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

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[Intervention Review]

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

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A B S T R A C T

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 more than one minute after the birth or when cord pulsation has ceased. The benefits and potential harms of each policy are debated.

Objectives

To determine the effects of early cord clamping compared with late cord clamping after birth on maternal and neonatal outcomes

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (13 February 2013).

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 15 trials involving a total of 3911 women and infant pairs. We judged the trials to have an overall moderate risk of bias.

Maternal outcomes: No studies in this review reported on maternal death or on severe maternal morbidity. There were no significant differences between early versus late cord clamping groups for the primary outcome of severe postpartum haemorrhage (risk ratio (RR) 1.04, 95% confidence interval (CI) 0.65 to 1.65; five trials with data for 2066 women with a late clamping event rate (LCER) of ~3.5%,

I^2 0%) or for postpartum haemorrhage of 500 mL or more (RR 1.17 95% CI 0.94 to 1.44; five trials, 2260 women with a LCER of ~12%, I^2 0%). There were no significant differences between subgroups depending on the use of uterotonic drugs. Mean blood loss was reported in only two trials with data for 1345 women, with no significant differences seen between groups; or for maternal haemoglobin values (mean difference (MD) -0.12 g/dL; 95% CI -0.30 to 0.06, I^2 0%) at 24 to 72 hours after the birth in three trials.

Neonatal outcomes: There were no significant differences between early and late clamping for the primary outcome of neonatal mortality (RR 0.37, 95% CI 0.04 to 3.41, two trials, 381 infants with a LCER of ~1%), or for most other neonatal morbidity outcomes, such as Apgar score less than seven at five minutes or admission to the special care nursery or neonatal intensive care unit. Mean birthweight was significantly higher in the late, compared with early, cord clamping (101 g increase 95% CI 45 to 157, random-effects model, 12 trials, 3139 infants, I^2 62%). Fewer infants in the early cord clamping group required phototherapy for jaundice than in the late cord clamping group (RR 0.62, 95% CI 0.41 to 0.96, data from seven trials, 2324 infants with a LCER of 4.36%, I^2 0%). Haemoglobin concentration in infants at 24 to 48 hours was significantly lower in the early cord clamping group (MD -1.49 g/dL, 95% CI -1.78 to -1.21; 884 infants, I^2 59%). This difference in haemoglobin concentration was not seen at subsequent assessments. However, improvement in iron stores appeared to persist, with infants in the early cord clamping over twice as likely to be iron deficient at three to six months compared with infants whose cord clamping was delayed (RR 2.65 95% CI 1.04 to 6.73, five trials, 1152 infants, I^2 82%). In the only trial to report longer-term neurodevelopmental outcomes so far, no overall differences between early and late clamping were seen for Ages and Stages Questionnaire scores.

Authors' conclusions

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 increases early haemoglobin concentrations and iron stores in infants. Delayed cord clamping is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.

PLAIN LANGUAGE SUMMARY

Effect of timing of umbilical cord clamping 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. This clamping is one part of the third stage of labour (the time from birth of the baby until delivery of the placenta) and the timing can vary according to clinical policy and practice. Although early cord clamping has been thought to reduce the risk of bleeding after birth (postpartum haemorrhage), this review of 15 randomised trials involving a total of 3911 women and infant pairs showed no significant difference in postpartum haemorrhage rates when early and late cord clamping (generally between one and three minutes) were compared. There were, however, some potentially important advantages of delayed cord clamping in healthy term infants, such as higher birthweight, early haemoglobin concentration, and increased iron reserves up to six months after birth. These need to be balanced against a small additional risk of jaundice in newborns that requires phototherapy.

BACKGROUND

Description of the condition

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 with 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 task takes place during the third stage of labour, which is the period of time from the birth of the infant to the delivery of the placenta.

Description of the intervention

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 (Begley 2011).

Expectant management is a non-interventionist approach to care in the third stage of labour that involves waiting for signs of placental separation and allowing the placenta to deliver spontaneously or aided by gravity, maternal effort or nipple stimulation. In many high-resource settings, and in some low-resource settings, this approach has frequently been replaced by more interventionist packages of care (active management), although variation in practice remains widespread.

