12 months) postpartum follow-up on iron status, physical and psychological health, as well as short and longer term neonatal and infant outcomes such as neurodevelopment.

ACKNOWLEDGEMENTS

Dr Chad Andersen, Consultant Neonatologist in the Department of Perinatal Medicine at the Children's Youth and Women's Health Service in Adelaide, Australia, who provided valuable feedback and comments on several versions of the review.

We wish to thank the Cochrane Pregnancy and Childbirth Review Group, particularly Sonja Henderson, Lynn Hampson and the Consumer Panel. We also wish to thank Jo Abbott and Shane Higgins who helped to write the protocol and carried out some of the data extraction for the review.

REFERENCES

References to studies included in this review

Cernadas 2006 *{published data only}*
Ceriani Cernadas JM, Carroli G, Otano L, Pellegrini L, Mariani GL, Ferreira M, et al.Effect of timing of cord clamping on postnatal hematocrit values and clinical outcome in term infants. A randomized controlled trial [abstract]. *Pediatric Research* 2004;**55 Suppl**:67.
* Ceriani Cernadas JM, Carroli G, Pellegrini L, Otano L, Ferreira M, Ricci C, et al.The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. *Pediatrics* 2006;**117**:779–86.

Chaparro 2006 *{published data only}*
Chaparro CM, Fornes R, Neufeld LM, Alavez GT, Cedillo RE, Dewey KG. Early umbilical cord clamping contributes to elevated blood lead levels among infants with higher lead exposure. *Journal of Pediatrics* 2007;**151**:506–12.
* Chaparro CM, Neufeld LM, Alavez GT, Cedillo RE-L, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. *Lancet* 2006;**367**: 1997–2004.

Emhamed 2004 *{published data only}*
Emhamed MO, van Rheenen P, Brabin BJ. The early effects of delayed cord clamping in term infants born to Libyan mothers. *Tropical Doctor* 2004;**34**:218–22.

Geethanath 1997 *{published data only}*
Geethanath RM, Ramji S, Thirupuram S, Rao YN. Effect of timing of cord clamping on the iron status of infants at 3 months. *Indian Pediatrics* 1997;**34**(2):103–6.

Gupta 2002 *{published data only}*
Gupta R, Ramji S. Effect of delayed cord clamping on iron stores in infants born to anemic mothers: a randomized controlled trial. *Indian Pediatrics* 2002;**39**(2):130–5.

McDonald 1996 *{published and unpublished data}*
McDonald S. Timing of interventions in the third stage of labour. International Confederation of Midwives 24th Triennial Congress; 1996 May 26-31; Oslo, Norway. 1996:143.
McDonald S. Timing of interventions in the third stage of labour. Proceedings of the 14th Annual Congress of the Australian Perinatal Society in conjunction with the New Zealand Perinatal Society; 1996 March 24-27; Adelaide, Australia. 1996:A23.
* McDonald SJ. *Management in the third stage of labour [dissertation]*. Perth: University of Western Australia, 1996.

Nelson 1980 *{published data only}*
Nelson NM, Enkin MW, Saigal S, Bennett KJ, Milner R, Sackett DL. A randomized clinical trial of the Leboyer approach to childbirth. *New England Journal of Medicine* 1980;**302**(12):655–60.

Oxford Midwives 1991 *{published data only}*
Oxford Midwives Research Group. A study of the relationship between the delivery to cord clamping interval and the time of cord separation. *Midwifery* 1991;**7**:167–76.

Saigal 1972 *{published data only}*
* Saigal S, O'Neill A, Surainder Y, Chua LB, Usher R. Placental transfusion and hyperbilirubinemia in the premature. *Pediatrics* 1972;**49**: 406–19.
Saigal S, Usher RH. Symptomatic neonatal plethora. *Biology of the Neonate* 1977;**32**:62–72.

Spears 1966 *{published data only}*

Spears RL, Anderson GV, Brotman S, Farrier J, Kwan J, Masto A, et al.The effect of early vs late cord clamping on signs of respiratory distress. *American Journal of Obstetrics and Gynecology* 1966;**95**:564–8.

van Rheenen 2007 *{published data only}*

van Rheenen P, de Moor L, Eschbach S, de Grooth H, Brabin B. Delayed cord clamping and haemoglobin levels in infancy: a randomised controlled trial in term babies. *Tropical Medicine and International Health* 2007;**12**(5):603–15.

References to studies excluded from this review

Abdel Aziz 1999 *{published data only}*

Abdel Aziz SF, Shaheen MY, Hussein S, Suliman MS. Early cord clamping and its effect on some haematological determinants of blood viscosity in neonates. www.obgyn.net/pb/articles/cordclamping_aziz_0699.htm (accessed May 2007).

Begley 1990 *{published data only}*

Begley CM. A comparison of 'active' and 'physiological' management of the third stage of labour. *Midwifery* 1990;**6**(1):3–17.

Botha 1968 *{published data only}*

Botha MC. The management of the umbilical cord in labour. *South African Journal of Obstetrics and Gynaecology* 1968;**6**:30–3.

Buckels 1965 *{published data only}*

Buckels LJ, Usher R. Cardiopulmonary effects of placental transfusion. *Journal of Pediatrics* 1965;**67**:239–46.

Colozzi 1954 *{published data only}*

Colozzi AE. Clamping of the umbilical cord; its effect on the placental transfusion. *New England Journal of Medicine* 1954;**250**(15):629–32.

Daily 1970 *{published data only}*

Daily W, Olsson T, Victorin L. Transthoracic impedance: V. Effects of early and late clamping of the umbilical cord with special reference to the ratio air-to-blood during respiration. *Acta Paediatrica Scandinavica* 1970;**207**(Suppl):57–72.

Duckman 1953 *{published data only}*

Duckman S, Merk H, Lehmann WX, Regan E. The importance of gravity in delayed ligation of the umbilical cord. *American Journal of Obstetrics and Gynecology* 1953;**66**(6):1214–33.

Emmanouilides 1971 *{published data only}*

Emmanouilides GC, Moss AJ. Respiratory distress in the newborn: effect of cord clamping before and after onset of respiration. *Biology of the Neonate* 1971;**18**(5):363–8.

Erkkola 1984 *{published data only}*

Erkkola R, Kero P, Kanto J, Korvenranta H, Nanto V, Peltonen T. Delayed cord clamping in cesarean section with general anesthesia. *American Journal of Perinatology* 1984;**1**(2):165–9.

Grajeda 1997 *{published data only}*

Grajeda R, Perez-Escamilla R, Dewey K. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of age. *American Journal of Clinical Nutrition* 1997;**65**:425–31.

Greenberg 1967 *{published data only}*

Greenberg M, Vuorenkoski V, Partanen TJ, Lind J. Behavior and cry patterns in the first two hours of life in early and late clamped newborn. *Annales Paediatriae Fenniae* 1967;**13**(2):64–70.

Johansen 1971 *{published data only}*

Johansen JK, Schacke E, Sturup AG. Feto-maternal transfusion and free bleeding from the umbilical cord. *Acta Obstetricia et Gynecologica Scandinavica* 1971;**50**:193–5.

Kemp 1971 *{published data only}*

Kemp J. A review of cord traction in the third stage of labour from 1963 to 1969. *Medical Journal of Australia* 1971;**1**(17):899–903.

Khan 1997 *{published data only}*

Khan GQ, John IS, Wani S, Doherty T, Sibai BM. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 1997;**177**(4):770–4.

Kliot 1984 *{published data only}*

Kliot D, Silverstein L. Changing maternal and newborn care. A study of the Leboyer approach to childbirth management. *New York State Journal of Medicine* 1984;**84**:169–74.

Linderkamp 1992 *{published data only}*

* Linderkamp O, Nelle M, Kraus M, Zilow EP. The effect of early and late cord-clamping on blood viscosity and other hemorheological parameters in full-term neonates. *Acta Paediatrica* 1992;**81**(10):745–50.

Nelle M, Zilow EP, Kraus M, Bastert G, Linderkamp O. The effect of Leboyer delivery on blood viscosity and other hemorheologic parameters in term neonates. *American Journal of Obstetrics and Gynecology* 1993;**169**:189–93.

Nelle 1996 *{published data only}*

* Nelle M, Kraus M, Bastert G, Linderkamp O. Effects of Leboyer childbirth on left- and right systolic time intervals in healthy term neonates. *Journal of Perinatal Medicine* 1996;**24**(5):513–20.

Nelle M, Zilow EP, Bastert G, Linderkamp O. Effect of Leboyer childbirth on cardiac output, cerebral and gastrointestinal blood flow velocities in full-term neonates. *American Journal of Perinatology* 1995;**12**:212–6.

Newton 1961 *{published data only}*

Newton M, Moody AR. Fetal and maternal blood in the human placenta. *Obstetrics & Gynecology* 1961;**18**:305–8.

* Newton M, Mosey LM, Egli GE, Gifford WB, Hull CT. Blood loss during and immediately after delivery. *Obstetrics & Gynecology* 1961;**17**:9–18.

Philip 1973 *{published data only}*

Philip AGS. Further observations on placental transfusion. *Obstetrics and Gynecology* 1973;**42**(3):334–43.

Prendiville 1988 *{published data only}*

Prendiville WJ, Harding JE, Elbourne DR, Stirrat GM. The Bristol third stage trial: active versus physiological management of third stage of labour. *BMJ* 1988;**297**:1295–300.

Rogers 1998 *{published data only}*

Rogers J, Wood J, McCandlish R, Ayers S, Truesdale A, Elbourne D. Active versus expectant management of third stage of labour: the Hinchingbrooke randomised controlled trial. *Lancet* 1998;**351**(9104):693–9.

Saigal 1981 *{published data only}*
Saigal S, Nelson NM, Bennett KJ, Enkin MW. Observations on the behavioral state of newborn infants during the first hour of life. A comparison of infants delivered by the Leboyer and conventional methods. *American Journal of Obstetrics and Gynecology* 1981;**139** (6):715–9.

Schindler 1981 *{published data only}*
Schindler AE, Schach R. [Clamped umbilical cord. Effect on the puerperium and the newborn's hematocrit]. *Fortschritte der Medizin* 1981;**99**(44):1849–51.

Siddall 1953 *{published data only}*
Siddall RS, Richardson RP. Milking or stripping the umbilical cord; effect on vaginally delivered babies. *Obstetrics and Gynecology* 1953; **1**(2):230–3.

Sorrells-Jones 1982 *{published data only}*
Sorrell-Jones J. A comparison of the effects of the Leboyer delivery and modern 'routine' childbirth. Personal communication with the Cochrane Pregnancy and Childbirth Group 1982.

Taylor 1963 *{published data only}*
Taylor PM, Bright NH, Birchard EL. Effect of early vs delayed clamping of the umbilical cord on the clinical condition of the newborn infant. *American Journal of Obstetrics and Gynecology* 1963;**86**:893–8.

Terry 1970 *{published data only}*
Terry MF. A management of the third stage to reduce feto-maternal transfusion. *The Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970;**77**(2):129–32.

Thilaganathan 1993 *{published data only}*
Thilaganathan B, Cutner A, Latimer J, Beard R. Management of the third stage of labour in women at low risk of postpartum haemorrhage. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 1993;**48**(1):19–22.

Walsh 1968 *{published data only}*
Walsh SZ. Maternal effects of early and late clamping of the umbilical cord. *Lancet* 1968;**1**(7550):996–7.

Walsh 1969 *{published data only}*
Walsh SZ. Early clamping versus stripping of cord: comparative study of electrocardiogram in neonatal period. *British Heart Journal* 1969;**31**(1):122–6.

Whipple 1957 *{published data only}*
Whipple GA, Thomas MD, Sisson RC, Lund CJ. Delayed ligation of the umbilical cord: its influence on the blood volume of the newborn. *Obstetrics and Gynecology* 1957;**10**(6):603–10.

Wu 1960 *{published data only}*
Wu PC, Ku TS. Early clamping of the umbilical cord: a study of its effect on the infant. *Chinese Medical Journal* 1960;**80**:351–5.

Yao 1971 *{published data only}*
Yao AC, Lind J, Vuorenkoski V. Expiratory grunting in the late clamped normal neonate. *Pediatrics* 1971;**48**(6):865–70.

Yao 1977 *{published data only}*
Yao AC, Lind J. Effect of early and late cord clamping on the systolic time intervals of the newborn infant. *Acta Paediatricia Scandinavica* 1977;**66**(4):489–93.

References to studies awaiting assessment

Dunn 1966 *{published data only}*
Dunn PM, Fraser ID, Raper AB. Influence of early cord ligation on the transplacental passage of foetal cells. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1966;**73**:757–60.

Lanzkowsky 1960 *{published data only}*
Lanzkowsky P. Effects of early and late clamping of umbilical cord on infant's haemoglobin level. *BMJ* 1960;**2**:1777–82.

References to ongoing studies

Beal 2006 *{unpublished data only}*
Beal JM. Timing of cord clamping and neonatal hemoglobin. http://clinicaltrials.gov/ct2/show/record/NCT00371228 (accessed 13 February 2008). [: NCT00371228]

Additional references

AAP 2004
American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;**114**(1):297–316.

Adamson 1996
Adamson P. A failure of imagination. *Progress of Nations*. New York: UNICEF, 1996:2–9.

Baskett 1992
Baskett TF. Management of the third stage of labour: a survey of practice among Canadian obstetricians. *Journal of the Society of Obstetricians & Gynaecologists of Canada* 1992;**14**:61–4.

Beischer 1986
Beischer NA, Mackay EV. *Obstetrics and the newborn*. Eastbourne: Bailliere Tindall, 1986.

Bonnar 2000
Bonnar J. Massive obstetric haemorrhage. *Baillière's Clinical Obstetrics and Gynaecology* 2000;**14**(1):1–18.

Brucker 2001
Brucker MC. Management of the third stage of labor: an evidence-based approach. *Journal of Midwifery and Women's Health* 2001;**46** (6):381–92.

Burchell 1980
Burchell RC. Postpartum haemorrhage. In: Quilligan ES editor (s). *Current therapy in obstetrics and gynecology*. Philadelphia: WB Saunders, 1980.

Cotter 2001
Cotter A, Ness A, Tolosa J. Prophylactic oxytocin for the third stage of labour. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD001808]

Gülmezoglu 2007
Gülmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for prevention of postpartum haemorrhage. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD000494.pub3]

Higgins 2006
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The

Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

Hutton 2007
Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates. *JAMA* 2007;**297**(11):1241–52.

ICM/FIGO 2006
Prevention and Treatment of Post-partum Haemorrhage; New Advances for Low Resource Settings: Joint Statement. International Confederation of Midwives (ICM); International Federation of Gynaecology and Obstetrics (FIGO) 2006, issue www.pphprevention.org/files/FIGO–ICM_Statement_November2006_Final.pdf.

Inch 1985
Inch S. Management of the third stage of labour: another cascade of intervention?. *Midwifery* 1985;**1**:114–22.

Kwast 1991
Kwast BE. Postpartum haemorrhage: its contribution to maternal mortality. *Midwifery* 1991;**7**:64–70.

Lapido 1972
Ladipo OA. Management of third stage of labour, with particular reference to reduction of feto-maternal transfusion. *British Medical Journal* 1972;**1**(5802):721–3.

Loke 2008
Loke YL, Price D, Herxheimer A on behalf of the Cochrane Adverse Effects Methods Groups. Chapter 14 Adverse effects. In: Higgins JPT, Green S (editors) editor(s). *Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK*. Chichester, UK: Wiley, 2008.

McDonald 2003
McDonald S. Physiology and management of the third stage of labour. In: Fraser D, Cooper M editor(s). *Myles textbook for midwives*. 14th Edition. Edinburgh: Churchill Livingstone, 2003.

McDonald 2004
McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: 10.1002/14651858.CD000201.pub2]

McDonald 2007
McDonald S. Management of the third stage of labor. *Journal of Midwifery and Women's Health* 2007;**52**:254–61.

Mercer 2001
Mercer JS. Current best evidence: a review of the literature on umbilical cord clamping. *Journal of Midwifery & Women's Health* 2001; **46**(6):402–14.

Mercer 2006
Mercer JS. Current best evidence: a review of the literature on umbilical cord clamping. In: Wickham S editor(s). *Midwifery: best practice*. Vol. **4**, Edinburgh: Elsevier, 2006:114–29.

Moerschel 2008
Moerschel SK, Cianciaruso LB, Tracy LR. A practical approach to neonatal jaundice. *American Family Physician* 2008;**77**(9):1255.

Oh 2007
Oh W. Timing of umbilical cord clamping at birth in fullterm infants. *JAMA* 2007;**297**(11):1257–8.

Patterson 1994
Patterson A, Davis J, Gregory M, Holt S, Pachulski A, Stamford D, et al.A study of the effects of low haemoglobin on postnatal women. *Midwifery* 1994;**10**:77–86.

Prendiville 1989
Prendiville W, Elbourne D. Care during the third stage of labour. In: Chalmers I, Enkin M, Keirse MJNC editor(s). *Effective care in pregnancy and childbirth*. Oxford: Oxford University Press, 1989: 1145–69.

Prendiville 2000
Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/14651858.CD000007]

Rabe 2004
Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: DOI: 10.1002/14651858.CD003248.pub2]

Rabe 2008
Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. *Neonataology* 2008;**93**:138–44.

RevMan 2003
The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003.

Smith 2006
Smith J, Brennan BG. Management of the third stage of labor. EMedicine from WebMD (last updated 27 June 2006) (accessed 28 January 2007).

UNICEF 2002
UNICEF. Maternal mortality. http://www.childiinfo.org/eddb/mat_mortal/index.htm (accessed 24 October 2002).

van Rheenen 2004
van Rheenen P, Brabin BJ. Late umbilical cord clamping as an intervention for reducing iron deficiency in term infants in developing and industrialised countries: a systematic review. *Annals of Tropical Medicine* 2004;**24**(1):3–16.

van Rheenen 2006
van Rheenen P, Brabin BJ. A practical approach to timing cord clamping in resource poor settings. *BMJ* 2006;**333**:954–8.

WHO 1990
World Health Organization. *The prevention and management of postpartum haemorrhage*. WHO report of technical working group. Report No. WHO/MCH/90.7. Geneva: WHO, 1990.

WHO 1996
World Health Organization. *Care in normal birth*. Geneva: WHO, 1996.

WHO 1998a
World Health Organization. *Postpartum care of the mother and newborn: a practical guide*. Geneva: WHO, 1998.

WHO 1998b
World Health Organization. *Care of the umbilical cord: a review of the evidence*. Geneva: WHO, 1998.

WHO 2000
World Health Organization. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors*. Geneva: WHO, 2000.

WHO 2002
World Health Organization. Making pregnancy safer (MPR). http://www.who.int/reproductive-health/mps/index.htm (accessed 24 October 2002).

WHO 2005
WHO. *The World Health Report 2005: making every mother and child count*. Geneva: WHO, 2005.

WHO 2007
WHO. Department of Making Pregnancy Safer. *WHO recommendations for the prevention of postpartum haemorrhage*. Geneva: WHO, 2007.

Winter 2007
Winter C, Macfarlane A, Deneux-Tharaux C, Zhang W-H, Alexander S, Brocklehurst P, et al.Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. *BJOG: an international journal of obstetrics and gynaecology* 2007;**114**:845–54.

Yao 1974
Yao AC, Lind J. Placental transfusion. *American Journal of Diseases of Children* 1974;**127**:128–41.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cernadas 2006

Methods	Randomised controlled trial. Computer-generated random numbers - stratified by hospital and then by mode of birth within each hospital. Variable length blocks were used. Allocation by sealed opaque sequentially numbered envelopes - the allocation was read out to the attending clinician. Staff responsible for random generation and allocation concealment processes were not involved in the recruitment phase of the trial. Blinding: paediatricians assessing the outcomes were unaware of the assigned interventions. Nature of the intervention meant that others could not be blinded. Losses to follow up: primary outcome was not measured in: early 3/93; late 1 min 1/91; late 3 min 0/92.
Participants	Women who had an uneventful cephalic vaginal or caesarean section birth, and singleton pregnancy at term; consented at 36 weeks' gestation visit. 276 women randomised. 2 obstetrical units in Argentina.

Cernadas 2006 (*Continued*)

	Exclusion criteria included diabetes, pre-eclampsia, hypertension, evidence of IUGR (estimated weight < 10th percentile), congenital malformation.
Interventions	3 interventions were compared. 1. Early umbilical cord clamping (within 1st 15 seconds of birth). n = 93 [88/93 received the intervention - no cause given for 5 changes]. 2. Cord clamping at 1 min after birth n = 91 [83/91 received the intervention - 8 changes (2 no breathing in the first 10 secs; 1 tight nuchal cord; 2 with both no breathing in first 10 secs and tight nuchal cord; 1 other cause; 2 no cause)]. 3. Cord clamping at 3 mins after birth. n = 92 [83/92 received the intervention - 9 changes (4 no breathing in the first 10 secs; 1 no breathing in the first 10 secs and tight nuchal cord; 1 secondary apnea; 1 spontaneous third stage; 1 amniotic fluid stained with meconium; 1 no cause)]. The latter 2 timing interventions were considered to be delayed. In vaginal births, if the cord clamping allocation was delayed, the infant was placed in the mother's arm while awaiting cord clamping. If a caesarean birth, the infant was placed on the mother's lap and swaddled to prevent heat loss while awaiting cord clamping. States no additional interventions were performed - interpret as no oxytocics?
Outcomes	Maternal outcomes: postpartum blood loss volume and maternal haematocrit at 24 hours post birth. Infant outcomes: newborn venous haematocrit at 6 hours after birth, neonatal haematocrit and plasma bilirubin levels at 24 and 48 hours of age, early neonatal mortality and morbidity (tachypnoea, respiratory grunting, respiratory distress, jaundice, seizures, sepsis, necrotising enterocolitis), admission to NICU, newborn length of hospital stay, any neonatal disease that occurred between birth and 1 month, weight and method of feeding at 1 month.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Chaparro 2006

Methods	Randomised controlled trial. Blocks of 4 generated by random digital generator in Microsoft Excel. Numbered index cards with allocation were sealed in numbered opaque envelopes ordered sequentially. Blinding: no mention of blinding. Losses to follow up: early group: 68/239 lost to follow up at 6 months (27 no longer interested, 7 moved away, 28 could not be located, 5 lack of time, 1 infant ill); leaving 171 who completed the study at 6 months. There were also 2 protocol violations (cord clamping more than 30 secs after the delivery of the infant's shoulders), 1 nuchal cord, 1 reason not recorded. 157 had full blood sample analysis. Late group: 50/237 lost to follow up at 6 months (25 no longer interested, 4 moved away, 16 could not be located, 3 lack of time, 1 infant died, 1 participation in other study), leaving 187 who completed the study at 6 months. There were also 52 protocol violations (clamping at less than 100 secs after delivery of infant's shoulders), 30 concerns for infant's condition, 15 forceps used, 3 infants born in labour room bed, 4 misunderstanding of treatment group. 171 had full blood analysis.
Participants	476 mother-infant pairs were randomised. Women at term (equal to or greater than 36 weeks' and less than 42 weeks' gestation, where a vaginal birth of a healthy singleton infant was anticipated, the woman planned to breastfeed for at least 6 months, was a non-smoker, was able to return for follow-up visits and there were no complicating medical or obstetric factors. Exclusion criteria applied after birth were low birthweight (< 2500 g) and major congenital malformations. Setting: large obstetrics hospital in Mexico City, Mexico.
Interventions	Early clamping (10 secs after birth) (n = 239);. late clamping (2 mins after birth) (n = 237). Any condition arising that necessitated earlier clamping was adhered to.
Outcomes	Maternal: estimated maternal blood loss at birth. Infant: haematological and iron status at 6 months of age, newborn haematocrit and reported neonatal jaundice between birth and 14 days of age, exclusive breastfeeding.
Notes	Jaundice was self report by mother, and so was not entered under the outcome of clinical jaundice.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Emhamed 2004

Methods	Randomised controlled trial. Consecutive allocation of opaque envelopes. Blinding: not stated. Losses to follow up: 1 mother/baby pair from each group (1/58 late; 1/46 early) left hospital before reassessment and so were not available for those outcomes measured 16-24 hours after birth. 4/50 pairs from the early group and 4/62 from the late group were excluded after randomisation because of intrapartum asphyxia.
Participants	112 (104) women in a large Libyan hospital who consented during first stage of labour. Exclusion criteria: women with known medical or obstetric problems, less than 37 weeks' or greater than 42 weeks' gestation. Post randomisation exclusions were an infant weighing less than 2500 g, instrumental births, respiratory distress, congenital abnormalities or the need for early cord clamping.
Interventions	Early (immediate) cord clamping (10 secs following birth (n = 46); late cord clamping (when cord pulsation ceased) (n = 58). Oxytocin given when cord clamping had been performed.
Outcomes	Maternal: pre and post birth haemoglobin and haematocrit. Infant: haemoglobin and haematocrit (including cord blood), polycythemia, hyperviscosity and jaundice.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Geethanath 1997

Methods	Allocation by opaque, sealed envelopes. Blinding: not reported. Losses to follow up: not reported.
Participants	107 women (anticipating a term vaginal birth and not experiencing any medical or obstetric complications including anaemia of < 10 g/dL). New Delhi hospital, India. Post randomisation exclusions were applied in the presence of birth asphyxia, major congenital malformations.
Interventions	Early cord clamping: cord clamped as soon as the infant was born; late clamping: cord clamped after the placenta had descended into the vagina during which time the infant was held 10 cm below the vaginal introitus.