Active management of the third stage of labour has been described in a recent World Health Organization (WHO) report as the "cornerstone" of obstetric and midwifery practice during the latter part of the 20th century (WHO 2012b). Active management has involved 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 reducing the risk of postpartum haemorrhage (PPH). The timing of when prophylactic uterotonic drugs are administered has varied over time and in practice from administration with crowning of the baby's head; to at the time of birth of the anterior of the baby; to shortly after complete birth of the baby. There are also 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 2007 (ergometrine-oxytocin and oxytocin)). In earlier descriptions of an active management strategy the umbilical cord was usually clamped within 60 seconds following birth of the infant, although there can be substantial variation in the application of policies for active management often related to the setting within which the policy is being applied. The WHO 2012b recommendation is for clamping of the cord to be performed between one to three minutes after the birth unless the baby is asphyxiated and requires resuscitation.

A major reason for practising active management is its association with reduced risk of PPH, the major complication of the third stage of labour (Prendiville 2000). The usual definition of PPH is that given by the WHO: blood loss of equal to or more than 500 mL from the genital tract during the first 24 hours postpartum (WHO 1990; WHO 2000; WHO 2012b). 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 clinical estimation (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 be well tolerated in some birth settings where there is access to adequate resuscitation measures if required. In other settings, particularly in low-income countries, where the prevalence of severe

anaemia is high, this amount of blood loss would be life threatening for many women (WHO 1996). Assessment of women with blood loss should always also take into account physical appearance and physiological observations such as pulse rate, blood pressure and conscious state. PPH is the most common fatal complication of pregnancy and childbirth in the world (UN 2010; UNICEF 2002; WHO 2007; WHO 2012) and is a major contributor to the conservatively estimated 287,000 maternal deaths occurring throughout the world annually (WHO 2012). Whilst the majority of maternal deaths (99%) occur in low-income countries (WHO 2002), the risk of PPH 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 whether individual components of the strategy lead to this reduced risk or whether it requires the full 'package' of strategies to be administered. Furthermore, It can be difficult to adhere to an active management strategy. Over time the type of uterotonic drug and the timing of its administration has been reported as being with crowning of the head of the baby, birth of the anterior shoulder of the infant after the birth of the baby or after the clamping of the cord. Variations in practice may be related to practical considerations such the number of staff available in the room at the time of birth, unexpected occurrences such as malpresentation (for example, a breech presentation) or shoulder dystocia (difficulty in delivering the infant's shoulders), local policy, or birth setting context. Some women also 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 the past, as part of an active management strategy, the umbilical cord has usually been clamped shortly following birth of the infant. This was generally advised to be carried out in the first 30 seconds after birth, regardless of whether the cord pulsation has ceased (McDonald 2003). As part of this strategy the infant may have been placed on the mother's abdomen, put to the breast or have been more closely examined on a warmed cot if resuscitation was required. Once the placenta was felt to have separated from the wall of the uterus, downward traction may have been 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). However, more recent guidelines for management of the third stage of labour no longer recommend immediate cord clamping, and cord traction is regarded as optional and is only suggested

when skilled staff are in attendance ([WHO 2012b](#)).

Delayed cord clamping

Definitions of what constitutes early and late cord clamping vary ([Prendiville 1989](#)). In practice, clamping the umbilical cord often takes place once cord pulsation has ceased or at least beyond the first minute of so following the birth of the baby.

How the intervention might work

Possible beneficial and adverse effects

Delayed 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](#); [Palethorpe 2010](#)). 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](#)). [Palethorpe 2010](#) and colleagues sought to evaluate studies related to the effects for mother and baby of alternative positions for the baby between birth and cord clamping to assess the influence of gravity on placental transfusion. However, no randomised controlled trials were identified for comparison and they concluded there was a need for large, well designed randomised controlled trials to be undertaken to ascertain what effect gravity may have on placental transfusion at vaginal and caesarean births related to short- and longer-term outcomes for mothers and babies.

The suggested neonatal benefits associated with this increased placental transfusion include higher haemoglobin concentrations ([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](#)).

Arguments against early cord clamping include the reduction in the amount of placental transfusion and 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 thought to be associated with higher risks for the preterm infant. This topic is the subject of a Cochrane systematic review ([Rabe 2012](#)), which has recently been updated.

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](#)).

Why it is important to do this review

Why this review is important

Active management, including early cord clamping is still 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 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](#)).

WHO recently updated its guidelines on preventing PPH ([WHO 2012b](#)). The International Confederation of Midwives and the International Federation of Gynaecology and Obstetrics also updated its statement on PPH in 2006 ([ICM/FIGO 2006](#)). Both statements refer to benefits of delaying cord clamping, and WHO recommend cord clamping one to three minutes after the birth although the quality of the evidence underpinning this recommendation was described as moderate. This review seeks to explore this issue further. Since evidence suggests that the effects of early versus late cord clamping may differ in preterm and term infants, these are the subjects of a separate review (*see* [Rabe 2012](#)). This review will concentrate on the effect of early versus late cord clamping on maternal and neonatal outcomes in term infants.

O B J E C T I V E S

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.

M E T H O D S

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 (including caesarean section).

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 2012.
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.

Primary outcomes
1. Severe PPH (measured blood loss 1000 mL or more, or, as defined by the trial authors)
2. Maternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors)
3. Neonatal mortality

Secondary outcomes
Maternal
1. Maternal death.
2. Individual components of severe morbidity (as listed above or as defined by the trial authors)
3. PPH (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors)

4. Length of third stage of labour
5. Mean blood loss
6. Manual removal of the placenta
7. Blood transfusion
8. Use of therapeutic uterotonics
9. Additional treatment for PPH (uterine tamponade, x-ray, embolisation)
10. Adverse effects reported either individually or as a composite where appropriate; e.g. vomiting, nausea, elevation of diastolic blood pressure, shivering, headache, chest pain, shortness of breath, pyrexia, diarrhoea
11. Postnatal anaemia (defined by trial authors, absolute or relative drop in haemoglobin)
12. Thrombo-embolic events
13. Cost

Neonatal
1. Birthweight
2. Apgar score less than seven at five minutes
3. Admission to neonatal intensive care unit or special care nursery
4. Respiratory distress
5. Hypoxia
6. Jaundice requiring phototherapy
7. Clinical jaundice
8. Cord haemoglobin concentrations
9. Not breastfed at discharge
10. Neonatal and infant anaemia up to four to six months post birth
11. Neonatal and infant haemoglobin concentrations
12. Neonatal and infant haematocrit
13. Neonatal and child neurodevelopmental outcome
14. Polycythaemia (haematocrit greater than 65%)
15. Neonatal and infant ferritin concentrations
16. Symptoms of infection in infants

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 (13 February 2013).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;

5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, 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 each 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.

Data extraction and management

We 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 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 risk of bias of included studies

We assessed the risk of bias in each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We have described for each included study the method used to generate the allocation sequence and assessed whether it was likely to produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non random process, e.g. odd or even date of birth; hospital or clinic record number);

- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We have described for each included study the method used to conceal the allocation sequence and assessed whether the treatment allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding (checking for possible performance or detection bias)

For this type of intervention blinding women and clinical staff is generally not feasible, although it may be possible to blind outcome assessors. We have assessed blinding for outcome assessors as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We have described for each included study the completeness of data including attrition and exclusions from the analysis. We have reported the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We assessed methods as:

- low, high or unclear risk of bias.

(5) Selective reporting bias

We have described for each included study whether we suspected any selective outcome reporting bias.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other sources of bias

We have described for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- (low risk of other bias);
- (high risk of other bias);
- unclear risk of other bias.