Geethanath 1997 (*Continued*)

Outcomes	Maternal: haemoglobin shortly after completion of birth. Infant: cord blood at birth and and venous blood sample at 3 months for ferritin and haemoglobin estimation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gupta 2002

Methods	Allocation by opaque sealed envelopes, with computer-generated random number sequences. Blinding: not stated. Losses to follow up: at 3 months, 58 (57%) of the original 102 mother-infant pairs were available, 29 pairs in each group.
Participants	102 infant-mother pairs - hospital born neonates born vaginally to pregnant women with anaemia (haemoglobin < 100 g/L at term) Exclusion criteria: medical or pregnancy related complications e.g. eclampsia, severe heart failure, severe antepartum haemorrhage or rH iso-immunisation. Infants who needed resuscitation at birth or who had major congenital malformations. Teaching hospital, New Delhi.
Interventions	Early cord clamping group (cord clamped immediately after the birth of the infant), n = 53. Late cord clamping (cord clamped after the placenta had descended into the vagina), n = 49 - during this time the infant was warmly wrapped and held below the level of the mothers abdomen but within 10 cm of the vagina. 4 ml of maternal venous blood was taken at the time of the birth, 4 ml of cord blood at birth and 4 ml venous blood from the infant at 3 months of age. Infants were not given any medicinal iron supplementation during the study period.
Outcomes	Maternal: haemoglobin at birth. Infant: haemoglobin at 3 months, weight gain, feeding patterns, respiratory infections and diarrhoea.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

McDonald 1996

Methods	Randomisation: list of computer-generated random numbers. Opaque, sealed, sequentially numbered envelopes kept at a central location in the delivery ward. Blinding: see notes. Losses to follow up: all women allocated to receive a particular timing option were included in the intended group with the exception of 37 women for whom no trial number was recorded (14/250 in early cord clamping and early uterotonic group; 6/250 in late cord clamping and early uterotonic group; 6/250 in early cord clamping and late uterotonic; and 11/250 in late cord clamping and late uterotonic group).
Participants	All women attending the antenatal clinic at King Edward Memorial Hospital, randomised when a vaginal birth was thought to be imminent. Exclusions: maternal refusal to participate in the study; caesarean section; breech delivery; multiple pregnancy; fetal indication (e.g., known fetal anomaly); preterm birth (< 37 completed weeks' gestation). 1000 women were randomised to the trial; the data of 37 women were excluded due to insufficient information available to include in the analyses, leaving data for 963 women available for analysis.
Interventions	4 arms: early cord clamping and early uterotonic administration (n = 236); late cord clamping and early uterotonic administration (n = 244); early cord clamping and late uterotonic administration (n = 244); late cord clamping and late uterotonic administration (n = 239). Definitions: early cord clamping involved clamping immediately following birth of the body of the baby; late cord clamping occurred when cord pulsation had ceased or at 5 mins if cord pulsation had not already ceased. This time limit was imposed to reduce the risk of compromising infants who may have any undiagnosed underlying conditions such as a PDA; early uterotonic administration involved administration at the time of birth of the anterior shoulder of the baby; late uterotonic administration was after the birth of the baby (literally) and if the cord clamping allocation was early, then it was allocated to be after the cord was clamped (ie not within 30 seconds).
Outcomes	Maternal: PPH = or > 500 ml, = or > 1000 ml; mean blood loss; need for blood transfusion; need for manual removal of placenta; length of third stage (> 30 mins and > 60 mins); need for therapeutic uterotonics; evacuation of retained products; inversion of the uterus; length of hospital stay. Neonatal: Apgar score < 6 at 5 mins; admission to NICU; jaundice requiring phototherapy (> 1 day); need for serum bilirubin test; breastfeeding at discharge.
Notes	Sample size: the initial sample size calculation was based on an anticipation that the PPH rate from a uterotonic choice trial (McDonald 1996) would be around 10%. It was calculated that a sample size of 3000 women would be required to have an 80% chance of detecting a 50% reduction in PPH at the 5% level of statistical significance. However, review during the trial by a Data Monitoring Committee determined that the PPH rate was greater than the 10% rate predicted, the actual recorded PPH rate being around 16%; this reduced the required sample size to ~1,100 women. Blood loss assessment: "the major endpoint of the study was PPH ascertained by measurement of collected blood spillage where possible and all other blood loss estimated by visual estimation. The trial could not be 'blind' at this point; the clinician carrying out the intervention was also attempting to assess the blood loss. The authors attempted to obtain objective indices of blood loss in the form of 1. postpartum haemoglobin, 2. calculation of the difference between antepartum and postpartum haemoglobin. Although these measures may not be reliable measures of the amount of blood loss by an individual, they are

McDonald 1996 (*Continued*)

	objective, independent of observer bias and were carried out on women in the trial without knowledge of which intervention was used". Jaundice assessment: Clinicians assessing jaundice are not likely to have been aware of the allocation to early and late clamping groups. The study was written up as a PhD thesis, a copy of which is available from the Pregnancy and Childbirth Group office. It has never been submitted for journal publication; submission is planned in 2008.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nelson 1980

Methods	Randomisation: "assigned randomly" - no further details provided. Blinding: 2nd observer blinded for Brazelton Neonatal Behavioural Assessment Scale, infant Bayley Scales of Infant Development assessed blind. Losses to follow up: 1/55 (dropped out from conventional (early clamping) group.
Participants	Women considered to be at low obstetrical risk, interested in the Leboyer approach to birth, and intending to attend psychoprophylactic prenatal classes. Exclusion criteria: giving birth before 36 weeks, not available for 3 day and 8 month assessments.
Interventions	Early ('conventional') birth with cord clamping within 1 min of birth (n = 26); median time of 45 secs. Late (Leboyer method with cord clamped when it stopped pulsating); n = 28; median time of 180 secs.
Outcomes	Maternal: length of first, second and third stages of labour, mother's experience of labour and birth, maternal psychological adjustment at 6 weeks, maternal perception of infant behaviour at 3 days, 6 weeks and 8 months postpartum (Carey Scales of Infant Temperament), PPH (blood loss threshold not defined), extension of episiotomy, infected episiotomy, endometritis, urinary tract infection. Infant: perinatal asphyxia, hypothermia (one or more axillary temp > 35 C), respiratory rate more than 60, polycythaemia (24 hour capillary haemoglobin more than 25 g per 100 ml [more than 15.51 mmol/L]), jaundice, hyperbilirubinaemia (serum bilirubin more than 12 mg per 100 ml [more than 205.2 umol/L]).
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Oxford Midwives 1991

Methods	Randomisation: generation by random-number tables (simple unblocked and unstratified); sealed opaque envelopes were consecutively numbered and centrally stored in the delivery suite.
Participants	554 women. Setting: large teaching hospital in Oxford, UK.
Interventions	Early clamping (as soon as possible after the birth) or late clamping (3 mins after the birth).
Outcomes	Maternal: PPH, manual removal of placenta. Neonatal: respiratory problems e.g. transient tachypnoea, grunting, rib recession, heart or cardiovascular problems, clinical jaundice (whether jaundice had been noted, the duration and level of jaundice as indicated by serum bilirubin if blood samples were taken, whether treated with phototherapy), birthweight, feeding method, duration of cord adherence.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Saigal 1972

Methods	Randomisation: "assigned prior to delivery according to a randomised study protocol" but no further details given. Blinding: not reported. Losses to follow up: not stated.
Participants	45 term infants born in 2 hospitals in Montreal, Canada. Full-term infants 38 to 42 weeks' gestation, vaginal births. Exclusion criteria: infants of diabetic mothers, malformed infants, infants who developed systemic infections, erythroblastic infants and infants who were small for date (below third percentile for gestational age).
Interventions	Immediate cord clamping - within 5 secs, median 2 secs (n = 15). Clamping at 1 min - held low, 30 cm below perineum (n = 15). All women: oxytocic agents were given only after the cord was clamped. No phototherapy was given for jaundice.
Outcomes	Infant: venous haematocrit, cord haematocrit, blood volume, red cell blood volume, plasma volume, bilirubin.
Notes	

Saigal 1972 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Spears 1966

Methods	Randomly allocated to early or late cord clamping group upon entering the delivery room. No description of how the allocation process was decided.
Participants	379 women who gave birth vaginally to a term infant weighing greater than 2500 gm at the Los Angeles County General Hospital USA.
Interventions	Early cord clamping was defined as within 1 min after birth (60% were clamped within 30 secs) (n = 192). Late cord clamping was defined as clamping as at 3 mins post birth. In both instances, the infant was held level with the mother's perineum while the cord was cut (n = 187). No mention of whether or when the mother received any uterotonic agent.
Outcomes	Infant: Apgar scores, respiratory distress.
Notes	No maternal outcomes reported that were of relevance to this review.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

van Rheenen 2007

Methods	Randomisation: sequentially numbered opaque sealed envelopes with unpredictable allocation code. Blinding: "partially blinded" study; "one of the investigators… monitored the delivery procedure and was therefore not blinded to treatment assignment". Losses to follow up: early group: 8/45 (4 at 2 months, 2 more at 4 months, 2 more at 6 months - 6 moved, 1 died, 1 refused further participation). Late group: 11/46 (3 at 2 months, 4 more at 4 months, 4 more at 6 months - 6 moved, 3 died, 2 refused further participation). Postrandomisation exclusions: 5/50 in the early group (1 low birthweight, 1 unexpected twin, 1 tight nuchal cord, 1 need for resuscitation, 1 refused further participation), 9/55 in the late group (2 low birthweight, 1 major congenital abnormalities, 2 unexpected twins, 3 tight nuchal cords, 1 need for resuscitation).
Participants	Full-term pregnant women giving birth in hospital. 105 randomised (50 to early and 55 to late cord clamping) - 45 and 46 analysed. Exclusion criteria: before randomisation: twin pregnancy; history of PPH; gestational diabetes; pre-eclampsia. After randomisation: placental separation before birth; caesarean section; tight nuchal cord necessitating early cutting; need for neonatal resuscitation; major congenital abnormalities. Infants who weighed less than 2500 g or with gestational age less than 37 weeks, were excluded. Setting: hospital in Zambia (malaria-endemic area).
Interventions	Immediate cord clamping within 20 secs of birth (n = 45) [mean 15 [SD 8] secs]. Cord clamped after cord stopped pulsating (n = 46) [mean 305 [SD 136] secs]. After vaginal birth all infants were placed between the legs of the mother (about 10 cm below the vaginal introitus) until the cord was clamped. Intramuscular oxytocin was given to mothers after clamping of the cord.
Outcomes	Infant: haemoglobin change from cord values; proportion of anaemic infants at 4 months after birth; duration infants remained free of anaemia (up to 6 months); adverse effects of delayed cord clamping in infants (packed cell volume changes 1 day postpartum; clinical signs of hyperviscosity syndrome or hyperbilirubinaemia) and mothers (haemoglobin change 1 day after birth, blood loss in third stage of labour); birthweight; jaundice; jaundice requiring phototherapy; ZPP levels; blood glucose; malaria; exclusive breastfeeding; infant mortality - 4 deaths (but not reported by early or late cord clamping group).
Notes	Anaemia = Hb concentration more than 2 SDs below the mean of similarly aged infants from an iron-supplemented USA reference population not exposed to malaria (9.4 g/dL at 2 months, 10.3 at 4 months and 10.5 at 6 months). Fetal anaemia = cord haemoglobin < 12.5 g/dL. Maternal anaemia = haemoglobin < 11 g/dL. Iron deficiency = ZPP levels above 80 umol/mol haem for infants and adults. Iron-deficiency anaemia in mothers and infants = combination of ZPP above the cutoff level, together with Hb more than 2 SD below the reference mean (and mean cell haemoglobin concentration below the cutoff level for 2 month follow up).

van Rheenen 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

IUGR: intrauterine growth retardation
mins: minutes
NICU: neonatal intensive care unit
PDA: patent ductus arteriosus
PPH: postpartum haemorrhage
SD: standard deviation
secs: seconds
ZPP: zinc protoporphyrin

Characteristics of excluded studies *[ordered by study ID]*

Abdel Aziz 1999	Quasi-randomised.
Begley 1990	This is a comparison of active versus expectant management of the third stage of labour and so is included in the Cochrane review of this topic.
Botha 1968	No mention of randomisation and allocation process not described.
Buckels 1965	No mention of randomisation and allocation process not described.
Colozzi 1954	No mention of randomisation and allocation process not described.
Daily 1970	Quasi-randomised - "every other child has early clamping and the others late clamping".
Duckman 1953	No mention of randomisation and allocation process not described.
Emmanouilides 1971	No mention of randomisation and allocation process not described.
Erkkola 1984	No mention of randomisation and allocation process not described.
Grajeda 1997	Quasi-randomised.
Greenberg 1967	No mention of randomisation and allocation process not described.

(*Continued*)

Johansen 1971	Quasi-randomised: control group comprised mothers born on odd dates; experimental group comprised mothers born on even dates.
Kemp 1971	Quasi-randomised: allocation method open to bias; "patients were allocated according to age: those whose age was an odd number became the group for abdominal manipulation, and those whose age was an even number formed the cord traction group".
Khan 1997	This is a comparison of active versus expectant management of the third stage of labour and so is included in the Cochrane review of this topic.
Kliot 1984	No mention of randomisation and allocation process not described.
Linderkamp 1992	No mention of randomisation and allocation process not described.
Nelle 1996	No mention of randomisation and allocation process not described.
Newton 1961	Quasi-randomised: allocation method by rotation.
Philip 1973	No clinical outcomes relevant to this review were measured.
Prendiville 1988	This is a comparison of active versus expectant management of the third stage of labour and so is included in the Cochrane review of this topic.
Rogers 1998	This is a comparison of active versus expectant management of the third stage of labour and so is included in the Cochrane review of this topic.
Saigal 1981	No clinical outcomes relevant to this review were measured.
Schindler 1981	This study compared clamped and unclamped cord management rather than early versus late timing of cord clamping. Note that although the full paper was in German, a translator was available; it was determined from the English abstract that this study could not be included.
Siddall 1953	Quasi-randomised: "in the first half of the experiment the boys cords were milked, while 50 girls had prompt clamping and ligation at delivery. The sexes were reversed for the second 100".
Sorrells-Jones 1982	No clinical outcomes relevant to this review were measured.
Taylor 1963	Quasi-randomised: allocation method by rotation.
Terry 1970	Quasi-randomised: allocation method by alternation.
Thilaganathan 1993	This is a comparison of active versus expectant management of the third stage of labour and so is included in the Cochrane review of this topic.

(*Continued*)

Walsh 1968	No mention of randomisation and allocation process not described.
Walsh 1969	No mention of randomisation and allocation process not described.
Whipple 1957	Allocation method, by rotation, open to bias.
Wu 1960	Quasi-randomised: allocation method by alternation.
Yao 1971	No mention of randomisation and allocation process not described.
Yao 1977	No clinical outcomes relevant to this review were measured.

Characteristics of ongoing studies *[ordered by study ID]*

Beal 2006

Trial name or title	Timing of cord clamping and neonatal hemoglobin - NCT00371228.
Methods	
Participants	150 women presenting for vaginal birth at Tulsa Regional Medical Centre, Oklahoma, USA.
Interventions	1) Clamping of umbilical cord within 6 seconds of delivery of the fetal shoulders. 2) Clamping the cord after a palpable pulse has ceased, or after 10 minutes.
Outcomes	Neonatal haemoglobin.
Starting date	September 2006.
Contact information	John M Beal; Sarah J McCoy, Oklahoma State University Center for Health Sciences email: sjmccoy98@aol.com
Notes	

DATA AND ANALYSES

Comparison 1. Early versus late cord clamping

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PPH/blood loss 500 ml or more	4	1878	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.96, 1.55]
1.1 uterotonic before clamping	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.74, 1.67]
1.2 uterotonic at, or after, clamping	2	574	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.95, 2.14]
1.3 use of uterotonic not specified	1	272	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.73, 1.74]
2 Severe PPH/blood loss 1000 ml or more	4	1684	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.48, 1.49]
2.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.46, 2.96]
2.2 uterotonic at, or after, clamping	2	574	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.22, 1.59]
2.3 use of uterotonic not specified	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.29, 2.49]
3 Mean blood loss (ml)	1	963	Mean Difference (IV, Fixed, 95% CI)	6.36 [-34.94, 47.66]
3.1 uterotonic before clamping	1	480	Mean Difference (IV, Fixed, 95% CI)	22.01 [-40.16, 84.16]
3.2 uterotonic at, or after, clamping	1	483	Mean Difference (IV, Fixed, 95% CI)	-6.01 [-61.25, 49.25]
4 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum	3	1128	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.30, 0.06]
4.1 uterotonic before clamping	1	480	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 uterotonic at, or after, clamping	1	483	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.42, 0.22]
4.3 use of uterotonic not specified	2	165	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.60, 0.04]
5 Need for blood transfusion	1	963	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.20, 3.15]
5.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.26, 9.20]
5.2 uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.06]
6 Need for manual removal of placenta	2	1515	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.78, 3.26]
6.1 uterotonic before clamping	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.94, 5.01]
6.2 uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.65]
7 Length of third stage > 30 mins	1	963	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.29, 3.41]
7.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	3.10 [0.32, 29.61]

7.2 uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.65]
8 Length of third stage > 60 mins	1	963	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.32, 2.04]
8.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.34, 3.16]
8.2 uterotonic at, or after clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.65]
9 Need for therapeutic uterotonics	1	963	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.74, 1.20]
9.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.78, 1.55]
9.2 uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.14]
10 Maternal ferritin (ug/L)	1	107	Mean Difference (IV, Fixed, 95% CI)	9.10 [7.86, 10.34]
10.1 use of uterotonic not specified	1	107	Mean Difference (IV, Fixed, 95% CI)	9.10 [7.86, 10.34]
11 Apgar score < 7 at 5 mins	2	1342	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.73, 2.07]
11.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.42, 7.13]
11.2 uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [0.60, 6.42]
11.3 use of uterotonic not specified	1	379	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.51, 1.85]
12 Admission to SCN or NICU	3	1293	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.56, 1.90]
12.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.47, 4.50]
12.2 uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.52, 4.72]
12.3 use of uterotonic not specified	2	330	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.20, 1.60]
13 Admission for respiratory distress	2	1008	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.18, 5.75]
13.1 uterotonic before clamping	1	480	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.08, 2.11]
13.2 uterotonic at, or after, clamping	2	528	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.48, 12.50]
14 Respiratory distress	1	379	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.65, 1.89]
14.1 use of uterotonic not specified	1	379	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.65, 1.89]
15 Jaundice requiring phototherapy	5	1762	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.38, 0.92]
15.1 uterotonic before clamping	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.11]
15.2 uterotonic at, or after, clamping	4	730	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.31, 1.11]
16 Clinical jaundice	5	1918	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
16.1 uterotonic before clamping	2	1022	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.18]
16.2 uterotonic at, or after, clamping	2	576	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.31]
16.3 use of uterotonic not specified	2	320	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.29, 1.39]

17 Polycythaemia	3	463	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.12, 1.27]
17.1 uterotonic at, or after, clamping	2	195	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.06, 2.48]
17.2 use of uterotonic not specified	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.09, 1.80]
18 Cord haemoglobin (g/dL)	4	314	Mean Difference (IV, Fixed, 95% CI)	0.42 [0.03, 0.80]
18.1 uterotonic at, or after, clamping	2	149	Mean Difference (IV, Fixed, 95% CI)	0.66 [0.13, 1.19]
18.2 use of uterotonic not specified	2	165	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.42, 0.71]
19 Newborn haemoglobin (g/dL)	3	671	Mean Difference (IV, Random, 95% CI)	-2.17 [-4.06, -0.28]
19.1 uterotonic at, or after, clamping	1	45	Mean Difference (IV, Random, 95% CI)	-4.45 [-5.33, -3.57]
19.2 use of uterotonic not specified	2	626	Mean Difference (IV, Random, 95% CI)	-1.07 [-2.03, -0.12]
20 Infant haemoglobin at 24-48 hours (g/dL)	2	382	Mean Difference (IV, Fixed, 95% CI)	-1.34 [-1.80, -0.88]
20.1 uterotonic at, or after, clamping	1	104	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.17, -0.63]
20.2 use of uterotonic not specified	1	278	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-1.88, -0.74]
21 Infant haemoglobin at 2-4 months (g/dL)	3	256	Mean Difference (IV, Random, 95% CI)	-0.30 [-1.25, 0.65]
21.1 uterotonic at, or after, clamping	1	91	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.88, 0.28]
21.2 use of uterotonic not specified	2	165	Mean Difference (IV, Random, 95% CI)	-0.27 [-1.94, 1.39]
22 Infant haemoglobin at 6 months (g/dL)	2	447	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.17, 0.23]
22.1 uterotonic at, or after, clamping	1	91	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.35, 1.15]
22.2 use of uterotonic not specified	1	356	Mean Difference (IV, Fixed, 95% CI)	Not estimable
23 Infant haematocrit < 45% at 6 hours	1	272	Risk Ratio (M-H, Fixed, 95% CI)	16.18 [2.05, 127.37]
23.1 use of uterotonic not specified	1	272	Risk Ratio (M-H, Fixed, 95% CI)	16.18 [2.05, 127.37]
24 Infant haematocrit < 45% at 24-48 hours	1	268	Risk Ratio (M-H, Fixed, 95% CI)	6.03 [2.27, 16.07]
24.1 use of uterotonic not specified	1	268	Risk Ratio (M-H, Fixed, 95% CI)	6.03 [2.27, 16.07]
25 Infant haemoglobin > 2 SDs below 10.3 g/dL at 4 months	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.96, 3.54]
25.1 uterotonic at, or after, clamping	1	91	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.96, 3.54]
26 Infant haemoglobin at 6 months	2	447	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.75, 1.48]
26.1 > 2 SD below 10.5 g/dL: uterotonic at, or after, clamping	1	91	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.61, 1.43]

26.2 < 12.2 g/dL: use of uterotonic not specified	1	356	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.70, 1.96]
27 Infant ferritin (ug/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
27.1 at 3 months: use of uterotonic not specified	1	107	Mean Difference (IV, Fixed, 95% CI)	-17.90 [-19.21, -16.59]
27.2 at 6 months: use of uterotonic not specified	1	315	Mean Difference (IV, Fixed, 95% CI)	-11.80 [-19.53, -4.07]
28 Exclusive breastfeeding	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 at discharge: uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.08]
28.2 at discharge: uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.97, 1.10]
28.3 1 month: use of uterotonic not specified	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.00, 1.20]
28.4 2 months: use of uterotonic not specified	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.75, 1.28]
28.5 3 months: use of uterotonic not specified	2	144	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.13]
28.6 4 months: use of uterotonic not specified	1	313	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.30]
28.7 6 months: use of uterotonic not specified	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.73, 1.33]

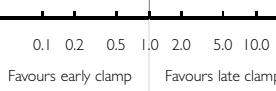
Analysis 1.1. Comparison 1 Early versus late cord clamping, Outcome 1 PPH/blood loss 500 ml or more.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 1 PPH/blood loss 500 ml or more

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	31/236	32/244		31.0 %	1.00 [0.63, 1.59]
Oxford Midwives 1991	12/256	9/296		8.2 %	1.54 [0.66, 3.60]
Subtotal (95% CI)	**492**	**540**		**39.2 %**	**1.11 [0.74, 1.67]**
Total events: 43 (early clamping), 41 (late clamping)					
Heterogeneity: Chi^2 = 0.77, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.53 (P = 0.60)					
2 uterotonic at, or after, clamping					
McDonald 1996	48/244	33/239		32.8 %	1.42 [0.95, 2.14]
van Rheenen 2007	0/45	0/46		0.0 %	0.0 [0.0, 0.0]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**289**	**285**		**32.8 %**	**1.42 [0.95, 2.14]**
Total events: 48 (early clamping), 33 (late clamping)					
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 1.71 (P = 0.087)					
3 use of uterotonic not specified					
Cernadas 2006	24/90	43/182		28.0 %	1.13 [0.73, 1.74]
Subtotal (95% CI)	**90**	**182**		**28.0 %**	**1.13 [0.73, 1.74]**
Total events: 24 (early clamping), 43 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					
Total (95% CI)	**871**	**1007**		**100.0 %**	**1.22 [0.96, 1.55]**
Total events: 115 (early clamping), 117 (late clamping)					
Heterogeneity: Chi^2 = 1.68, df = 3 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 1.64 (P = 0.10)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours early clamp Favours late clamp

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 1 PPH/blood loss 500 ml or more

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	31/236	32/244		31.0 %	1.00 [0.63, 1.59]
Oxford Midwives 1991	12/256	9/296		8.2 %	1.54 [0.66, 3.60]
Subtotal (95% CI)	**492**	**540**		**39.2 %**	**1.11 [0.74, 1.67]**
Total events: 43 (early clamping), 41 (late clamping)					
Heterogeneity: Chi^2 = 0.77, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.53 (P = 0.60)					

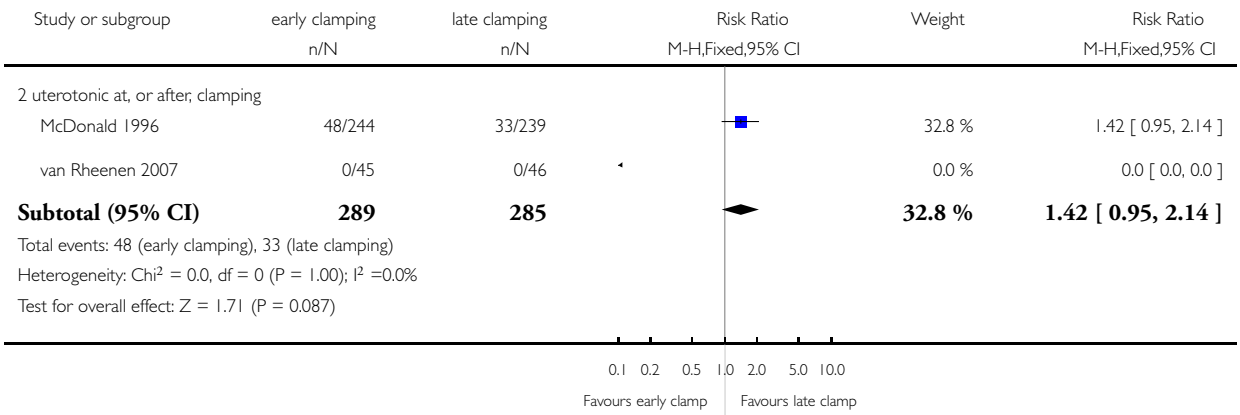
0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favours early clamp Favours late clamp

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

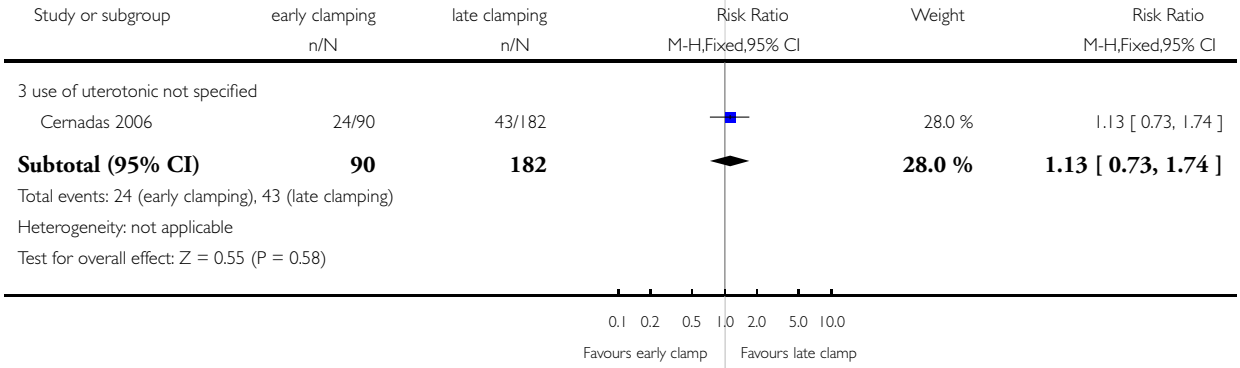
Outcome: 1 PPH/blood loss 500 ml or more



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 1 PPH/blood loss 500 ml or more

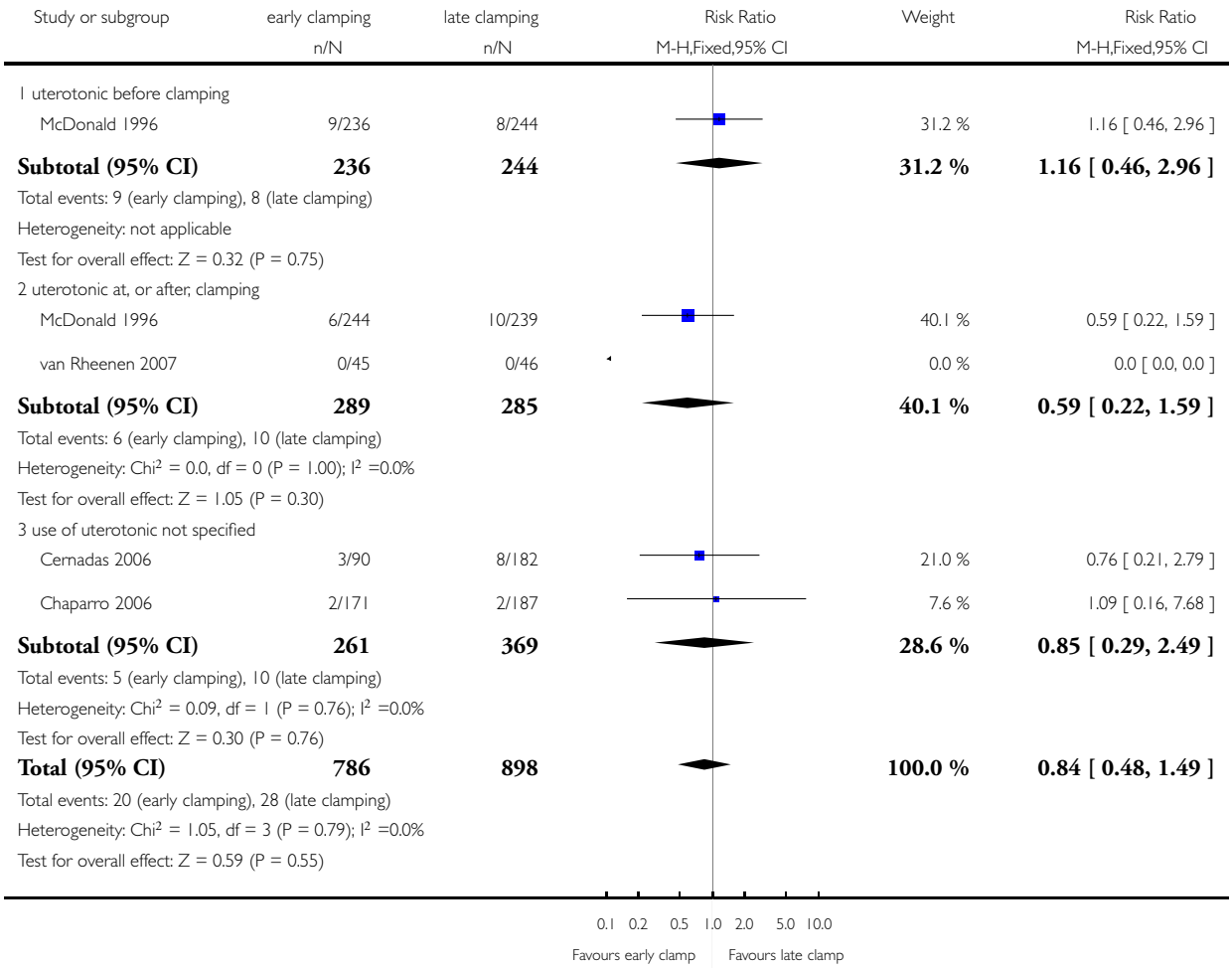


Analysis 1.2. Comparison 1 Early versus late cord clamping, Outcome 2 Severe PPH/blood loss 1000 ml or more.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

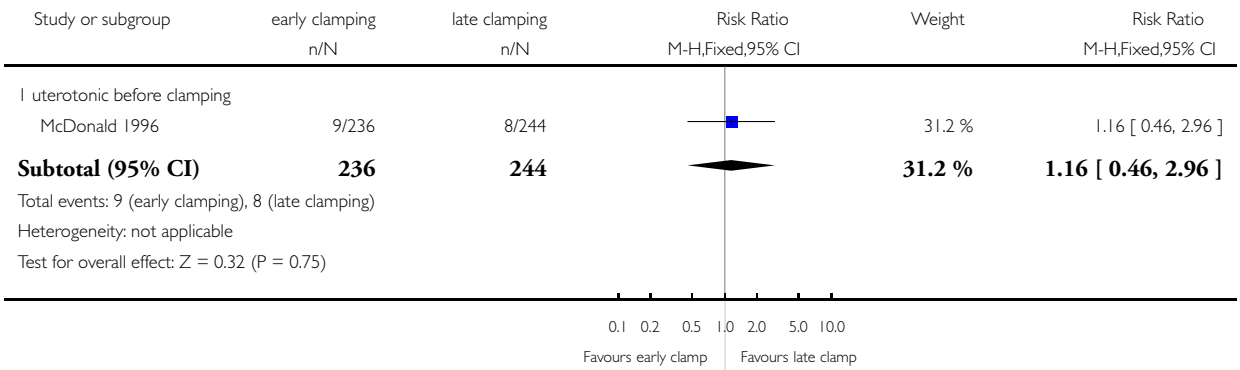
Outcome: 2 Severe PPH/blood loss 1000 ml or more



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

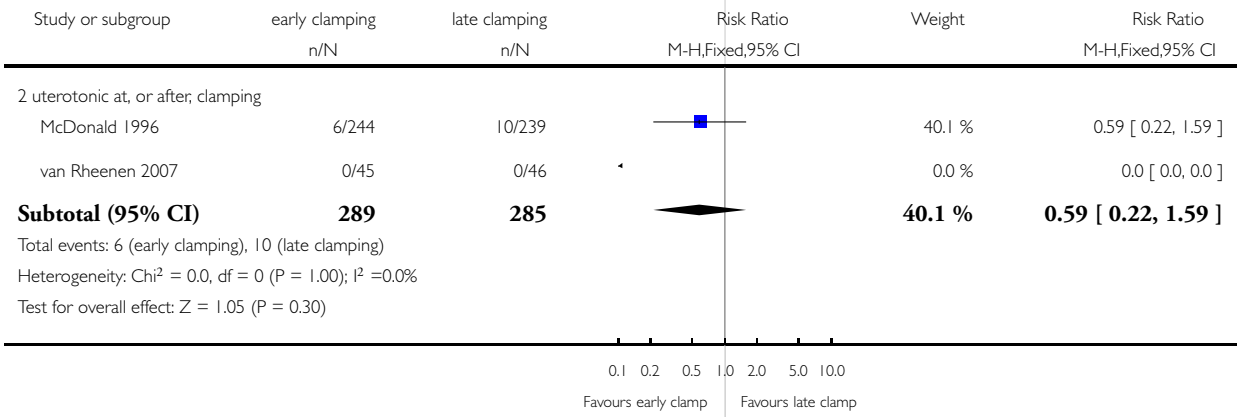
Outcome: 2 Severe PPH/blood loss 1000 ml or more



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 2 Severe PPH/blood loss 1000 ml or more



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 2 Severe PPH/blood loss 1000 ml or more

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 use of uterotonic not specified					
Cernadas 2006	3/90	8/182		21.0 %	0.76 [0.21, 2.79]
Chaparro 2006	2/171	2/187		7.6 %	1.09 [0.16, 7.68]
Subtotal (95% CI)	**261**	**369**		**28.6 %**	**0.85 [0.29, 2.49]**
Total events: 5 (early clamping), 10 (late clamping)					
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 0.30 (P = 0.76)					

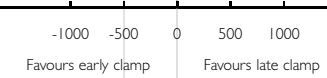
Analysis 1.3. Comparison 1 Early versus late cord clamping, Outcome 3 Mean blood loss (ml).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 3 Mean blood loss (ml)

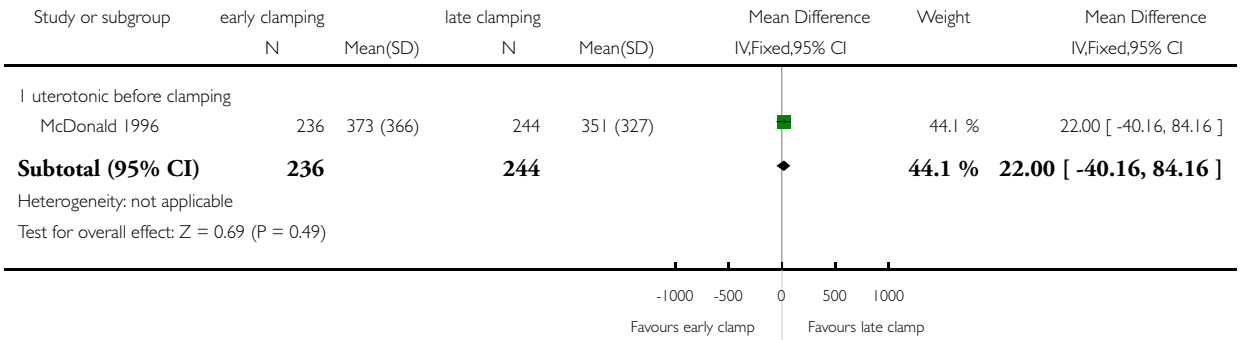
Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic before clamping							
McDonald 1996	236	373 (366)	244	351 (327)		44.1 %	22.00 [-40.16, 84.16]
Subtotal (95% CI)	**236**		**244**			**44.1 %**	**22.00 [-40.16, 84.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
2 uterotonic at, or after, clamping							
McDonald 1996	244	353 (278)	239	359 (338)		55.9 %	-6.00 [-61.25, 49.25]
Subtotal (95% CI)	**244**		**239**			**55.9 %**	**-6.00 [-61.25, 49.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.21 (P = 0.83)							
Total (95% CI)	**480**		**483**			**100.0 %**	**6.36 [-34.94, 47.66]**
Heterogeneity: Chi^2 = 0.44, df = 1 (P = 0.51); I^2 =0.0%							
Test for overall effect: Z = 0.30 (P = 0.76)							
Test for subgroup differences: Chi^2 = 0.44, df = 1 (P = 0.51), I^2 =0.0%							



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

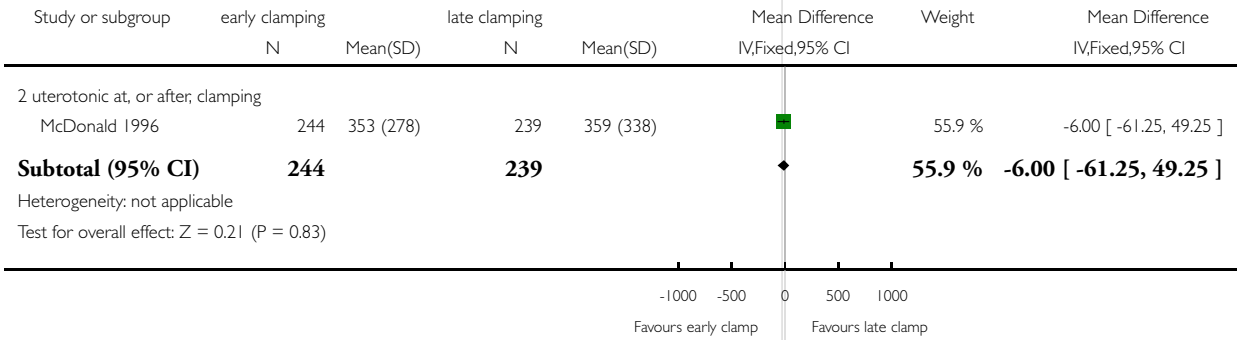
Outcome: 3 Mean blood loss (ml)



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 3 Mean blood loss (ml)



Analysis 1.4. Comparison 1 Early versus late cord clamping, Outcome 4 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 4 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic before clamping							
McDonald 1996	236	10.8 (1.8)	244	10.8 (1.6)		35.6 %	0.0 [-0.31, 0.31]
Subtotal (95% CI)	**236**		**244**			**35.6 %**	**0.0 [-0.31, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 uterotonic at, or after, clamping							
McDonald 1996	244	11.1 (1.7)	239	11.2 (1.9)		32.0 %	-0.10 [-0.42, 0.22]
Subtotal (95% CI)	**244**		**239**			**32.0 %**	**-0.10 [-0.42, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							
3 use of uterotonic not specified							
Geethanath 1997	48	12.5 (1.7)	59	12.7 (1.8)		7.5 %	-0.20 [-0.87, 0.47]
Gupta 2002	29	8.9 (0.8)	29	9.2 (0.6)		25.0 %	-0.30 [-0.66, 0.06]
Subtotal (95% CI)	**77**		**88**			**32.5 %**	**-0.28 [-0.60, 0.04]**
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 1.70 (P = 0.089)							
Total (95% CI)	**557**		**571**			**100.0 %**	**-0.12 [-0.30, 0.06]**
Heterogeneity: Chi^2 = 1.60, df = 3 (P = 0.66); I^2 =0.0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Test for subgroup differences: Chi^2 = 1.54, df = 2 (P = 0.46), I^2 =0.0%							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 4 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic before clamping							
McDonald 1996	236	10.8 (1.8)	244	10.8 (1.6)		35.6 %	0.0 [-0.31, 0.31]
Subtotal (95% CI)	**236**		**244**			**35.6 %**	**0.0 [-0.31, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 4 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 uterotonic at, or after, clamping							
McDonald 1996	244	11.1 (1.7)	239	11.2 (1.9)		32.0 %	-0.10 [-0.42, 0.22]
Subtotal (95% CI)	**244**		**239**			**32.0 %**	**-0.10 [-0.42, 0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.61 (P = 0.54)							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 4 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
3 use of uterotonic not specified							
Geethanath 1997	48	12.5 (1.7)	59	12.7 (1.8)		7.5 %	-0.20 [-0.87, 0.47]
Gupta 2002	29	8.9 (0.8)	29	9.2 (0.6)		25.0 %	-0.30 [-0.66, 0.06]
Subtotal (95% CI)	**77**		**88**			**32.5 %**	**-0.28 [-0.60, 0.04]**
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 1.70 (P = 0.089)							

Analysis 1.5. Comparison 1 Early versus late cord clamping, Outcome 5 Need for blood transfusion.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 5 Need for blood transfusion

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	3/236	2/244		43.8 %	1.55 [0.26, 9.20]
Subtotal (95% CI)	**236**	**244**		**43.8 %**	**1.55 [0.26, 9.20]**
Total events: 3 (early clamping), 2 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
2 uterotonic at, or after, clamping					
McDonald 1996	0/244	2/239		56.2 %	0.20 [0.01, 4.06]
Subtotal (95% CI)	**244**	**239**		**56.2 %**	**0.20 [0.01, 4.06]**
Total events: 0 (early clamping), 2 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
Total (95% CI)	**480**	**483**		**100.0 %**	**0.79 [0.20, 3.15]**

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 3 (early clamping), 4 (late clamping)					
Heterogeneity: Chi^2 = 1.36, df = 1 (P = 0.24); I^2 =27%					
Test for overall effect: Z = 0.34 (P = 0.74)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 5 Need for blood transfusion

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	3/236	2/244		43.8 %	1.55 [0.26, 9.20]
Subtotal (95% CI)	**236**	**244**		**43.8 %**	**1.55 [0.26, 9.20]**
Total events: 3 (early clamping), 2 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 5 Need for blood transfusion

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 uterotonic at, or after, clamping					
McDonald 1996	0/244	2/239		56.2 %	0.20 [0.01, 4.06]
Subtotal (95% CI)	**244**	**239**		**56.2 %**	**0.20 [0.01, 4.06]**
Total events: 0 (early clamping), 2 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					

Analysis 1.6. Comparison 1 Early versus late cord clamping, Outcome 6 Need for manual removal of placenta.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 6 Need for manual removal of placenta

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	8/236	5/244		41.9 %	1.65 [0.55, 4.98]
Oxford Midwives 1991	8/256	3/296		23.7 %	3.08 [0.83, 11.50]
Subtotal (95% CI)	**492**	**540**		**65.6 %**	**2.17 [0.94, 5.01]**
Total events: 16 (early clamping), 8 (late clamping)					
Heterogeneity: Chi^2 = 0.51, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.82 (P = 0.069)					
2 uterotonic at, or after, clamping					
McDonald 1996	2/244	4/239		34.4 %	0.49 [0.09, 2.65]
Subtotal (95% CI)	**244**	**239**		**34.4 %**	**0.49 [0.09, 2.65]**
Total events: 2 (early clamping), 4 (late clamping)					
Heterogeneity: not applicable					

(*Continued* . . .)