(7) Overall risk of bias

We have made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias, and whether we considered it was likely to impact on the findings. We explored the impact of possible bias through undertaking sensitivity analyses - *see* Sensitivity analysis. Overall findings for our assessment of risk of bias in the included studies are set out in Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
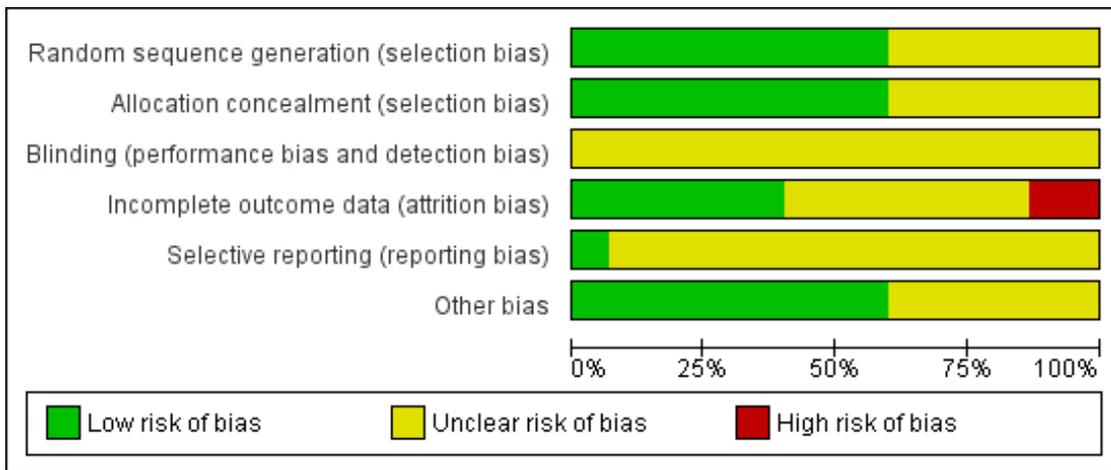
Figure 2.   'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Measures of treatment effect

Dichotomous data

For dichotomous data, we have presented results as summary risk ratio with 95% confidence intervals (CI).

Continuous data

For continuous data, we used the mean difference as outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials along with individually-randomised trials. In this updated version of the review no cluster-randomised trials were identified in the search. In future versions, if any such trials are identified and assessed as eligible for inclusion, we will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will note this and carried out sensitivity analyses to investigate the effect of variation in ICC. We will synthesise the findings from individually- and cluster-randomised trials provided that there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Dealing with missing data

For included studies, we noted levels of attrition in the Characteristics of included studies tables.
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.
For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. For all primary

outcomes the denominator for each outcome in each trial is the number of women randomised.

Assessment of heterogeneity

We used the I² and T² statistics to quantify heterogeneity along with the Chi² test for heterogeneity. If we identified substantial heterogeneity (I² greater than 30%), we have drawn attention to this in the text and have advised readers to interpret results with caution. For primary outcomes where moderate or high levels of heterogeneity were identified we also planned to calculate the 95% prediction interval which gives the range of effects expected across different settings; in this version of the review we did not identify high levels of heterogeneity for primary outcomes.

Assessment of reporting biases

For primary outcomes, provided sufficient studies contributed data, we planned to generate funnel plots. In this version of the review insufficient studies contributed data for any of our primary outcomes. In future updates, if further data are added, we will visually examine plots to see whether there is any evidence of asymmetry suggesting different treatment effects in smaller studies, which may indicate publication bias (Harbord 2006).

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). 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. Random-effects meta-analysis estimates the average treatment effect and this may not always be clinically meaningful. Further, where there is high heterogeneity the applicability of the overall effect estimate is likely to vary in different settings and we therefore advise caution in the interpretation of results.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:
1. whether or not uterotonics (oxytocic drugs used to stimulate the uterus to contract) were used as part of the third stage management;
2. whether or not 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 tables), or selection bias. We only used primary outcomes in subgroup analysis.

We visually examined the forest plots of subgroup analyses to look at whether there was overlap between 95% CIs for the effects in different groups; with non-overlapping CIs suggesting a difference between subgroups. We also conducted formal statistical analyses to examine any possible differences between subgroups classifying whole trials by interaction tests as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and available in RevMan 2011, We reported the results of interaction tests in the text.

Sensitivity analysis

We planned sensitivity analysis for primary outcomes by risk of bias; we did this by dividing the studies into subgroups according to whether they were at low risk of bias as opposed to unclear or high risk of bias for allocation concealment to see what impact this would have on the treatment effect. In this version of the review, all studies reporting on our primary outcomes were at low risk of bias for allocation concealment.

R E S U L T S

Description of studies

Results of the search

The search strategy identified 74 reports representing 58 studies (some studies resulted in several publications or reports). We included 15 studies and excluded 37. In addition, four studies are awaiting assessment (Jaleel 2009; Li 2012; Nardozza 2012; Ping 2010); we have contacted three of the study authors for more information so that we can assess eligibility for inclusion. Two studies are still ongoing and we hope to include these in future updates of the review (Beal 2006; Hanson 2012). (See Characteristics of studies awaiting classification and Characteristics of ongoing studies for more information about these trials). The most recent search was carried out in February 2013.

Included studies

Fifteen studies with 3911 women contribute data to the review; all of the studies examined the effects of different timing of umbilical cord clamping in term infants. However, there were some differences between trials in the participants, settings, and the interventions (timing of cord clamping in the experimental and control groups and co-interventions). There were also differences

in the outcomes measured, and in the way outcomes were measured in different studies; not all studies reported results for our primary outcomes, and for some outcomes relatively few studies contributed data. Therefore, when describing the effects of interventions we have indicated the number of studies and participants included in each analysis

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. Three studies (Andersson 2011; Cernadas 2006; Nelson 1980) included data for caesarean section birth. While in the Andersson 2011 and Nelson 1980 trials most women had vaginal births, in the trial by Cernadas 2006 over a quarter of the women randomised (79/276) had caesarean births.

Settings

Studies were conducted in Argentina (Cernadas 2006), Australia (McDonald 1996), Canada (Nelson 1980; Saigal 1972), India (Geethanath 1997; Gupta 2002), Iran (Jahazi 2008), Libya (Emhamed 2004), Mexico (Chaparro 2006), Saudi Arabia (Al-Tawil 2012), Sweden (Andersson 2011), UK (Oxford Midwives 1991; Philip 1973), USA (Spears 1966) and Zambia (van Rheenen 2007).

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;
- more than 10 seconds after the doctor or midwife thought that the baby was breathing well (mean time 94 seconds after birth) (Philip 1973);
- two minutes in Chaparro 2006;
- three minutes in Al-Tawil 2012, Andersson 2011; Cernadas 2006; Jahazi 2008; Oxford Midwives 1991; and 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 (i.e. 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 Philip 1973 and Saigal 1972 it was given after the cord was clamped.

The remaining nine trials did not specify either use or timing of any uterotonic (Al-Tawil 2012, Andersson 2011; Cernadas 2006; Chaparro 2006; Geethanath 1997; Gupta 2002; Jahazi 2008; Nelson 1980; Spears 1966).

See tables of Characteristics of included studies for further details of the included trials.

Excluded studies

We excluded 37 studies. The main reason for excluding studies was that they were not randomised controlled trials or it was not clear that they were randomised trials. Twenty-eight studies were excluded for this reason; some of these studies used quasi-randomisation methods (for example alternate allocation) while in other cases the way participants were allocated to groups was not described. Five studies (Begley 1990; Khan 1997; Prendiville 1988; Rogers 1998; Thilaganathan 1993) examined active management of the third stage of labour which involves other interventions in addition to early cord clamping. Active management of the third stage of labour has been examined in a related Cochrane Review (Begley 2011). Four studies were excluded for other reasons - *see* Characteristics of excluded studies tables for more information.

Risk of bias in included studies

Allocation

Seven trials used methods to generate the randomisation sequence that we assessed as low risk of bias such as computer randomisation or the use of random number tales (Andersson 2011; Cernadas 2006; Chaparro 2006; Geethanath 1997; Gupta 2002; McDonald 1996; Oxford Midwives 1991) and van Rheenen 2007 stated that the sequence was unpredictable (although the method of generation was not specified). Jahazi 2008 used a coin toss to generate the sequence, and in the remaining trials the method was either not stated or was not clear (Al-Tawil 2012; Emhamed 2004; Nelson 1980; Philip 1973; Saigal 1972; Spears 1966).

Nine studies used sequentially numbered sealed opaque envelopes to conceal allocation to randomisation groups (Andersson 2011; Cernadas 2006; Chaparro 2006; Emhamed 2004; Geethanath 1997; Gupta 2002; McDonald 1996; Oxford Midwives 1991; van Rheenen 2007). The remaining trials had unclear allocation concealment methods (Al-Tawil 2012, Jahazi 2008; Nelson 1980; Philip 1973; Saigal 1972; Spears 1966).