(. . . *Continued*)

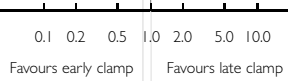
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.83 (P = 0.41)					
Total (95% CI)	**736**	**779**		**100.0 %**	**1.59 [0.78, 3.26]**
Total events: 18 (early clamping), 12 (late clamping)					
Heterogeneity: Chi^2 = 2.85, df = 2 (P = 0.24); I^2 =30%					
Test for overall effect: Z = 1.27 (P = 0.20)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 6 Need for manual removal of placenta

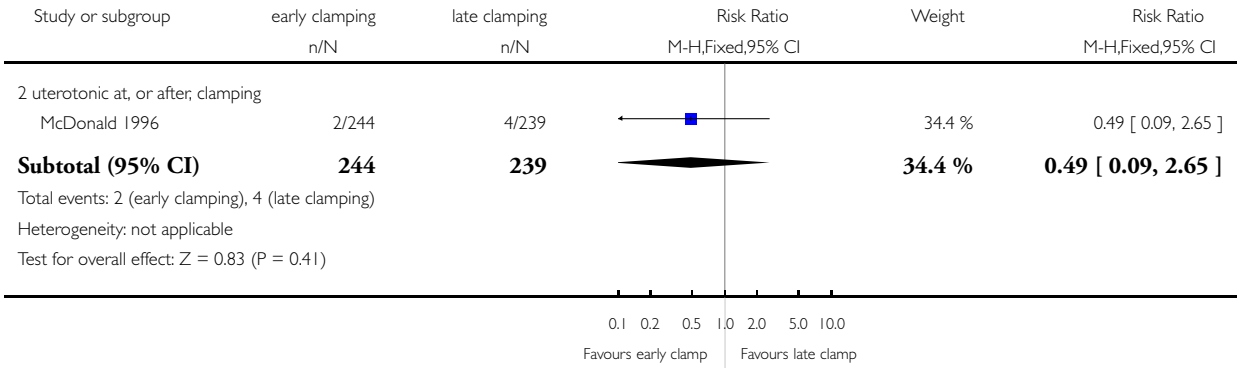
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	8/236	5/244		41.9 %	1.65 [0.55, 4.98]
Oxford Midwives 1991	8/256	3/296		23.7 %	3.08 [0.83, 11.50]
Subtotal (95% CI)	**492**	**540**		**65.6 %**	**2.17 [0.94, 5.01]**
Total events: 16 (early clamping), 8 (late clamping)					
Heterogeneity: Chi^2 = 0.51, df = 1 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.82 (P = 0.069)					



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 6 Need for manual removal of placenta

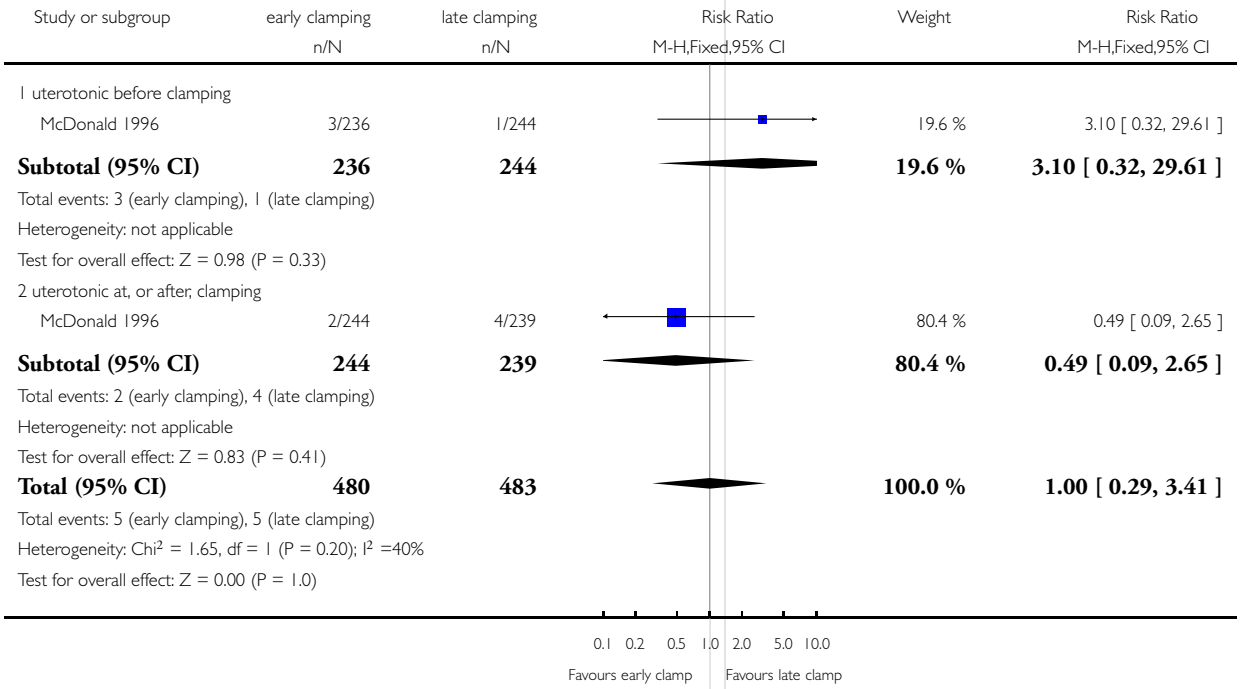


Analysis 1.7. Comparison 1 Early versus late cord clamping, Outcome 7 Length of third stage > 30 mins.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

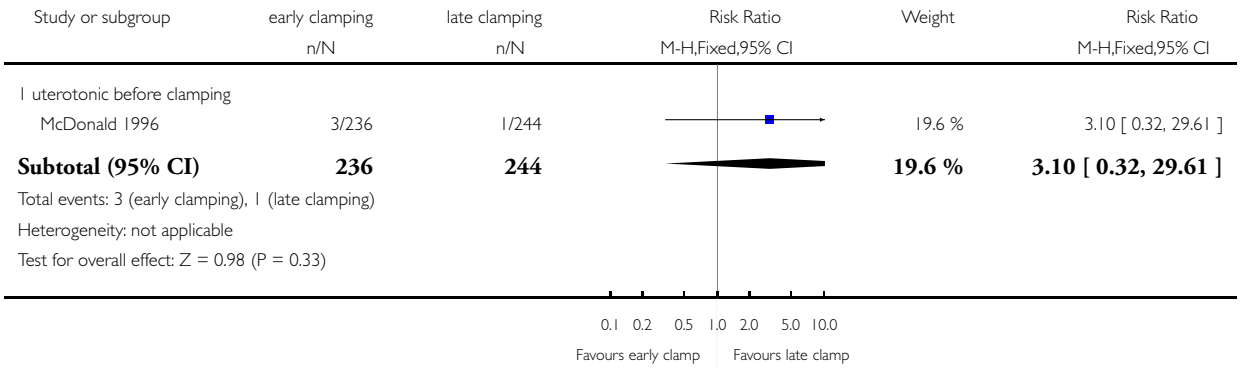
Outcome: 7 Length of third stage > 30 mins



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

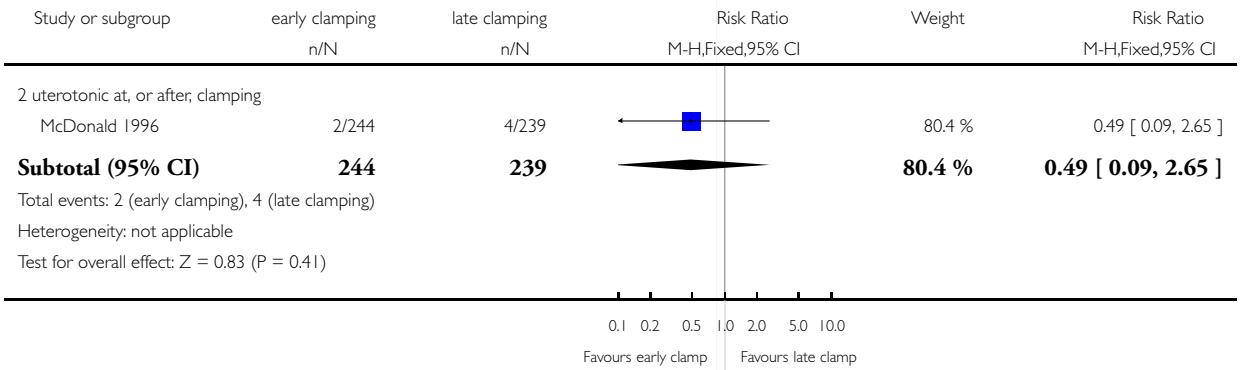
Outcome: 7 Length of third stage > 30 mins



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 7 Length of third stage > 30 mins

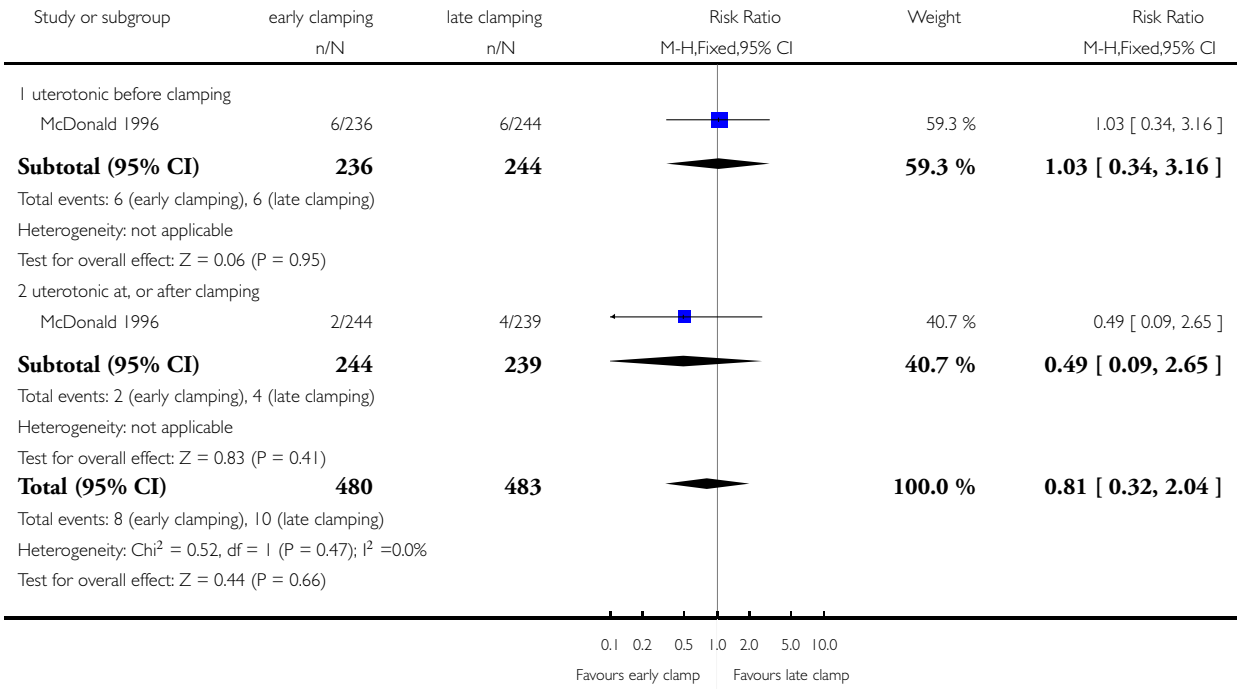


Analysis 1.8. Comparison 1 Early versus late cord clamping, Outcome 8 Length of third stage > 60 mins.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

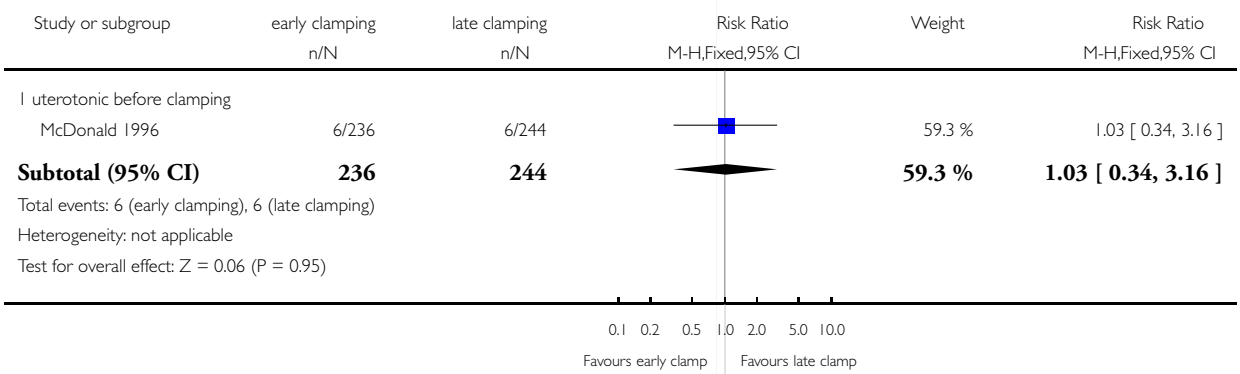
Outcome: 8 Length of third stage > 60 mins



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

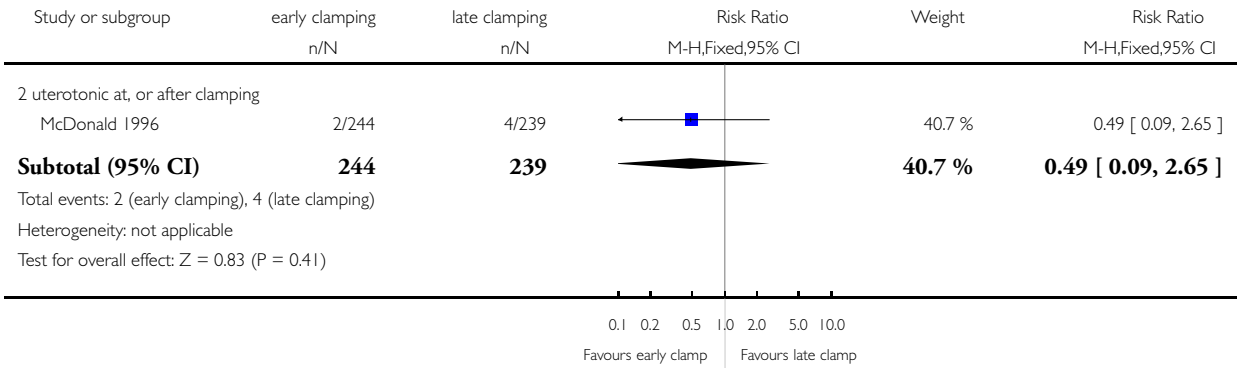
Outcome: 8 Length of third stage > 60 mins



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 8 Length of third stage > 60 mins



Analysis 1.9. Comparison 1 Early versus late cord clamping, Outcome 9 Need for therapeutic uterotonics.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 9 Need for therapeutic uterotonics

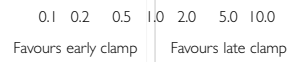
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	52/236	49/244		45.1 %	1.10 [0.78, 1.55]
Subtotal (95% CI)	**236**	**244**		**45.1 %**	**1.10 [0.78, 1.55]**
Total events: 52 (early clamping), 49 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
2 uterotonic at, or after, clamping					
McDonald 1996	48/244	58/239		54.9 %	0.81 [0.58, 1.14]
Subtotal (95% CI)	**244**	**239**		**54.9 %**	**0.81 [0.58, 1.14]**
Total events: 48 (early clamping), 58 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
Total (95% CI)	**480**	**483**		**100.0 %**	**0.94 [0.74, 1.20]**
Total events: 100 (early clamping), 107 (late clamping)					
Heterogeneity: Chi^2 = 1.50, df = 1 (P = 0.22); I^2 =33%					
Test for overall effect: Z = 0.50 (P = 0.62)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 9 Need for therapeutic uterotonics

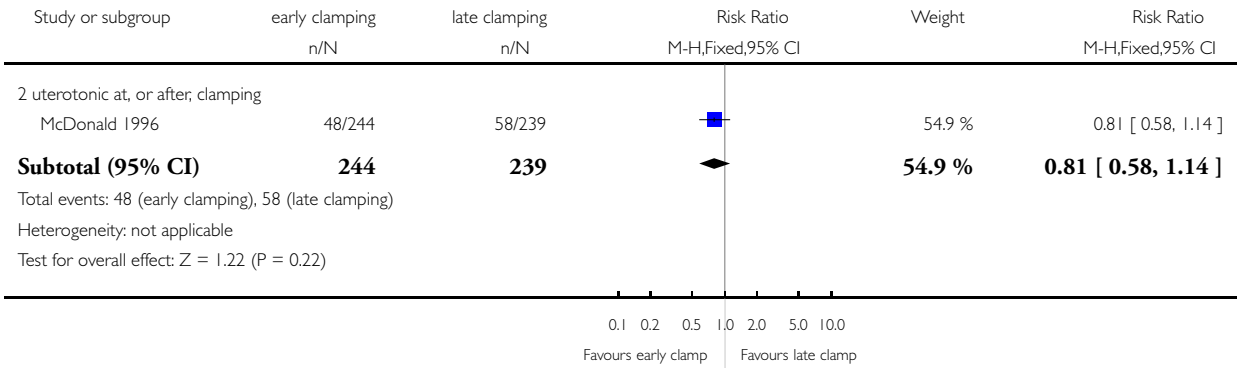
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	52/236	49/244		45.1 %	1.10 [0.78, 1.55]
Subtotal (95% CI)	**236**	**244**		**45.1 %**	**1.10 [0.78, 1.55]**
Total events: 52 (early clamping), 49 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 9 Need for therapeutic uterotonics

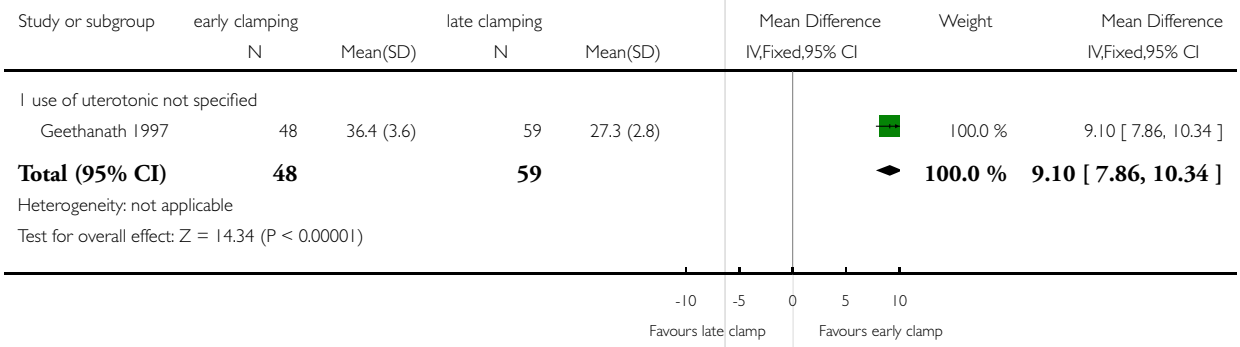


Analysis 1.10. Comparison 1 Early versus late cord clamping, Outcome 10 Maternal ferritin (ug/L).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 10 Maternal ferritin (ug/L)



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 10 Maternal ferritin (ug/L)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 use of uterotonic not specified							
Geethanath 1997	48	36.4 (3.6)	59	27.3 (2.8)		100.0 %	9.10 [7.86, 10.34]

Analysis 1.11. Comparison 1 Early versus late cord clamping, Outcome 11 Apgar score < 7 at 5 mins.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 11 Apgar score < 7 at 5 mins

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	5/236	3/244		12.2 %	1.72 [0.42, 7.13]
Subtotal (95% CI)	**236**	**244**		**12.2 %**	**1.72 [0.42, 7.13]**
Total events: 5 (early clamping), 3 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					
2 uterotonic at, or after, clamping					
McDonald 1996	8/244	4/239		16.7 %	1.96 [0.60, 6.42]
Subtotal (95% CI)	**244**	**239**		**16.7 %**	**1.96 [0.60, 6.42]**
Total events: 8 (early clamping), 4 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
3 use of uterotonic not specified					
Spears 1966	17/192	17/187		71.1 %	0.97 [0.51, 1.85]
Subtotal (95% CI)	**192**	**187**		**71.1 %**	**0.97 [0.51, 1.85]**
Total events: 17 (early clamping), 17 (late clamping)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
Total (95% CI)	**672**	**670**		**100.0 %**	**1.23 [0.73, 2.07]**
Total events: 30 (early clamping), 24 (late clamping)					
Heterogeneity: Chi^2 = 1.32, df = 2 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.78 (P = 0.43)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

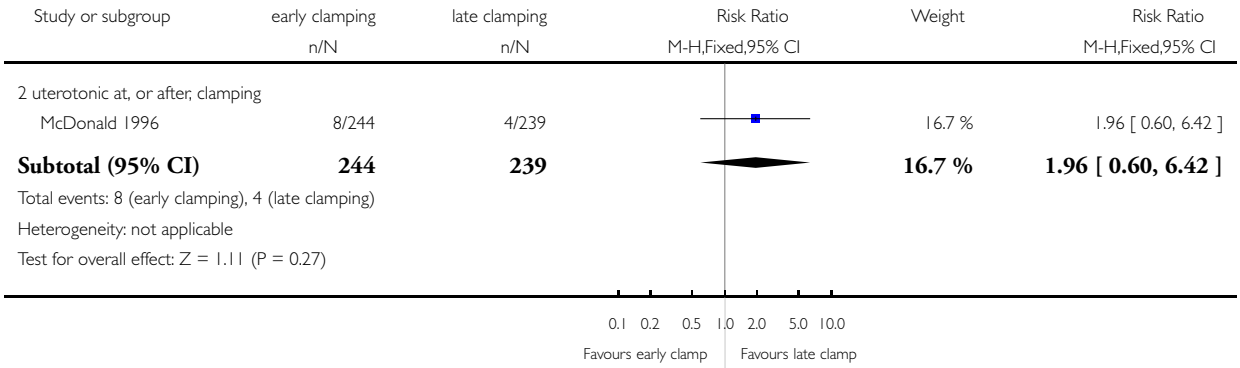
Outcome: 11 Apgar score < 7 at 5 mins

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	5/236	3/244		12.2 %	1.72 [0.42, 7.13]
Subtotal (95% CI)	**236**	**244**		**12.2 %**	**1.72 [0.42, 7.13]**
Total events: 5 (early clamping), 3 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

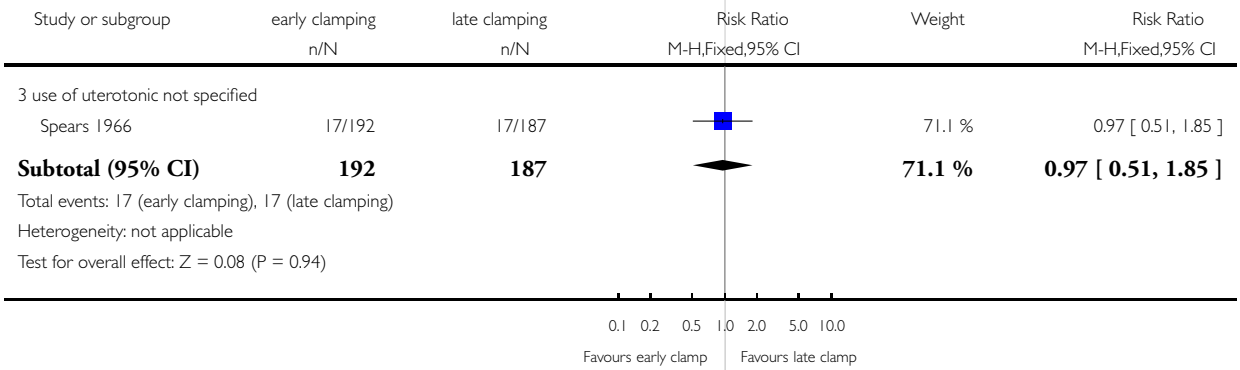
Outcome: 11 Apgar score < 7 at 5 mins



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 11 Apgar score < 7 at 5 mins



Analysis 1.12. Comparison 1 Early versus late cord clamping, Outcome 12 Admission to SCN or NICU.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

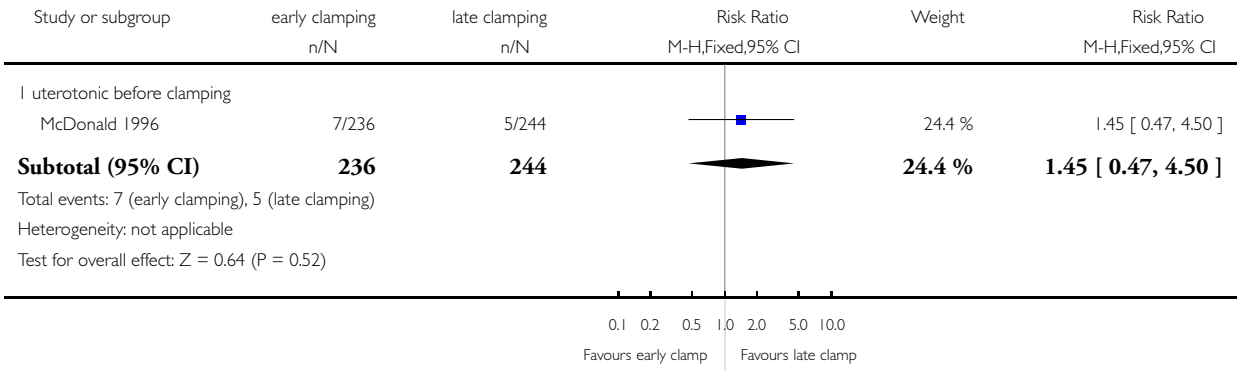
Outcome: 12 Admission to SCN or NICU

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	7/236	5/244		24.4 %	1.45 [0.47, 4.50]
Subtotal (95% CI)	**236**	**244**		**24.4 %**	**1.45 [0.47, 4.50]**
Total events: 7 (early clamping), 5 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.64 (P = 0.52)					
2 uterotonic at, or after, clamping					
McDonald 1996	8/244	5/239		25.0 %	1.57 [0.52, 4.72]
Subtotal (95% CI)	**244**	**239**		**25.0 %**	**1.57 [0.52, 4.72]**
Total events: 8 (early clamping), 5 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
3 use of uterotonic not specified					
Cernadas 2006	4/93	13/183		43.4 %	0.61 [0.20, 1.81]
Nelson 1980	0/26	1/28		7.2 %	0.36 [0.02, 8.42]
Subtotal (95% CI)	**119**	**211**		**50.6 %**	**0.57 [0.20, 1.60]**
Total events: 4 (early clamping), 14 (late clamping)					
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.07 (P = 0.28)					
Total (95% CI)	**599**	**694**		**100.0 %**	**1.03 [0.56, 1.90]**
Total events: 19 (early clamping), 24 (late clamping)					
Heterogeneity: Chi^2 = 2.24, df = 3 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.11 (P = 0.92)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

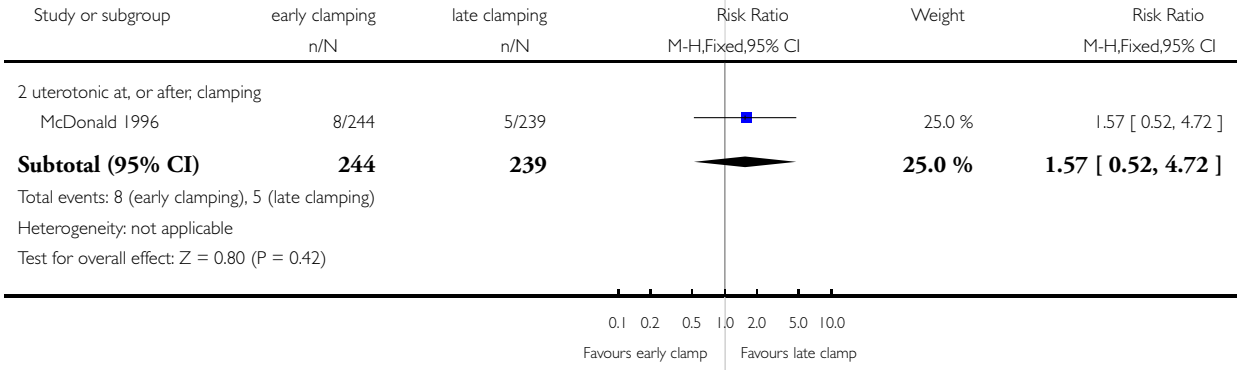
Outcome: 12 Admission to SCN or NICU



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 12 Admission to SCN or NICU



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 12 Admission to SCN or NICU

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 use of uterotonic not specified					
Cernadas 2006	4/93	13/183		43.4 %	0.61 [0.20, 1.81]
Nelson 1980	0/26	1/28		7.2 %	0.36 [0.02, 8.42]
Subtotal (95% CI)	**119**	**211**		**50.6 %**	**0.57 [0.20, 1.60]**
Total events: 4 (early clamping), 14 (late clamping)					
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.07 (P = 0.28)					

Analysis 1.13. Comparison 1 Early versus late cord clamping, Outcome 13 Admission for respiratory distress.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 13 Admission for respiratory distress

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 uterotonic before clamping					
McDonald 1996	2/236	5/244		50.0 %	0.41 [0.08, 2.11]
Subtotal (95% CI)	**236**	**244**		**50.0 %**	**0.41 [0.08, 2.11]**
Total events: 2 (early clamping), 5 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
2 uterotonic at, or after, clamping					
McDonald 1996	5/244	2/239		50.0 %	2.45 [0.48, 12.50]
Saigal 1972	0/15	0/30		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**259**	**269**		**50.0 %**	**2.45 [0.48, 12.50]**
Total events: 5 (early clamping), 2 (late clamping)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 1.08 (P = 0.28)					
Total (95% CI)	**495**	**513**		**100.0 %**	**1.01 [0.18, 5.75]**
Total events: 7 (early clamping), 7 (late clamping)					
Heterogeneity: $Tau^2 = 0.89$; $Chi^2 = 2.29$, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 0.01 (P = 0.99)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

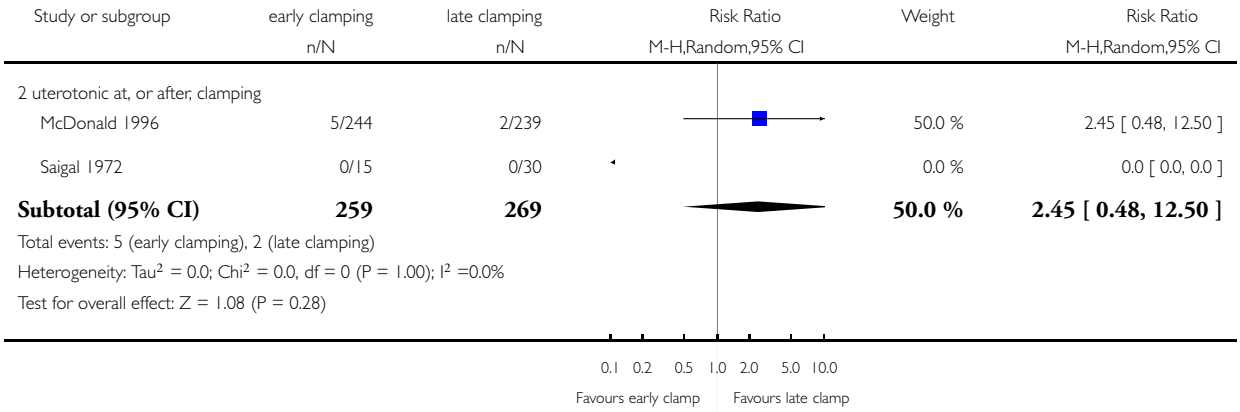
Outcome: 13 Admission for respiratory distress

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 uterotonic before clamping					
McDonald 1996	2/236	5/244		50.0 %	0.41 [0.08, 2.11]
Subtotal (95% CI)	**236**	**244**		**50.0 %**	**0.41 [0.08, 2.11]**
Total events: 2 (early clamping), 5 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 13 Admission for respiratory distress

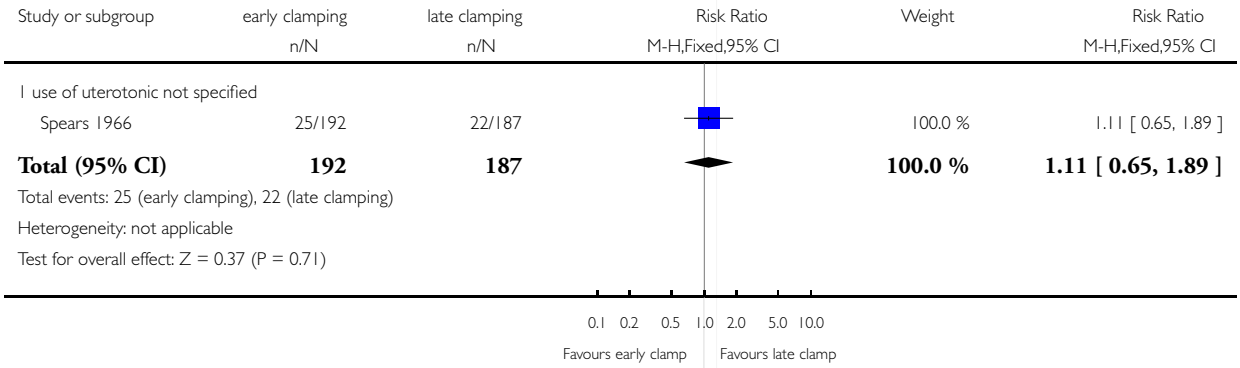


Analysis 1.14. Comparison 1 Early versus late cord clamping, Outcome 14 Respiratory distress.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 14 Respiratory distress



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 14 Respiratory distress

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 use of uterotonic not specified					
Spears 1966	25/192	22/187		100.0 %	1.11 [0.65, 1.89]

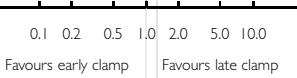
Analysis 1.15. Comparison 1 Early versus late cord clamping, Outcome 15 Jaundice requiring phototherapy.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 15 Jaundice requiring phototherapy

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	12/236	16/244		31.8 %	0.78 [0.37, 1.60]
Oxford Midwives 1991	3/256	11/296		20.6 %	0.32 [0.09, 1.12]
Subtotal (95% CI)	**492**	**540**		**52.4 %**	**0.59 [0.32, 1.11]**
Total events: 15 (early clamping), 27 (late clamping)					
Heterogeneity: Chi^2 = 1.48, df = 1 (P = 0.22); I^2 =32%					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 uterotonic at, or after, clamping					
Emhamed 2004	2/45	0/57		0.9 %	6.30 [0.31, 128.10]
McDonald 1996	10/244	21/239		42.8 %	0.47 [0.22, 0.97]
Nelson 1980	1/26	2/28		3.9 %	0.54 [0.05, 5.59]
van Rheenen 2007	0/45	0/46		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**360**	**370**		**47.6 %**	**0.58 [0.31, 1.11]**
Total events: 13 (early clamping), 23 (late clamping)					
Heterogeneity: Chi^2 = 2.76, df = 2 (P = 0.25); I^2 =28%					



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.65 (P = 0.10)					
Total (95% CI)	**852**	**910**		**100.0 %**	**0.59 [0.38, 0.92]**
Total events: 28 (early clamping), 50 (late clamping)					
Heterogeneity: Chi^2 = 4.26, df = 4 (P = 0.37); I^2 =6%					
Test for overall effect: Z = 2.32 (P = 0.020)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 15 Jaundice requiring phototherapy

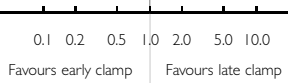
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic before clamping					
McDonald 1996	12/236	16/244		31.8 %	0.78 [0.37, 1.60]
Oxford Midwives 1991	3/256	11/296		20.6 %	0.32 [0.09, 1.12]
Subtotal (95% CI)	**492**	**540**		**52.4 %**	**0.59 [0.32, 1.11]**
Total events: 15 (early clamping), 27 (late clamping)					
Heterogeneity: Chi^2 = 1.48, df = 1 (P = 0.22); I^2 =32%					
Test for overall effect: Z = 1.64 (P = 0.10)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 15 Jaundice requiring phototherapy

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 uterotonic at, or after, clamping					
Emhamed 2004	2/45	0/57		0.9 %	6.30 [0.31, 128.10]
McDonald 1996	10/244	21/239		42.8 %	0.47 [0.22, 0.97]
Nelson 1980	1/26	2/28		3.9 %	0.54 [0.05, 5.59]
van Rheenen 2007	0/45	0/46		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**360**	**370**		**47.6 %**	**0.58 [0.31, 1.11]**
Total events: 13 (early clamping), 23 (late clamping)					
Heterogeneity: Chi^2 = 2.76, df = 2 (P = 0.25); I^2 =28%					
Test for overall effect: Z = 1.65 (P = 0.10)					

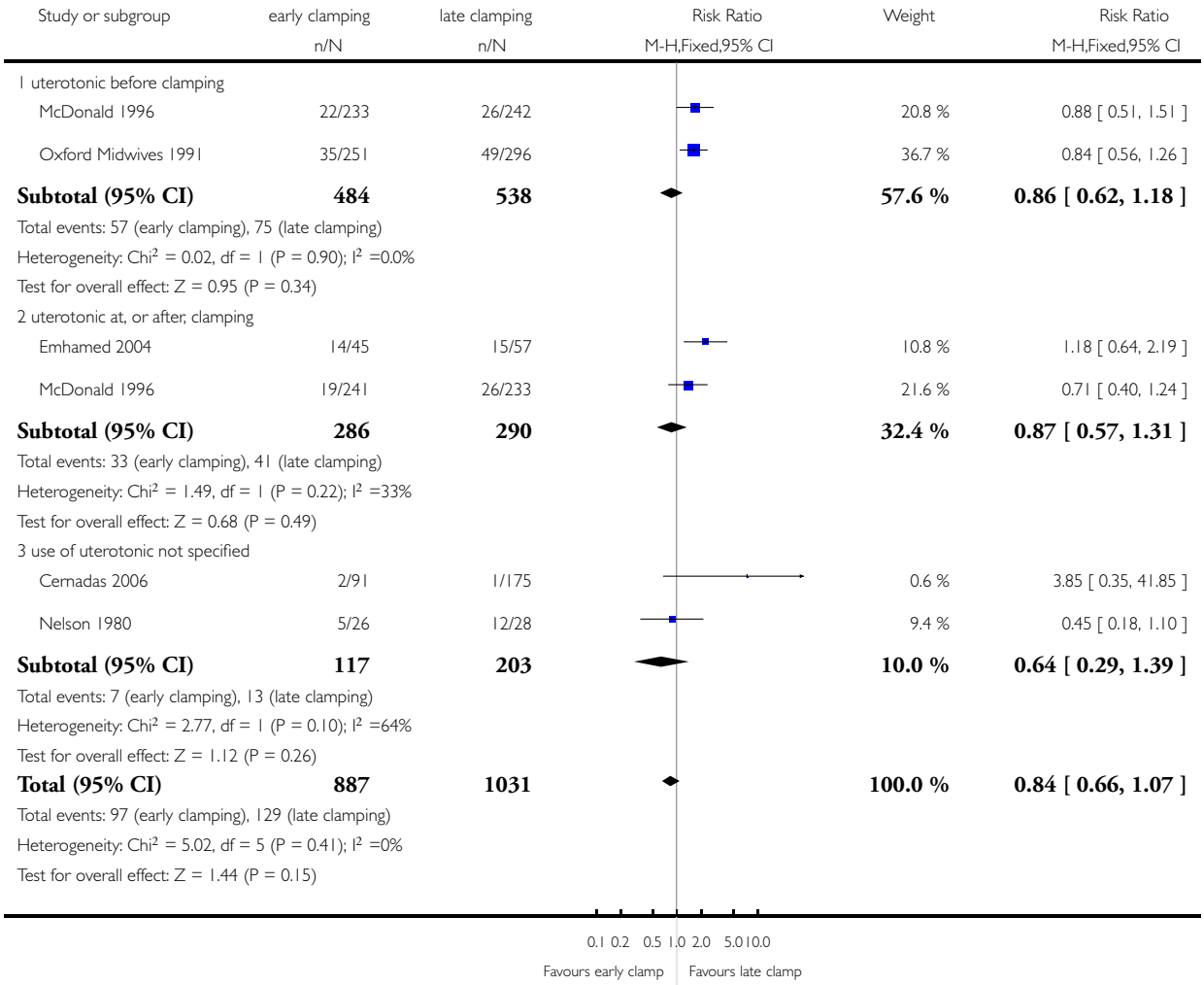


Analysis 1.16. Comparison 1 Early versus late cord clamping, Outcome 16 Clinical jaundice.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

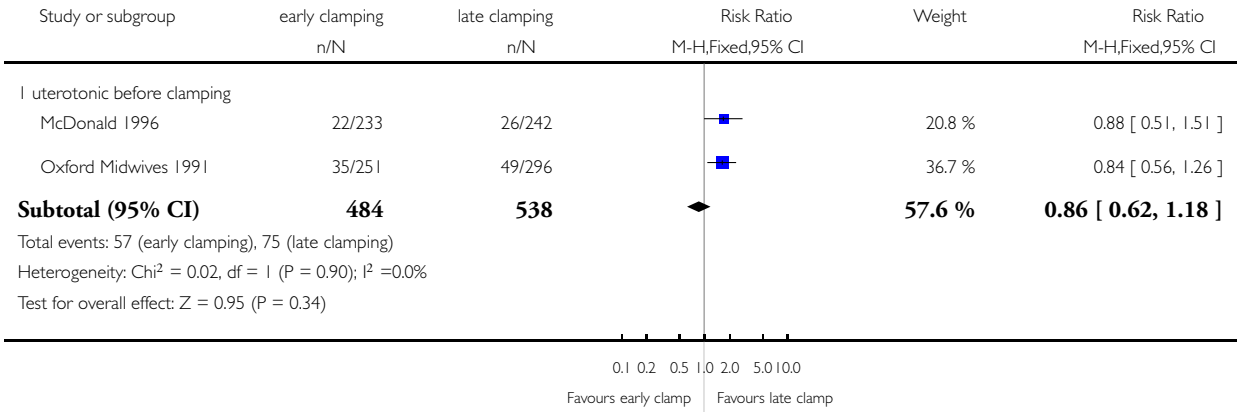
Outcome: 16 Clinical jaundice



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

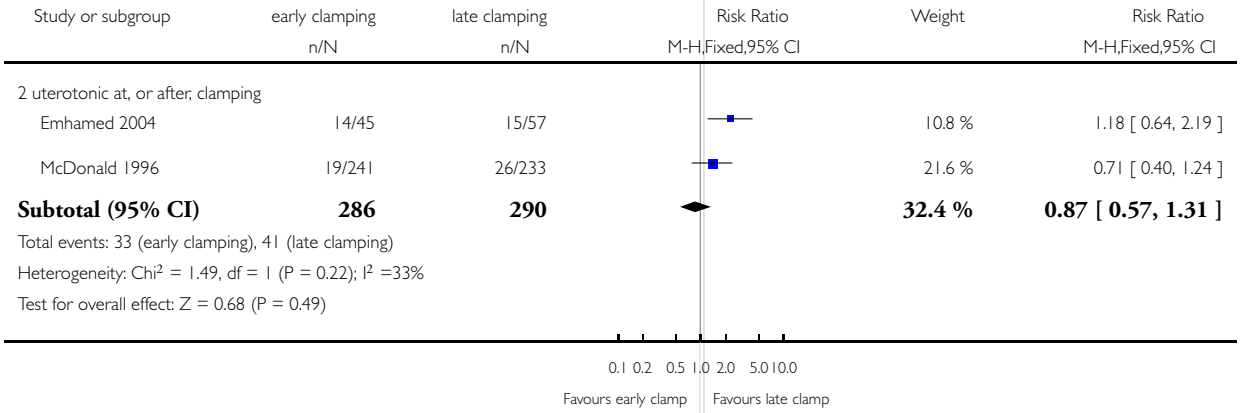
Outcome: 16 Clinical jaundice



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

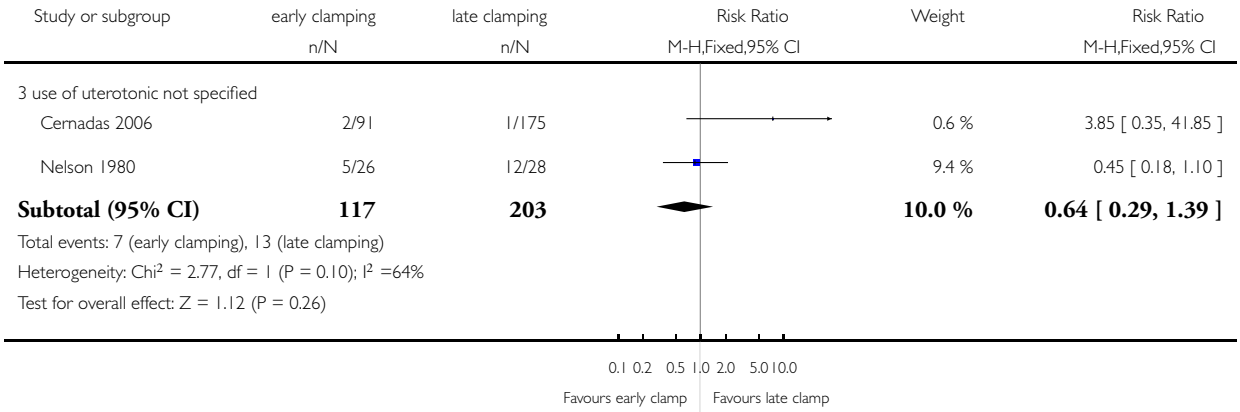
Outcome: 16 Clinical jaundice



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 16 Clinical jaundice

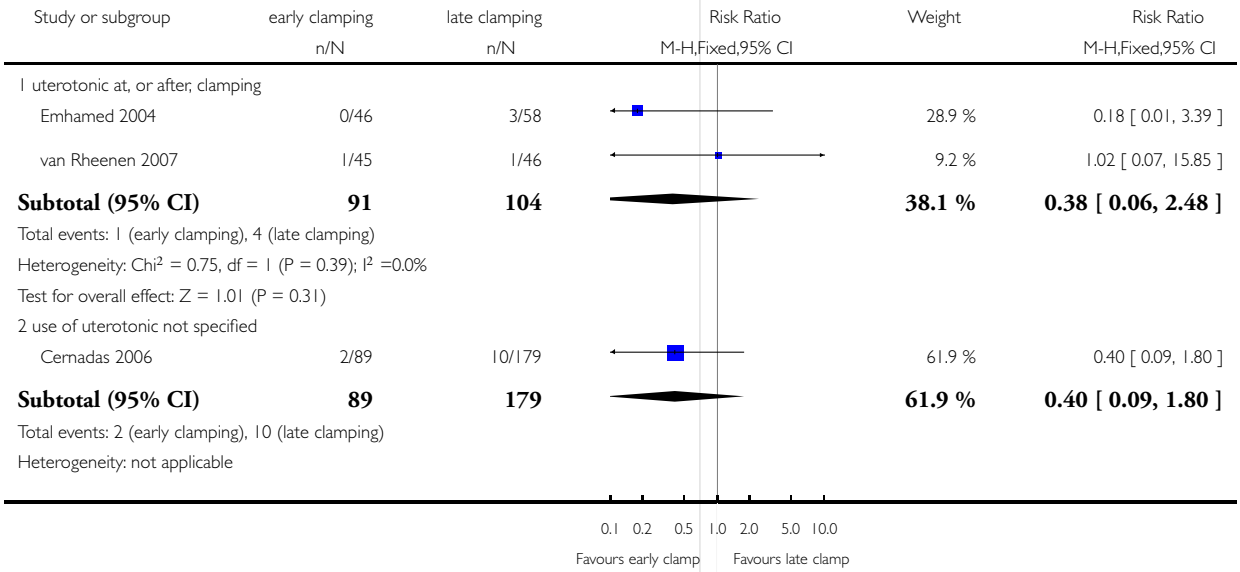


Analysis 1.17. Comparison 1 Early versus late cord clamping, Outcome 17 Polycythaemia.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 17 Polycythaemia