Blinding

Blinding women and the staff providing care is not possible when assessing the management of third stage of labour and the impact of lack of blinding on outcomes is difficult to assess. It may be feasible to blind staff collecting data for some outcomes. However, the assessment of many outcomes, particularly blood loss, could, in theory, have been unconsciously affected by people's beliefs. Having chosen maternal haemoglobin less than 9 g/dL as a hard outcome relating to blood loss at the protocol stage, we have now also included the mean postnatal haemoglobin values to help in understanding the blood loss estimations. Haemoglobin assessment would usually be performed by a technician who would be blind to the trial allocation. Seven of the studies reported that an attempt was made to blind the collection of at least some of the outcome data to reduce detection bias (Al-Tawil 2012, Andersson 2011; Cernadas 2006; McDonald 1996; Oxford Midwives 1991; Nelson 1980; van Rheenen 2007). In the 'Risk of bias' tables, we have provided a single assessment of risk of bias associated with blinding but have noted where authors report blinding outcome assessment for some or all outcomes.

Incomplete outcome data

Even low loss to follow-up may cause serious risk of bias for rare outcomes. Attrition was relatively low in the studies by Cernadas 2006; McDonald 1996; and Nelson 1980, and more than 80% of the randomised samples were available at follow-up in the studies by Andersson 2011; Emhamed 2004; and Geethanath 1997. In the Oxford Midwives 1991 study, there were protocol deviations but there was an intention-to-treat (ITT) analysis for all women according to randomisation group. In Chaparro 2006, 29% of participants were lost to follow-up at six months and van Rheenen 2007 had lost about 33% of participants (including post-randomisation exclusions) by six months, and there was very high attrition

in the study by Gupta 2002. In four trials, loss to follow-up was either not stated or unclear (Jahazi 2008; Philip 1973; Saigal 1972; Spears 1966). In the trial by Al-Tawil 2012, although sample attrition was modest (11%), there appeared to have been exclusions after randomisation, which were not reported by randomisation group, and there was no ITT analysis. Most of our outcomes relate to the period just after the birth when sample attrition in most studies was likely to have been low.

Selective reporting

Most of the studies were assessed as unclear for selective reporting bias as we did not have access to study protocols and under these circumstances it was difficult to know whether investigators had omitted important findings.

Other potential sources of bias

We identified few other obvious sources of bias; study groups appeared comparable at baseline. In three studies there was very little information about study methods and therefore, we assessed these studies as unclear for other bias (Jahazi 2008; Saigal 1972; Spears 1966). It is possible that if staff carrying out interventions were deviating from 'routine' this may have introduced bias; for example, in Andersson 2011 early clamping was routine before the trial, and staff may have had views about late clamping which may have affected the way the intervention was delivered for the late clamping group. In the Oxford Midwives 1991 trial, it was unclear whether pilot data were included in the main trial data and whether or not data were collected in the same way.

In the study by Cernadas 2006, more than a quarter of the women included had caesarean births. This may mean data from this study are affected by neonatal clinicians attending the delivery. In the past, babies delivered by caesarean were routinely admitted to special, or neonatal intensive care. In this study, the number of caesarean births was balanced in the intervention and control groups so the impact of including data for these women is not clear.

In summary, trials were judged to be at moderate risk of bias, largely due to lack of reporting and therefore necessitating a high proportion of unclear judgements.

Effects of interventions

We included 15 trials involving a total of 3911 women and infant pairs.

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

Primary

Severe postpartum haemorrhage ≥ 1000 mL

This outcome was measured in five trials with data for 2066 women. There were no significant differences between early and late cord clamping groups for severe postpartum haemorrhage (risk ratio (RR) 1.04 95% confidence interval (CI) 0.65 to 1.65, with a late clamping event rate (LCER) of ~3.5%, I^2 0%). Overall, relatively few women experienced severe haemorrhage (unweighted percentages 3.6% versus 3.5% in the early and late clamping groups) and the 95% CIs for this outcome were wide. There were no significant differences between subgroups depending on whether, and when uterotonics were administered (Analysis 1.1). All except one of these studies were assessed as being at low risk of bias for allocation concealment.