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.19 (P = 0.23)					
Total (95% CI)	**180**	**283**		**100.0 %**	**0.39 [0.12, 1.27]**
Total events: 3 (early clamping), 14 (late clamping)					
Heterogeneity: Chi^2 = 0.74, df = 2 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 1.56 (P = 0.12)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 17 Polycythaemia

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 uterotonic at, or after, clamping					
Emhamed 2004	0/46	3/58		28.9 %	0.18 [0.01, 3.39]
van Rheenen 2007	1/45	1/46		9.2 %	1.02 [0.07, 15.85]
Subtotal (95% CI)	**91**	**104**		**38.1 %**	**0.38 [0.06, 2.48]**
Total events: 1 (early clamping), 4 (late clamping)					
Heterogeneity: Chi^2 = 0.75, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 1.01 (P = 0.31)					

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 17 Polycythaemia

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 use of uterotonic not specified					
Cernadas 2006	2/89	10/179		61.9 %	0.40 [0.09, 1.80]
Subtotal (95% CI)	**89**	**179**		**61.9 %**	**0.40 [0.09, 1.80]**
Total events: 2 (early clamping), 10 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.19 (P = 0.23)					

Analysis 1.18. Comparison 1 Early versus late cord clamping, Outcome 18 Cord haemoglobin (g/dL).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 18 Cord haemoglobin (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic at, or after, clamping							
Emhamed 2004	46	15.4 (1.4)	58	14.9 (1.7)		41.8 %	0.50 [-0.10, 1.10]
Saigal 1972	15	16.8 (1.7)	30	15.55 (2.1)		11.4 %	1.25 [0.11, 2.39]
Subtotal (95% CI)	**61**		**88**			**53.1 %**	**0.66 [0.13, 1.19]**
Heterogeneity: Chi^2 = 1.30, df = 1 (P = 0.25); I^2 =23%							
Test for overall effect: Z = 2.45 (P = 0.014)							
2 use of uterotonic not specified							
Geethanath 1997	48	16.1 (2.2)	59	15.5 (2.3)		20.3 %	0.60 [-0.26, 1.46]
Gupta 2002	29	13.9 (1.5)	29	14.1 (1.4)		26.6 %	-0.20 [-0.95, 0.55]
Subtotal (95% CI)	**77**		**88**			**46.9 %**	**0.15 [-0.42, 0.71]**
Heterogeneity: Chi^2 = 1.91, df = 1 (P = 0.17); I^2 =48%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Total (95% CI)	**138**		**176**			**100.0 %**	**0.42 [0.03, 0.80]**

(*Continued . . .*)

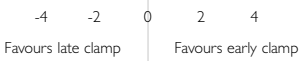
(. . . *Continued*)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI

Heterogeneity: $Chi^2 = 4.92$, df = 3 (P = 0.18); $I^2 = 39\%$

Test for overall effect: Z = 2.13 (P = 0.033)

Test for subgroup differences: $Chi^2 = 1.71$, df = 1 (P = 0.19), $I^2 = 41\%$



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 18 Cord haemoglobin (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic at, or after, clamping							
Emhamed 2004	46	15.4 (1.4)	58	14.9 (1.7)		41.8 %	0.50 [-0.10, 1.10]
Saigal 1972	15	16.8 (1.7)	30	15.55 (2.1)		11.4 %	1.25 [0.11, 2.39]
Subtotal (95% CI)	**61**		**88**			**53.1 %**	**0.66 [0.13, 1.19]**

Heterogeneity: $Chi^2 = 1.30$, df = 1 (P = 0.25); $I^2 = 23\%$

Test for overall effect: Z = 2.45 (P = 0.014)

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 18 Cord haemoglobin (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 use of uterotonic not specified							
Geethanath 1997	48	16.1 (2.2)	59	15.5 (2.3)		20.3 %	0.60 [-0.26, 1.46]
Gupta 2002	29	13.9 (1.5)	29	14.1 (1.4)		26.6 %	-0.20 [-0.95, 0.55]
Subtotal (95% CI)	**77**		**88**			**46.9 %**	**0.15 [-0.42, 0.71]**
Heterogeneity: Chi^2 = 1.91, df = 1 (P = 0.17); I^2 =48%							
Test for overall effect: Z = 0.51 (P = 0.61)							

-4 -2 0 2 4

Favours late clamp Favours early clamp

Analysis 1.19. Comparison 1 Early versus late cord clamping, Outcome 19 Newborn haemoglobin (g/dL).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 19 Newborn haemoglobin (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 uterotonic at, or after, clamping							
Saigal 1972	15	16.8 (1.27)	30	21.25 (1.67)		32.3 %	-4.45 [-5.33, -3.57]
Subtotal (95% CI)	**15**		**30**			**32.3 %**	**-4.45 [-5.33, -3.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.94 (P < 0.00001)							
2 use of uterotonic not specified							
Cernadas 2006	90	17.83 (2.33)	182	19.4 (1.98)		33.7 %	-1.57 [-2.13, -1.01]
Chaparro 2006	171	19.3 (2.3)	183	19.9 (2.4)		34.0 %	-0.60 [-1.09, -0.11]
Subtotal (95% CI)	**261**		**365**			**67.7 %**	**-1.07 [-2.03, -0.12]**
Heterogeneity: Tau^2 = 0.40; Chi^2 = 6.52, df = 1 (P = 0.01); I^2 =85%							
Test for overall effect: Z = 2.22 (P = 0.027)							
Total (95% CI)	**276**		**395**			**100.0 %**	**-2.17 [-4.06, -0.28]**
Heterogeneity: Tau^2 = 2.69; Chi^2 = 56.40, df = 2 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 2.25 (P = 0.025)							

-10 -5 0 5 10

Favours late clamp Favours early clamp

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 19 Newborn haemoglobin (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 uterotonic at, or after, clamping							
Saigal 1972	15	16.8 (1.27)	30	21.25 (1.67)		32.3 %	-4.45 [-5.33, -3.57]
Subtotal (95% CI)	**15**		**30**			**32.3 %**	**-4.45 [-5.33, -3.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.94 (P < 0.00001)							

-10 -5 0 5 10

Favours late clamp Favours early clamp

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 19 Newborn haemoglobin (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
2 use of uterotonic not specified							
Cernadas 2006	90	17.83 (2.33)	182	19.4 (1.98)		33.7 %	-1.57 [-2.13, -1.01]
Chaparro 2006	171	19.3 (2.3)	183	19.9 (2.4)		34.0 %	-0.60 [-1.09, -0.11]
Subtotal (95% CI)	**261**		**365**			**67.7 %**	**-1.07 [-2.03, -0.12]**
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 6.52$, df = 1 (P = 0.01); $I^2 = 85\%$							
Test for overall effect: Z = 2.22 (P = 0.027)							

-10 -5 0 5 10

Favours late clamp Favours early clamp

Analysis 1.20. Comparison 1 Early versus late cord clamping, Outcome 20 Infant haemoglobin at 24-48 hours (g/dL).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 20 Infant haemoglobin at 24-48 hours (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic at, or after, clamping							
Emhamed 2004	46	17.1 (1.9)	58	18.5 (2.1)		35.4 %	-1.40 [-2.17, -0.63]
Subtotal (95% CI)	**46**		**58**			**35.4 %**	**-1.40 [-2.17, -0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.56 (P = 0.00037)							
2 use of uterotonic not specified							
Cernadas 2006	89	17.03 (2.3)	189	18.34 (2.18)		64.6 %	-1.31 [-1.88, -0.74]
Subtotal (95% CI)	**89**		**189**			**64.6 %**	**-1.31 [-1.88, -0.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.50 (P < 0.00001)							
Total (95% CI)	**135**		**247**			**100.0 %**	**-1.34 [-1.80, -0.88]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 5.74 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.85), I^2 =0.0%							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

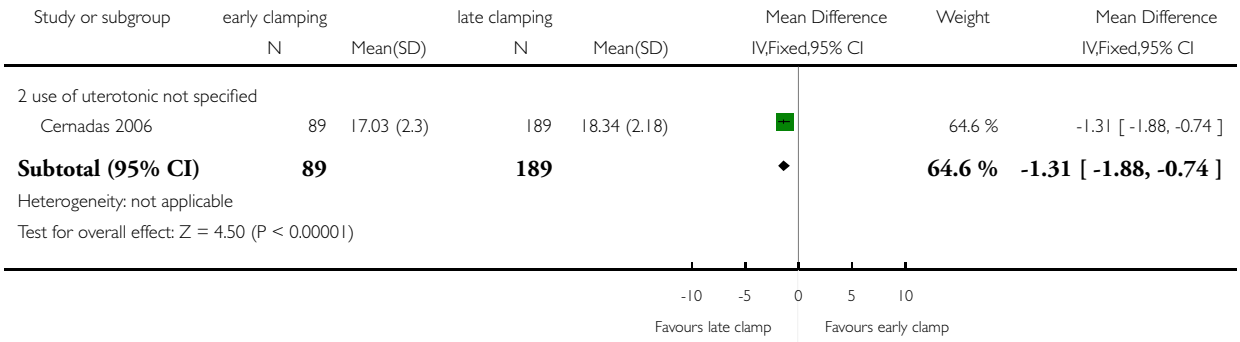
Outcome: 20 Infant haemoglobin at 24-48 hours (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic at, or after, clamping							
Emhamed 2004	46	17.1 (1.9)	58	18.5 (2.1)		35.4 %	-1.40 [-2.17, -0.63]
Subtotal (95% CI)	**46**		**58**			**35.4 %**	**-1.40 [-2.17, -0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.56 (P = 0.00037)							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 20 Infant haemoglobin at 24-48 hours (g/dL)



Analysis 1.21. Comparison 1 Early versus late cord clamping, Outcome 21 Infant haemoglobin at 2-4 months (g/dL).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 21 Infant haemoglobin at 2-4 months (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 uterotonic at, or after, clamping							
van Rheenen 2007	45	11.2 (1.3)	46	11.5 (1.5)		33.3 %	-0.30 [-0.88, 0.28]
Subtotal (95% CI)	**45**		**46**			**33.3 %**	**-0.30 [-0.88, 0.28]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 use of uterotonic not specified							
Geethanath 1997	48	8.9 (1.6)	59	8.3 (2.1)		31.5 %	0.60 [-0.10, 1.30]
Gupta 2002	29	8.8 (0.8)	29	9.9 (0.9)		35.2 %	-1.10 [-1.54, -0.66]
Subtotal (95% CI)	**77**		**88**			**66.7 %**	**-0.27 [-1.94, 1.39]**
Heterogeneity: Tau^2 = 1.36; Chi^2 = 16.23, df = 1 (P = 0.00006); I^2 =94%							
Test for overall effect: Z = 0.32 (P = 0.75)							
Total (95% CI)	**122**		**134**			**100.0 %**	**-0.30 [-1.25, 0.65]**
Heterogeneity: Tau^2 = 0.62; Chi^2 = 17.08, df = 2 (P = 0.00020); I^2 =88%							
Test for overall effect: Z = 0.61 (P = 0.54)							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 21 Infant haemoglobin at 2-4 months (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 uterotonic at, or after, clamping							
van Rheenen 2007	45	11.2 (1.3)	46	11.5 (1.5)		33.3 %	-0.30 [-0.88, 0.28]
Subtotal (95% CI)	**45**		**46**			**33.3 %**	**-0.30 [-0.88, 0.28]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 21 Infant haemoglobin at 2-4 months (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
2 use of uterotonic not specified							
Geethanath 1997	48	8.9 (1.6)	59	8.3 (2.1)		31.5 %	0.60 [-0.10, 1.30]
Gupta 2002	29	8.8 (0.8)	29	9.9 (0.9)		35.2 %	-1.10 [-1.54, -0.66]
Subtotal (95% CI)	**77**		**88**			**66.7 %**	**-0.27 [-1.94, 1.39]**

Heterogeneity: $Tau^2 = 1.36$; $Chi^2 = 16.23$, df = 1 (P = 0.00006); $I^2 = 94\%$

Test for overall effect: Z = 0.32 (P = 0.75)

Analysis 1.22. Comparison 1 Early versus late cord clamping, Outcome 22 Infant haemoglobin at 6 months (g/dL).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 22 Infant haemoglobin at 6 months (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic at, or after, clamping							
van Rheenen 2007	45	10.6 (1.5)	46	10.2 (2.1)		7.2 %	0.40 [-0.35, 1.15]
Subtotal (95% CI)	**45**		**46**			**7.2 %**	**0.40 [-0.35, 1.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.05 (P = 0.29)							
2 use of uterotonic not specified							
Chaparro 2006	171	12.7 (0.9)	185	12.7 (1.1)		92.8 %	0.0 [-0.21, 0.21]
Subtotal (95% CI)	**171**		**185**			**92.8 %**	**0.0 [-0.21, 0.21]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**216**		**231**			**100.0 %**	**0.03 [-0.17, 0.23]**
Heterogeneity: Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =2%							
Test for overall effect: Z = 0.28 (P = 0.78)							
Test for subgroup differences: Chi^2 = 1.02, df = 1 (P = 0.31), I^2 =2%							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

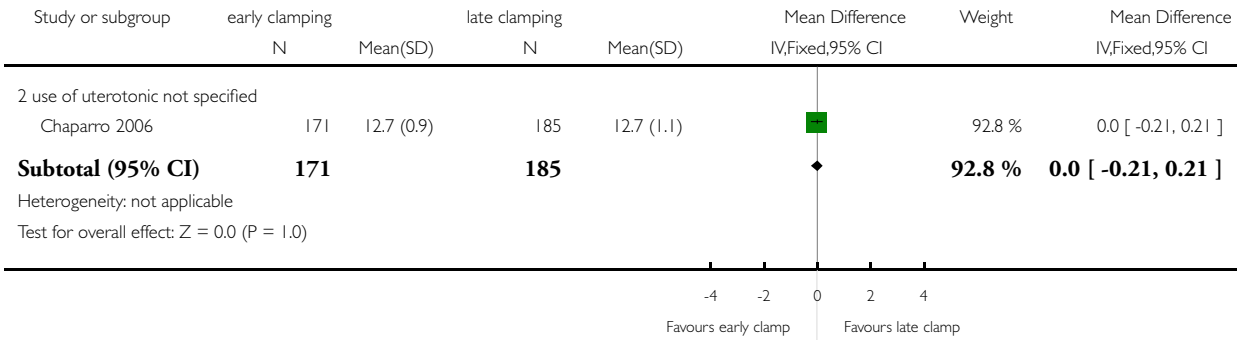
Outcome: 22 Infant haemoglobin at 6 months (g/dL)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 uterotonic at, or after, clamping							
van Rheenen 2007	45	10.6 (1.5)	46	10.2 (2.1)		7.2 %	0.40 [-0.35, 1.15]
Subtotal (95% CI)	**45**		**46**			**7.2 %**	**0.40 [-0.35, 1.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.05 (P = 0.29)							

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 22 Infant haemoglobin at 6 months (g/dL)

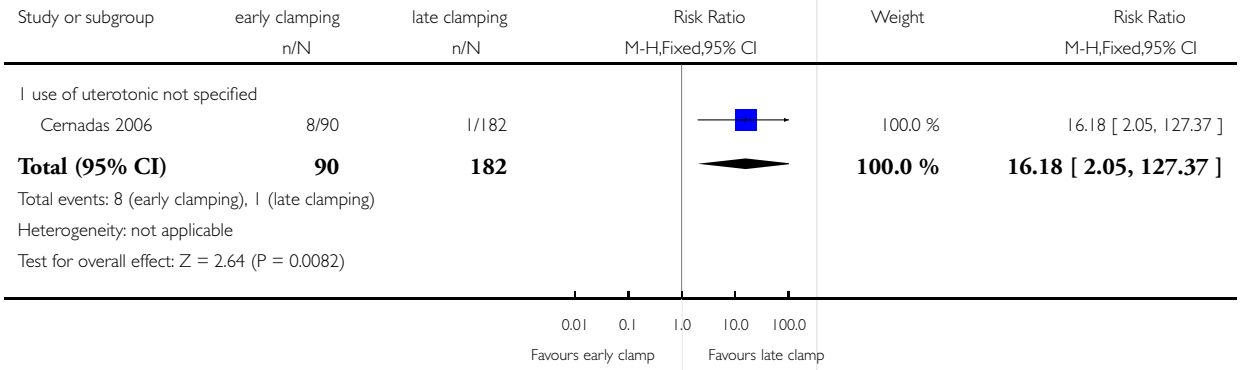


Analysis 1.23. Comparison 1 Early versus late cord clamping, Outcome 23 Infant haematocrit < 45% at 6 hours.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

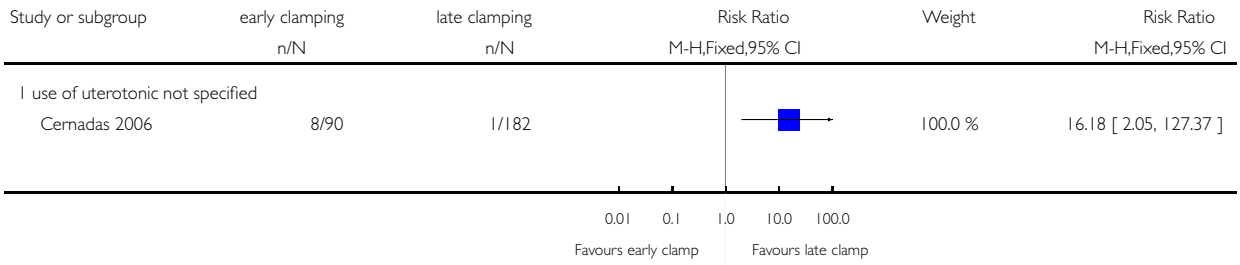
Outcome: 23 Infant haematocrit < 45% at 6 hours



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 23 Infant haematocrit < 45% at 6 hours

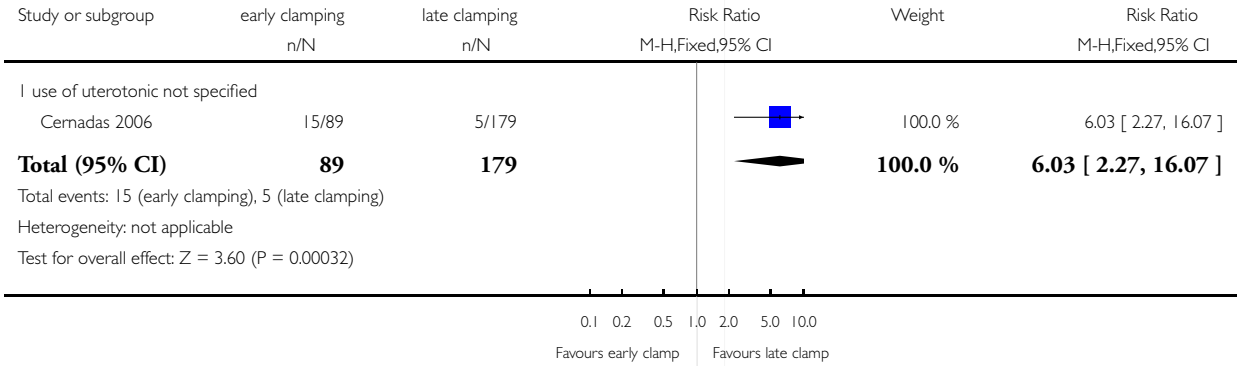


Analysis 1.24. Comparison 1 Early versus late cord clamping, Outcome 24 Infant haematocrit < 45% at 24-48 hours.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

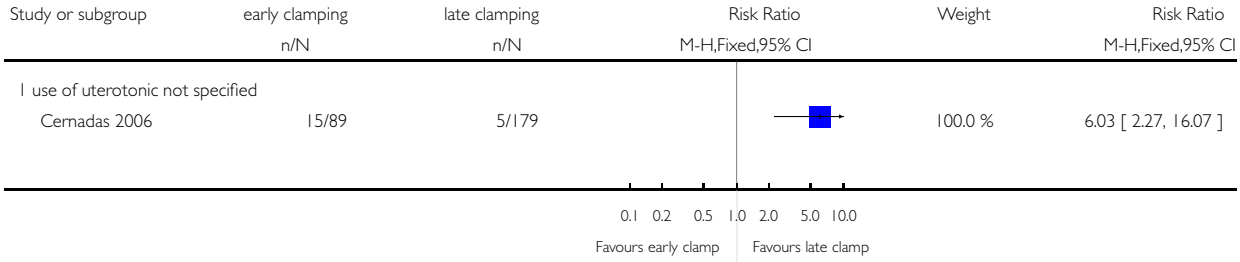
Outcome: 24 Infant haematocrit < 45% at 24-48 hours



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 24 Infant haematocrit < 45% at 24-48 hours

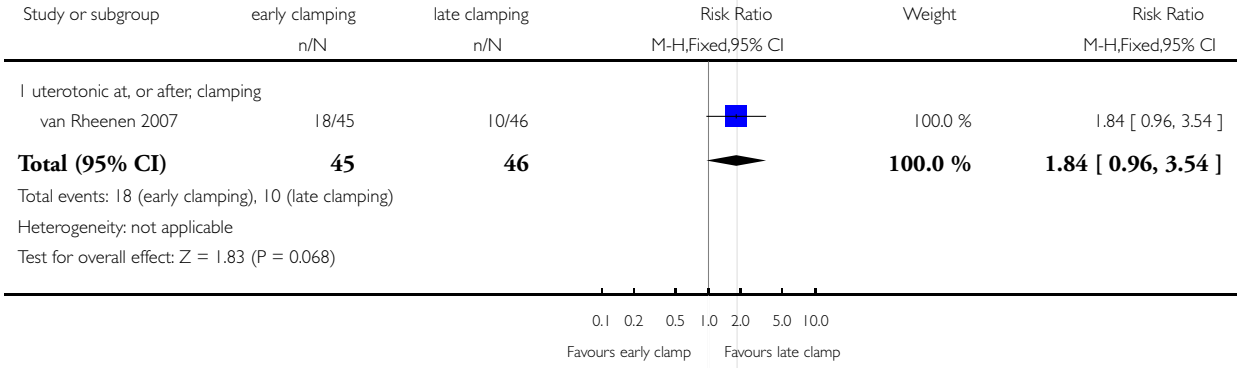


Analysis 1.25. Comparison 1 Early versus late cord clamping, Outcome 25 Infant haemoglobin > 2 SDs below 10.3 g/dL at 4 months.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

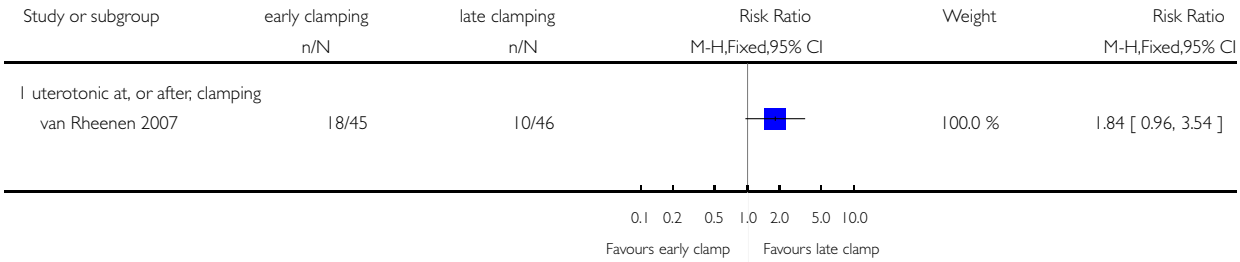
Outcome: 25 Infant haemoglobin > 2 SDs below 10.3 g/dL at 4 months



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 25 Infant haemoglobin > 2 SDs below 10.3 g/dL at 4 months

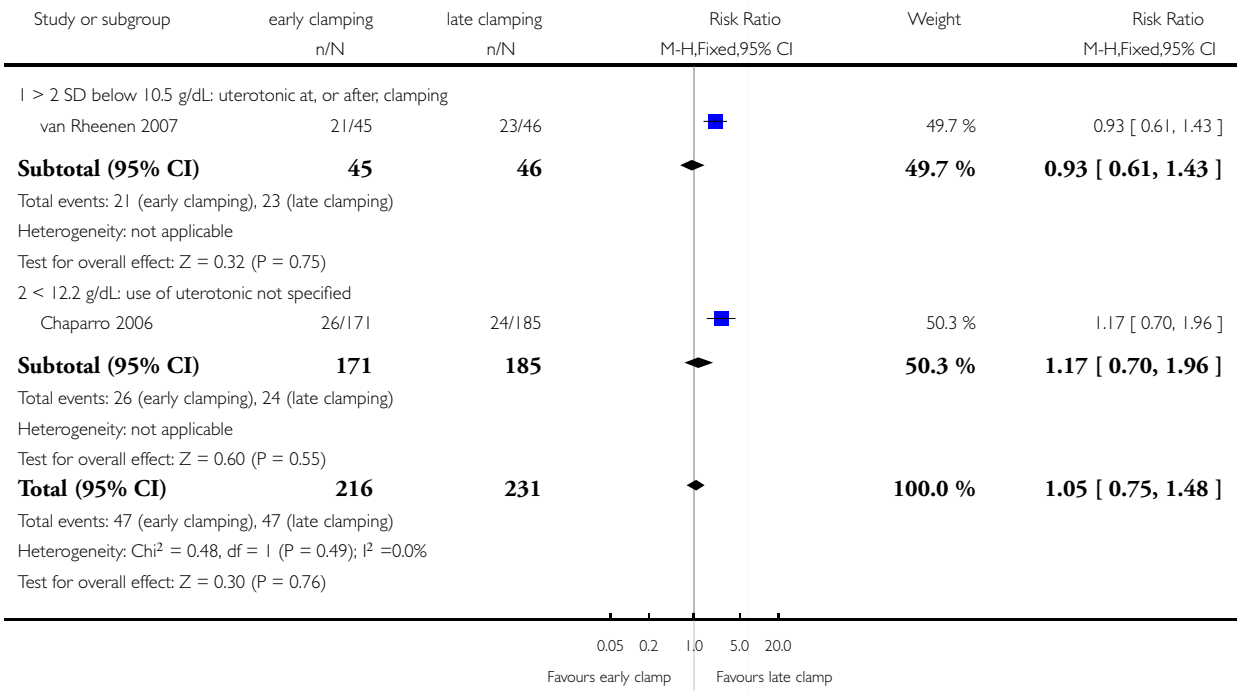


Analysis 1.26. Comparison 1 Early versus late cord clamping, Outcome 26 Infant haemoglobin at 6 months.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

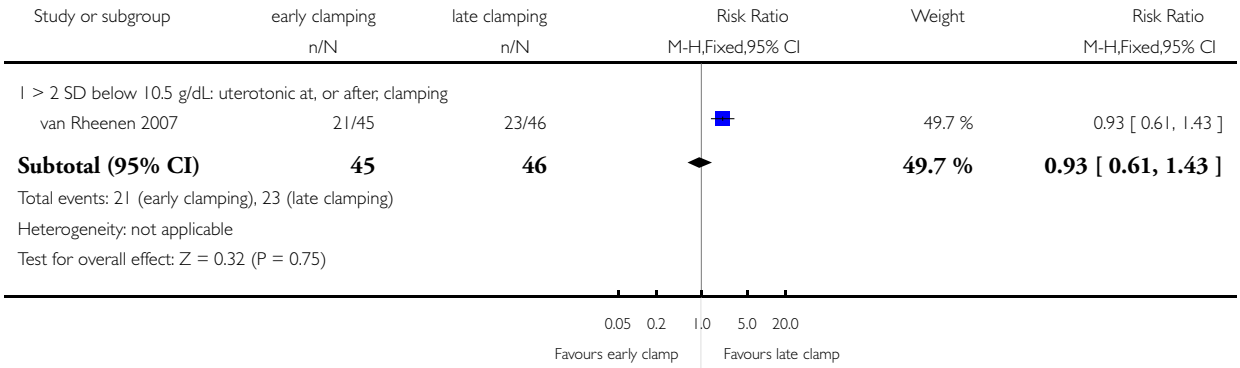
Outcome: 26 Infant haemoglobin at 6 months



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

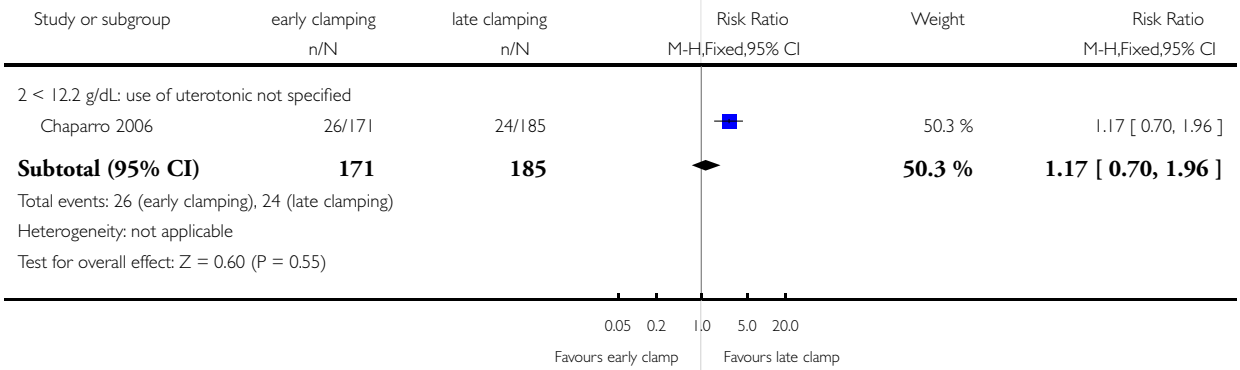
Outcome: 26 Infant haemoglobin at 6 months



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 26 Infant haemoglobin at 6 months

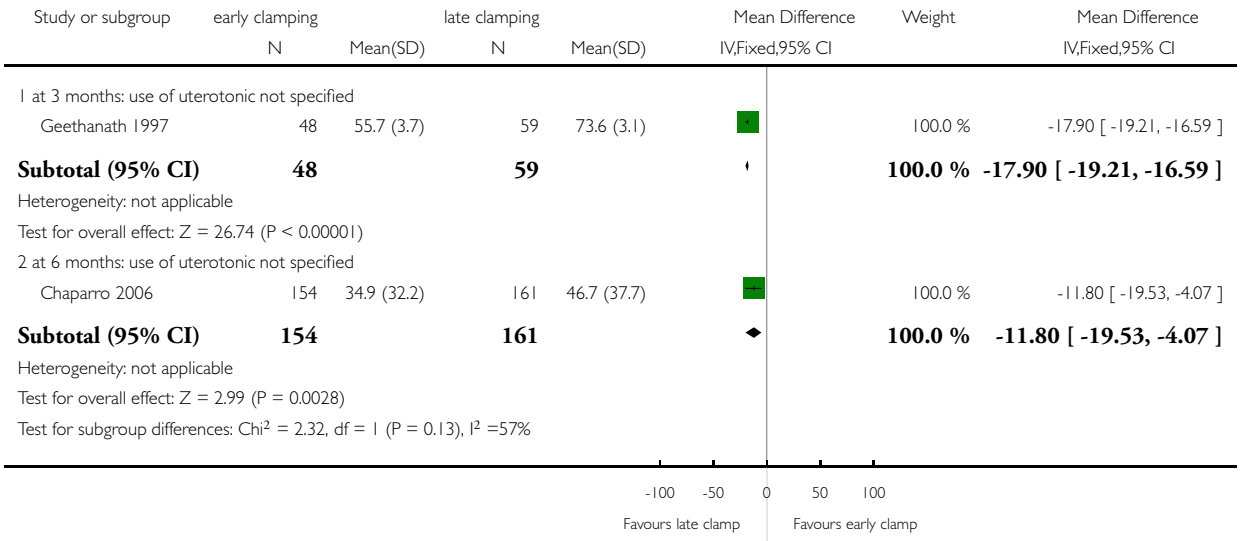


Analysis 1.27. Comparison 1 Early versus late cord clamping, Outcome 27 Infant ferritin (ug/L).

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

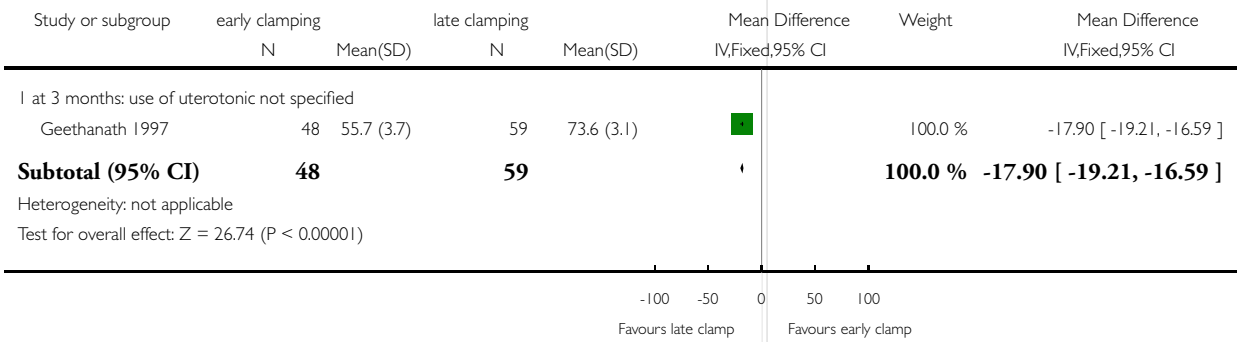
Outcome: 27 Infant ferritin (ug/L)



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 27 Infant ferritin (ug/L)



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 27 Infant ferritin (ug/L)

Study or subgroup	early clamping N	Mean(SD)	late clamping N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 at 6 months: use of uterotonic not specified							
Chaparro 2006	154	34.9 (32.2)	161	46.7 (37.7)		100.0 %	-11.80 [-19.53, -4.07]
Subtotal (95% CI)	**154**		**161**			**100.0 %**	**-11.80 [-19.53, -4.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.99 (P = 0.0028)							

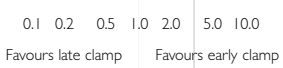
Analysis 1.28. Comparison 1 Early versus late cord clamping, Outcome 28 Exclusive breastfeeding.

Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 28 Exclusive breastfeeding

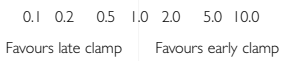
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 at discharge: uterotonic before clamping					
McDonald 1996	212/236	216/244		100.0 %	1.01 [0.95, 1.08]
Subtotal (95% CI)	**236**	**244**		**100.0 %**	**1.01 [0.95, 1.08]**
Total events: 212 (early clamping), 216 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
2 at discharge: uterotonic at, or after, clamping					
McDonald 1996	219/244	208/239		100.0 %	1.03 [0.97, 1.10]
Subtotal (95% CI)	**244**	**239**		**100.0 %**	**1.03 [0.97, 1.10]**
Total events: 219 (early clamping), 208 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
3 1 month: use of uterotonic not specified					
Cernadas 2006	82/90	148/178		100.0 %	1.10 [1.00, 1.20]



(*Continued* . . .)

(. . . *Continued*)

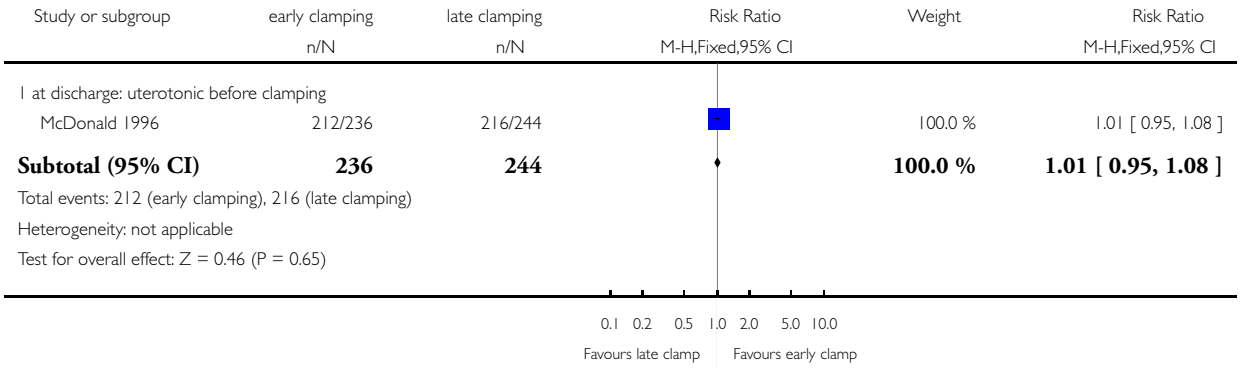
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**90**	**178**		**100.0 %**	**1.10 [1.00, 1.20]**
Total events: 82 (early clamping), 148 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.052)					
4 2 months: use of uterotonic not specified					
Chaparro 2006	59/142	68/160		100.0 %	0.98 [0.75, 1.28]
Subtotal (95% CI)	**142**	**160**		**100.0 %**	**0.98 [0.75, 1.28]**
Total events: 59 (early clamping), 68 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					
5 3 months: use of uterotonic not specified					
Geethanath 1997	36/40	43/46		62.5 %	0.96 [0.85, 1.09]
Gupta 2002	26/29	24/29		37.5 %	1.08 [0.88, 1.33]
Subtotal (95% CI)	**69**	**75**		**100.0 %**	**1.01 [0.90, 1.13]**
Total events: 62 (early clamping), 67 (late clamping)					
Heterogeneity: Chi^2 = 0.96, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 0.14 (P = 0.89)					
6 4 months: use of uterotonic not specified					
Chaparro 2006	60/147	68/166		100.0 %	1.00 [0.76, 1.30]
Subtotal (95% CI)	**147**	**166**		**100.0 %**	**1.00 [0.76, 1.30]**
Total events: 60 (early clamping), 68 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
7 6 months: use of uterotonic not specified					
Chaparro 2006	54/171	60/187		100.0 %	0.98 [0.73, 1.33]
Subtotal (95% CI)	**171**	**187**		**100.0 %**	**0.98 [0.73, 1.33]**
Total events: 54 (early clamping), 60 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

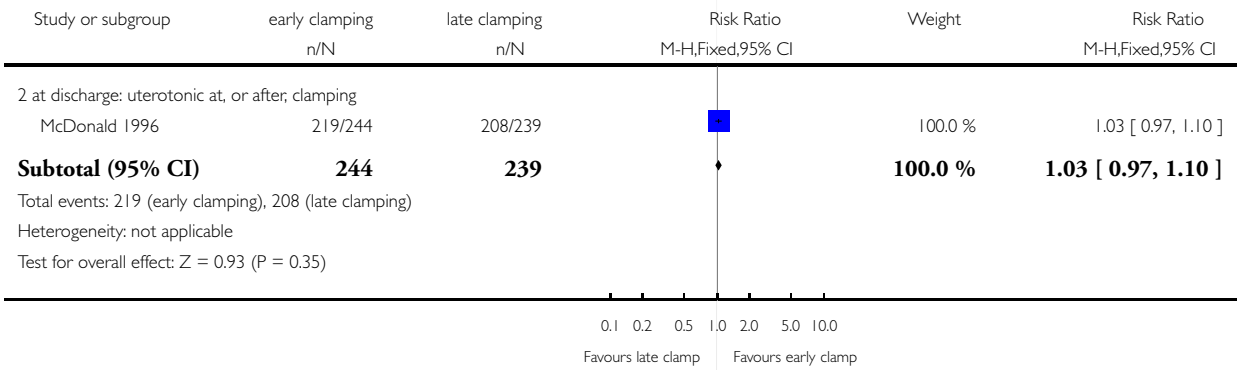
Outcome: 28 Exclusive breastfeeding



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

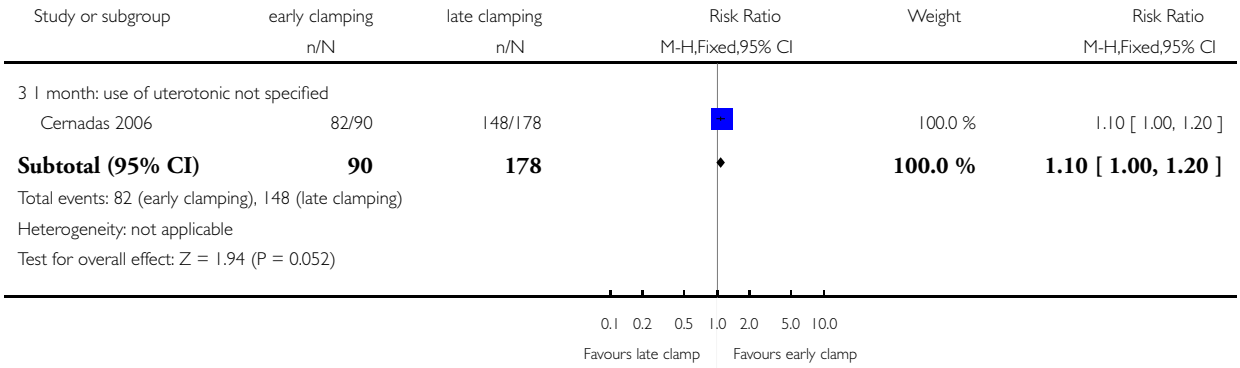
Outcome: 28 Exclusive breastfeeding



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

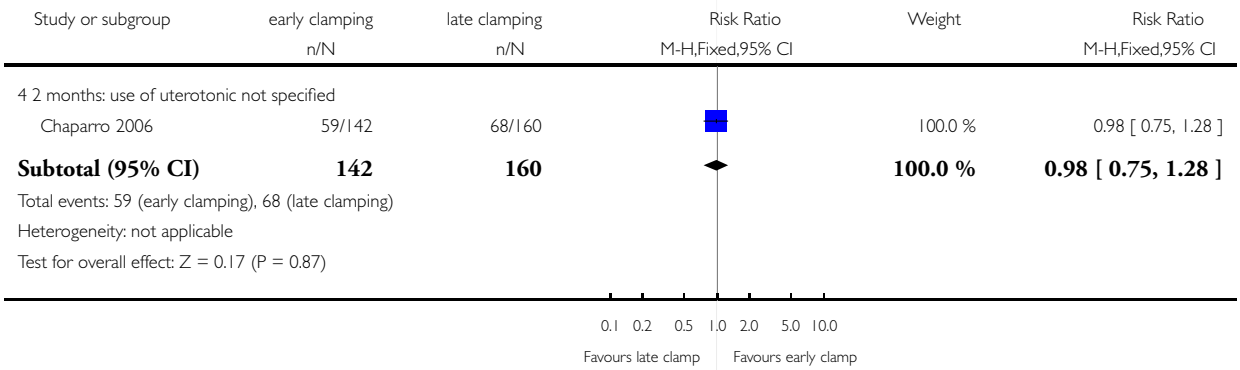
Outcome: 28 Exclusive breastfeeding



Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 28 Exclusive breastfeeding

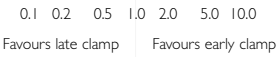


Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 28 Exclusive breastfeeding

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
5 3 months: use of uterotonic not specified					
Geethanath 1997	36/40	43/46		62.5 %	0.96 [0.85, 1.09]
Gupta 2002	26/29	24/29		37.5 %	1.08 [0.88, 1.33]
Subtotal (95% CI)	**69**	**75**		**100.0 %**	**1.01 [0.90, 1.13]**
Total events: 62 (early clamping), 67 (late clamping)					
Heterogeneity: Chi^2 = 0.96, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 0.14 (P = 0.89)					

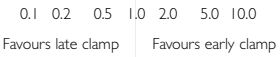


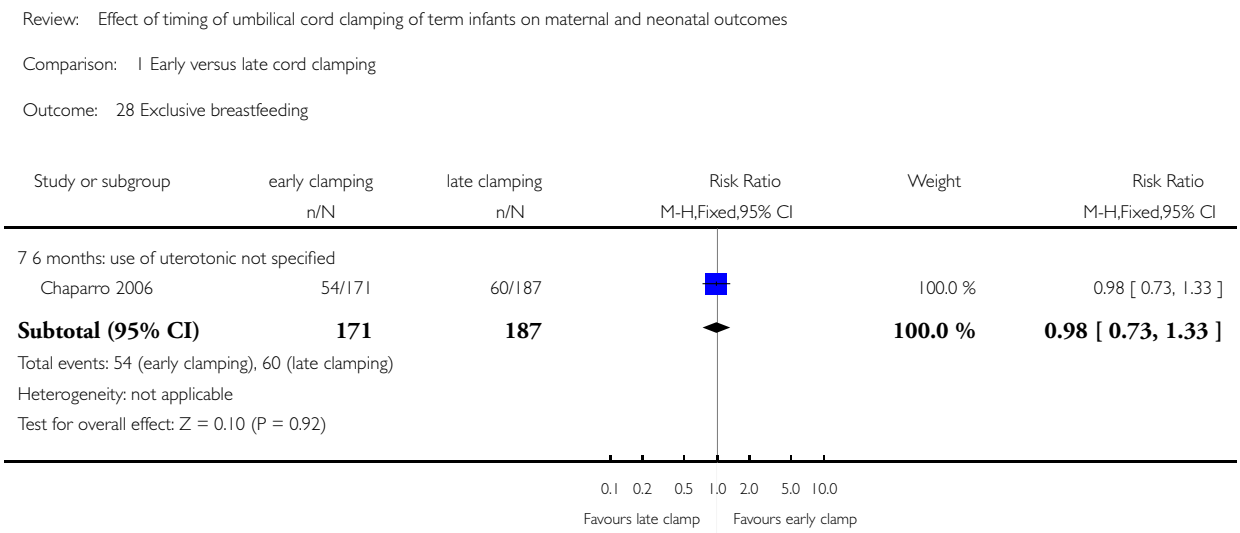
Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Comparison: 1 Early versus late cord clamping

Outcome: 28 Exclusive breastfeeding

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
6 4 months: use of uterotonic not specified					
Chaparro 2006	60/147	68/166		100.0 %	1.00 [0.76, 1.30]
Subtotal (95% CI)	**147**	**166**		**100.0 %**	**1.00 [0.76, 1.30]**
Total events: 60 (early clamping), 68 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					





FEEDBACK

Erickson-Owens and Mercer, 21 April 2008

Summary

First we would like to thank Susan J MacDonald and Philippa Middleton on completion of the huge task of reviewing all of the literature on delayed cord clamping in term infants. This is a daunting task and they are to be commended.

However, we do have two serious concerns that we feel significantly weaken this Cochrane review. Our first concern is that the evidence for an increase in 'jaundice requiring phototherapy' is based upon one 12 year old unpublished trial done by the lead author of this Cochrane Review (MacDonald) in Australia. When that one trial is removed from data (offered in Analysis 1.15) the variable of 'jaundice requiring phototherapy' does not reach significance. A recent meta-analysis found in JAMA did not agree with the outcome that delayed cord clamping (DCC) leads to 'jaundice requiring phototherapy' (Hutton and Hassan, 2007). We question the emphasis given to the outcome drawn from this one study.

There are several reasons in this Cochrane Review why 'jaundice needing phototherapy' (associated with DCC) may be misleading. First, no information is offered to tell the reader if the providers ordering the phototherapy in the MacDonald trial were blinded to the infants grouping. Secondly, guidelines to treat jaundice have changed over time and no mention is given of what the guidelines were in Australia 12 years ago. How high were the bilirubin levels? What was the age of the infants at the time that phototherapy was indicated? Did any of the infants require further treatment such as exchange transfusions? What were the feeding policies at the time and how many mothers were breastfeeding and bottle feeding? What was the racial mix and was metabolic screening to rule out G6PD, galactosemia and other conditions considered? These questions suggest competing factors and other potential influences rather than DCC only on the incidence of jaundice needing phototherapy in McDonald's 12 year old unpublished controlled trial.

Our second main concern is that harm to infants from DCC is inferred but not demonstrated in this review. The use of the word 'severe' in the Plain Language Summary is particularly misleading. Was there 'harm' to any of the infants in the MacDonald study or simply more infants receiving phototherapy? What were peak bilirubin levels? The use of phototherapy does not necessary imply 'severe' jaundice. Maisals (2006) recommends that the term severe be used when the total serum bilirubin level is 20 mg/dL (340 umol/L) or higher. The issue of hyperbilirubinemia is extremely complex (AAP, Technical Report 7/04). Recent information on bilirubin tells us that it is an anti-oxidant and that the elevations seen after birth especially in breastfed infants may be initially protective (Hammerman C et al, 2002). It does everyone an injustice to infer 'harm' in the face of the evidence from the two large randomized controlled trials published in 2006. These trials indicate less anemia and better iron stores at 6 months of age in infants with DCC at birth (Cernadas et al 2006; Chaparro et al, 2006).

In analysis 1.16 'Clinical Jaundice' did not result in significant differences between the delayed group and the immediate clamped group even though the 90 infants who were clamped at 3 minutes in the Cernadas study (2006) with no increase in jaundice are left out and the MacDonald study results are included here as well.

It is important to blind pediatric providers when one is using a management decision as an outcome variable. Strauss (2008) recently published findings on 105 preterm neonates randomized to immediate clamping or a one minute delay in cord clamping. Use of phototherapy was an outcome variable and the providers caring for the infants were not blinded to the infants grouping. He reported that even though there were "no differences in serum bilirubin values prompting therapy or in intensity of therapy required", more infants with the delay in cord clamping group received phototherapy (Strauss, 2008). This information concerning treatment when neonatologists are unblinded to an infant's grouping suggests that the belief that DCC causes jaundice effects clinical practice. It demonstrates the need for pediatric providers to be blinded in trials using jaundice requiring phototherapy as an outcome variable. Fortunately, Strauss balanced his variables and reported that there were no differences in initial bilirubin levels at decision to treat or in the extent of phototherapy used.

In order to prevent regional biases, we suggest that the Cochrane Collaboration recommend groups of authors representing more than one country, one continent, and one specialty. This is imperative to offer balance for such an important review.

Other points are:

1. The abstract offers that both benefits and harm are shown for late cord clamping. The evidence of harm in this review is much too weak (based on one unpublished study's findings) to be stated so definitively.
2. Under 'Significant increase in infants needing jaundice', five trials are listed but only one trial gives any weight to this finding and that is a 12 year old unpublished study.
3. Under Authors' Comments, the authors state "One definition of active management [of third stage labor]" but do not refer to the current definition as offered by WHO, ICM, and FIGO. It is imperative that such documents use and refer to the most current definitions.

References

AAP Technical Report. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004, 114(1):e130-153.

Cernadas, J., et al. (2006). The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: A randomized controlled trial. Obstetrical & Gynecological Survey, 61(9):564-565.

Chaparro, C.M., et al. (2006). Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. Lancet, 367 (9527):1997-2004.

Hammerman C, Goldschmidt, D, Caplan, M. S, Kaplan, M. Bromiker, R. Eidelman, A. I.et al. (2002) Protective Effect of Bilirubin in Ischemia?Reperfusion Injury in the Rat Intestine Journal of Pediatric Gastroenterology and Nutrition, 35:344?349.

Hutton, E.K. and Hassan, E.S. (2007). Late vs. early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA, 297(11):1241-52.

Maisels, MJ. (2006). What?s in a Name? Physiologic and pathologic jaundice: the conundrum of defining normal bilirubin levels in the newborn. Pediatrics, 118(2):805-807.

Strauss, R.G. et al. (2008). A randomized clinical trial comparing immediate versus delayed clamping of the umbilical cord in preterm infants: short-term clinical and laboratory endpoints. Transfusion, 48(4):658-65.

Reply

Jaundice requiring phototherapy

Emphasis

Debra Erickson-Owens and Judith Mercer question the emphasis we have placed in the review on this outcome. We believe that our presentation of jaundice requiring phototherapy accurately reflects the data. As the largest trial, the McDonald study (appropriately) contributes the most data, so it is not surprising that its removal from the analysis also removes the statistical significance. Three of the other four trials contributing data to this outcome are small. The fourth trial of 556 babies (Oxford Midwives 1991) shows a risk difference of approximately similar magnitude to McDonald 1996 (2.5% versus 3.1%).

Blinding

In the McDonald 1996 trial it would have been highly unlikely for clinicians making decisions about phototherapy to have known the trial allocation. We did include a brief mention of blinding of outcome assessment in the text of the review, but have add extra detail in the Characteristics of Included studies.

Guidelines for treating jaundice

We agree with the statement that these guidelines have changed over time. In the case of the McDonald 1996 trial, the level of jaundice requiring phototherapy depended on the age and weight of the infants (all were under 4 days). Approximately 90% of babies were breastfed at discharge (89% in the delayed clamping group and 91% in the early clamping group).

Other factors

The other factors mentioned would have been distributed between the two groups of the McDonald 1996 study, as it was a securely randomised trial with adequate allocation concealment.

Ignoring results from Cernadas and Chaparro

We do not understand this, as these trials are fully included (along with other trials reporting haemoglobin and iron levels).

Inferring harm from delayed cord clamping

We think there is a slight misinterpretation about the Plain language Summary saying that the jaundice was severe - our actual words were "a possible additional risk of jaundice severe enough to require phototherapy". However, we can see that this wording could be easily misinterpreted and we will change it and also the applicable wording in the Conclusions.
We feel it would be irresponsible to ignore or downplay potential harms and in fact to do so would be contrary to the Cochrane Collaboration's guidelines (Loke 2008). We believe we have appropriately pointed out a potential risk (albeit one which is preventable through phototherapy), noting that this risk would be minimal in facilities that have the equipment to test for and treat jaundice. Although Moerschel 2008 have recently stated, "every hospital that cares for newborns should be able to provide intensive phototherapy", we recognise that this is not always the case.

Clinical jaundice

Thank you for picking up that we missed reporting the third arm of Cernadas for clinical jaundice. The addition of these data change the total RR from 0.83, 95% CI 0.65 to 1.06 to 0.84, 95% CI 0.66 to 1.07. We have made this change in the review.

Current definitions of active management

The point of our comment in the conclusions in the abstract was to highlight that active management takes a number of forms, as evidenced by the Winter 2007 survey that we cite in the background. Part of this variation will always exist, as conditions at birth sometimes mean that components of intended active management or expectant management cannot be carried out. We will refer to the current definitions in the review and add the appropriate reference.

Contributors

Feedback received from Judith S Mercer, PhD, CNM, FACNM and Debra A Erickson-Owens, PhD(c), CNM
Reply from Susan J McDonald and Philippa Middleton

Simon, 26 May 2008

Summary

'Delayed clamping' of the umbilical cord at birth appears to be regarded as a novel alternative to a longstanding protocol for immediate disconnection of an infant from placental circulation within seconds of birth.

How many prospective parents are aware of the protocol for clamping the umbilical cord immediately at birth? How many prospective parents are fully informed about randomized controlled trials before assenting to random assignment to one group or another?

The infant does not gain 30 per cent more blood volume when the cord is left intact until pulsations cease. On the contrary the infant loses 30 per cent of its blood volume if placental circulation is clamped off immediately at birth.

The placenta is the respiratory organ of the child until its blood is transferred to the capillaries surrounding the alveoli and the lungs become fully functional. Pulsations in the cord are from the infant's heart continuing to make use of fetal circulation back to the placenta until the foramen ovale, ductus arteriosus, and pulmonary bypass circulation have closed. Clamping a pulsating umbilical cord arbitrarily terminates postnatal placental circulation. Redistribution of blood to the lungs, the brain, the gut will be variable from infant to infant.

Randomized controlled trials show that most healthy newborn babies somehow adjust, but findings like increased bilirubin levels are insufficient justification for promoting continued use of the obstetric clamp.

Oxygen insufficiency is the greatest danger of disrupted umbilical blood-flow, prenatally, during labor, when the cord is wrapped around the neck, and after birth. Bilirubin is only a danger if the blood-brain-barrier is disrupted, as demonstrated by research like that of Lucey et al (1964) and Lou et al (1977). Why is evidence of this kind, obtained in experiments with animals overlooked in favor of randomized controlled experiments with human children?

References (with notes from my recent comment to the Interagency Autism Coordinating Committee, IACC)

1. Lucey JF, Hibbard E, Behrman RE, Esquival FO, Windle WF. Kernicterus in asphyxiated newborn monkeys. Exp Neurol 1964 Jan; 9(1):43-58.
Lucey et al induced hyperbiliruninemia in fourteen newborn monkeys by injecting a solution of bilirubin into the bloodstream every six hours. Bilirubin levels of 20 to 35 mg were maintained for up to 96 hours. Then, "Six healthy full-term monkeys were asphyxiated at birth. A rubber bag filled with saline solution was placed over the fetal head as it was delivered from the uterus before the first breath. The umbilical cord was then clamped and asphyxiation carried out for 10 or 12 minutes" [p45]. Hyperbilirubinemia was then induced in the asphyxiated monkeys as in the fourteen control animals.
Lucey et al described the monkeys made hyperbilirubinemic as showing marked yellow coloration of skin and mucous membranes. Those not asphyxiated became slightly lethargic but none developed signs of neurological impairment. Monkeys subjected to asphyxia before induction of hyperbilirubinemia developed tremors, seizures, and prolonged periods of opisthotonus (a postural state with arched back and neck).
"Hyperbilirubinemia alone did not result in selective staining of nuclei in the brain, such as is associated with human kernicterus - the brains had a diffuse, faint to moderate, yellow color, but no extravascular bilirubin was seen" [p50].
Bilirubin is not directly toxic to the brain. Asphyxia appears to break down the blood-brain barrier, which then allows bilirubin to get into neural cells. As Zimmerman and Yannet noted in 1933, 'any intravital dye will localize in zones of injury and will leave unstained tissues which are not damaged.' [4, p757]
2. Lou HC, Tweed WA, Johnson G, Jones M, Lassen NA. Breakdown of blood/brain barrier in kernicterus. Lancet. 1977 May 14;1(8020):1062-3.
Lou et al (1977) addressed what appeared to be the primary concern over "delayed" cord clamping allowing placental transfusion [5]. Citing the paper by Lucey et al (1964) they stated:
"Asphyxiated infants are especially susceptible to kernicterus, even if their plasma-bilirubin levels are low. Furthermore, it is very difficult to produce clinical and pathological signs of kernicterus by injection of bilirubin intravenously in normal infant monkeys, while kernicterus was readily produced in previously asphyxiated monkeys." [p1062] Mossakowski et al (1968) used Evans blue dye

to investigate the blood-brain barrier in newborn monkeys subjected to asphyxia by clamping the umbilical cord and obstructing the airway [6]. Lou et al also used Evans blue dye in fetal lambs subjected to oxygen insufficiency for 1-2 hours:
"The fetuses were asphyxiated by partially inflating a cuff around the umbilical cord.
Asphyxia developed over a period of 1-2 h (pH about 690)." [p1062] The initial response of the fetal lambs was a slowing of heart rate and increased blood pressure during the first half- to one-hour period of umbilical cord blood flow restriction. After that the blood pressure declined and remained low. Twinning is frequent in lambs, and Lou et al used the twin as a control for the fate of Evans blue dye, and reported:
"We have found, in experimental asphyxia lasting 1-2 h, a striking discoloration throughout cortex and basal ganglia after intravenous injection of 3 ml/kg of a 2% solution of Evans blue in eight non-exteriorised fetal lambs, in contrast to the uncoloured brain tissue in non-asphyxiated twins acting as controls." [p1062] In conclusion they commented:
"We suggest that the breakdown of the fetal blood/brain barrier to albumin is due to a combination of the initial moderate hypertension and severe vasodilation during asphyxia. The permeability of the blood/brain barrier to albumin in asphyxiated babies would facilitate the transport of bilirubin from plasma to neurones and thus explain the increased susceptibility to kernicterus." [p1063] If a baby does not breathe right away at birth, should the umbilical cord be clamped off right away? Respiratory depression in infants born alive is a current concern and topic for research [7, 8]. If an infant is born alive, it has been receiving oxygen through the umbilical cord up to the time of birth. Shouldn't that lifeline be left intact until the lungs become functional?
Breakdown of the blood brain barrier by asphyxia has been shown to allow bilirubin and other substances in the circulation to enter the brain. High levels of bilirubin won't affect the brain if the blood-brain barrier has not been breached. Immediate clamping has been too long defended as a means to avoid circulatory overload and hyperbilirubinemia.
Lou et al (1979) reported results of more research on the vulnerability of the blood-brain barrier to circulatory insufficiency in fetal lambs [3].

3. Lou HC, Lassen NA, Tweed WA, Johnson G, Jones M, Palahniuk RJ. Pressure passive cerebral blood flow and breakdown of the blood-brain barrier in experimental fetal asphyxia. Acta Paediatr Scand. 1979 Jan;68(1):57-63.

4. Zimmerman HM, Yannet H. Kernicterus: jaundice of the nuclear masses of the brain. American Journal of Diseases of Children 1933 Apr; 45:740-759.
Before discovery of Rh factor sensitivity, Zimmerman and Yannet in 1933 summarized a large number of case reports of kernicterus. They concluded that kernicterus was caused by bilirubin staining of subcortical nuclei already injured by sepsis or oxygen deprivation. They further commented, "This differs in no way from the well known fact that any intravital dye will localize in zones of injury and will leave unstained tissues which are not damaged," [p757].
Fear of elevated bilirubin levels became a prime reason 40 years later for advocating immediate clamping of the umbilical cord at birth to minimize placental transfusion [4].

5. Saigal S, O'Neill A, Surainder Y, Chua LB, Usher R. Placental transfusion and hyperbilirubinemia in the premature. Pediatrics. 1972 Mar;49(3):406-19.
Is it safe to allow a placental transfusion? By the 1970s the practice of clamping the cord was so widespread, at least in obstetric practice associated with academic institutions, that whether a placental transfusion should be allowed became a major topic for research. Thus the opening comment of this highly influential report states:
"In full-term infants placental transfusion increases the blood volume of the newborn by 40% to 60% within 5 minutes of birth. Most of the excess blood volume is eliminated within 4 hours by an extravasation of plasma from the circulation. For the remainder of the neonatal period, such infants retain a 50% larger red cell volume dispersed through a slightly enlarged blood volume, with higher hematocrit values than are found in infants whose umbilical cords are clamped immediately at birth." [p406] "If delayed cord clamping is adopted as a means to reduce the incidence of respiratory distress syndrome in premature births, there will be accompanying augmentation of hyperbilirubinemia to deal with." [p418] This paper, with its single focus on bilirubin danger, has been one of the most influential in adopting immediate clamping of the umbilical cord at birth as a standard protocol.

6. Mossakowski MJ, Long DM, Myers RE, DeCuret HR, Klatzo I. The early histochemical and ultrastructural changes in perinatal asphyxia. J Neuropathol Exp Neurol. 1968 Jul;27(3):500-516.

7. Baskett TF, Allen VM, O'Connell CM, Allen AC. Predictors of respiratory depression at birth in the term infant. BJOG. 2006 Jul;113(7):769-74.

8. Milsom I, Ladfors L, Thiringer K, Niklasson A, Odeback A, Thornberg E. Influence of maternal, obstetric and fetal risk factors on the prevalence of birth asphyxia at term in a Swedish urban population. Acta Obstet Gynecol Scand. 2002 Oct;81(10):909-17.

Reply

A reply from the authors will be published as soon as it is available.

Contributors

Feedback from Eileen Nicole Simon, PhD, RN

Buckley, 16 July 2008

Summary

I am very concerned about one of the studies used for this conclusion: Following birth, there was a significant increase in infants needing phototherapy for jaundice (RR 0.59, 95% CI 0.38 to 0.92; five trials of 1762 infants) in the late compared with early clamping group. This finding (analysis 1.15) is significantly influenced by results from the Oxford Midwives study (Oxford Midwives 1991), which is quoted here as showing jaundice requiring phototherapy amongst 3/256 immediate cord-clamped (ICC) babies and 11/296 delayed cord clamped (DCC) babies.
However, a close reading of this paper shows a significant disparity in these groups in relation to exposure to synthetic oxytocin in labour: 33/256 (12.9%) in ICC group and 72/296 (24.3%) in the DCC group: see table 1
Study authors note this (and the association between exposure to synthetic oxytocin in labour and jaundice), and, in table 6 of this paper, reanalyze the groups in relation to oxytocin exposure, finding 5/70 DCC vs 2/33 ICC babies exposed to oxytocin required phototherapy for jaundice, and 6/222 DCC vs 1/218 ICC unexposed to oxytocin . In this analysis, the confidence intervals were wide and the differences between ICC and DCC babies were not significant in either group.
I am concerned that the reviewers have not adjusted for this confounding factor, which is very salient to the findings and to the overall review conclusions, and would welcome a reanalysis of table 1.15.
There were some other worrying elements in this study:

- Lack of blinding to allocation, leaving the possibility that clinicians may have referred more jaundiced DCC babies for phototherapy because of their own beliefs.
- A sizeable unexplained disparity in numbers randomized to each arm: 296 DCC vs 256 ICC
- A large number of protocol deviations in the DCC arm (32 vs 3 ICC)

I also note the small numbers of events used in analysis 1.15.
I (and many others interested in this area) would also welcome access to detail from the unpublished study (McDonald 96) that seems to have influenced this finding.
(Feedback received from Dr Sarah J Buckley)

Reply

A reply from the authors will be published as soon as it is available.

Contributors

Feedback from Dr Sarah J Buckley

Oddie, 7 July 2008

Summary

Why is the weight of the infants not reported in the review? These data will be available to the reviewers and will answer some of the questions as to how large the placental transfusion actually is in reality.
Where this practice has not yet been adopted, or further studies are planned, these data are very relevant.
(Feedback from Sam Oddie)

Reply

A reply from the authors will be published as soon as it is available.

Contributors

Feedback from Sam Oddie

Oddie, 7 July 2008

Summary

Feedback: I am really interested in the data and have reviewed some of the original trials, as well as taking an active ongoing interest in the issue.
I remain unconvinced that DCC ought to be adopted widely in iron replete areas.
But my feedback is: Why is infant weight not reported?
Justification: If the size of the transfusion is anywhere near as big as many suggest, then it must be the case that a difference in weight can be shown as so many women have been randomised. If no such weight effect is shown, then either the transfusion is smaller than is suggested, randomisation is in some way ineffective, or there is still inadequate power for these RCTs to show us the size of the transfusion. It seems unlikely that the latter is true.
Many who write on this subject are increasingly keen on DCC. This is obviously fine, but for those of us who are not yet practising it, or who are planning further work, the actual size of the transfusion is relevant. Partic when there are a suite of trials and a way to answer the question. I do know of som ewho are suspicious as to why the weight data is as yet unpublished.
As birthweight will undoubtedly have been recorded in the trials, lets report it here!
(Feedback from Sam Oddie)

Reply

A reply from the authors will be published as soon as it is available.

Contributors

Feedback from Sam Oddie

WHAT'S NEW

Last assessed as up-to-date: 30 December 2007.

27 May 2008	Feedback has been incorporated	We have replied to the feedback from DA Erickson-Owens and JS Mercer. New feedback from SJ Buckley and S Oddie added.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 2, 2008

4 May 2008	Feedback has been incorporated	Added feedback from Erickson-Owens and Mercer and feedback from Eileen Nicole Simon.
23 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Sue McDonald wrote the review and Philippa Middleton assisted with data extraction, methodological help and editing.

Jo Abbott and Shane Higgins were involved in drafting the protocol and in the early stages of preparing the review (e.g. some of the data extraction) but were unable to continue in the preparation of the review.

DECLARATIONS OF INTEREST

The contact review author (S McDonald) is the author of one of the included studies. The other review authors assessed this trial for potential inclusion and data extraction.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.

External sources

- Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since the publication of the protocol for this review, we have broadened the criteria to include caesarean births and to widen the definition of early cord clamping from less than 30 seconds to less than 60 seconds since two trials specified early clamping as under one minute. We have added several outcomes which measure biochemical parameters in infants such as haemoglobin and ferritin. We added the outcome of polycythaemia because we considered that information regarding polycythaemia would be of clinical interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Constriction; Infant, Newborn; Iron [blood]; Jaundice, Neonatal [*etiology; therapy]; Labor Stage, Third; Phototherapy; Placental Circulation [physiology]; Postpartum Hemorrhage [*prevention & control]; Randomized Controlled Trials as Topic; Time Factors; *Umbilical Cord

MeSH check words

Female; Humans; Pregnancy