Maternal death or severe morbidity

No trials in this review reported on maternal death or on severe maternal morbidity.

Neonatal death

There were very sparse data on neonatal death. In the study by Cernadas 2006, there were no neonatal deaths in either the early or late clamping groups and in the trial by van Rheenen 2007 there were four deaths with no significant difference between groups (RR 0.37 95% CI 0.04 to 3.41, with a LCER of ~1%, I^2 not applicable) (Analysis 1.2). Spears 1966 reported six neonatal deaths but these are described only as being randomly spread across the groups; no further explanation or detail is offered.

Maternal Secondary Outcomes

Postpartum haemorrhage ≥ 500 mL

The timing of cord clamping was not shown to be of any statistical significance with regard to postpartum haemorrhage of 500 mL or more (RR 1.17 95% CI 0.94 to 1.44, five trials, 2260 women). There was no evidence of differences between subgroups depending on the use and timing of uterotonic drugs (Analysis 1.3).

Mean blood loss

There were no significant differences in mean blood loss between women in early and late cord clamping groups; this outcome was reported in only two trials with data for 1345 women (mean difference (MD) 5.11 mL 95% CI -23.18 to 33.39) (Analysis 1.4). There were no significant differences between subgroups relating to the timing of uterotonic drugs.

Maternal postpartum haemoglobin

Maternal haemoglobin values were not significantly different between women in the early and late cord clamping groups (MD -0.12 g/dL, 95% CI -0.30 to 0.06, three trials, 1128 women) at 24 to 72 hours after the birth; there were no significant differences between subgroups relating to the use of uterotonic drugs (Analysis 1.5).

Need for blood transfusion

In two trials, there were no statistically significant differences in need for blood transfusion between the early and late cord clamping groups (RR 1.02 95% CI 0.44 to 2.37; 1345 women) (Analysis 1.6) and there was no significant indication that this differed by whether uterotonics were given before or after clamping.

Need for manual removal of placenta

In two trials with 1515 women, no significant 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) with no significant indication that this differed by whether the uterotonic drugs were given before of after the clamping (Analysis 1.7).

Length of third stage of labour

In two trials, neither instances of women experiencing third stage labour greater than 30, nor 60, minutes were significantly different between the early and late cord clamping groups (1345 women) (Analysis 1.8; Analysis 1.9).

Therapeutic uterotonics

McDonald 1996 showed no significant differences in the 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) (Analysis 1.10).

Other Outcomes

Other prespecified maternal outcomes including adverse effects (such as vomiting and headache) were not reported.

Neonatal secondary outcomes

Apgar score

Three trials reported on the number of babies with an Apgar score less than seven at five minutes; in one trial all babies had scores above seven (Philip 1973). For the two trials with estimable data there was no significant difference between the early and late cord clamping groups (McDonald 1996 and Spears 1966) (RR 1.23

95% CI 0.73 to 2.07; estimable data for 1342 neonates) (Analysis 1.11).

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

This outcome was reported in four trials with data for 1675 infants. There was no significant difference seen between groups for SCN or NICU admission (RR 0.79, 95% CI 0.48 to 1.31) (Analysis 1.12).

Respiratory distress

Three trials reported the number of infants showing signs of respiratory distress. There appeared to be considerable differences in reported event rates between studies for this outcome and so we presented a random-effects analysis. There was no strong evidence of differences between groups (RR 0.70 95% CI 0.22 to 2.19; 835 infants). Al-Tawil 2012 reported no events in either arm. In the trial by Cernadas 2006, event rates were relatively low (4/184 in the early clamping group versus 6/92 in the late clamping group), whereas in the study by Spears 1966, distress was reported for a much greater number of infants (25/192 versus 22/187 respectively); this latter study may have reported less severe or more transient distress (Analysis 1.13).

Jaundice requiring phototherapy

This outcome was reported in seven trials with data for 2324 infants. Significantly fewer infants in the early cord clamping group required phototherapy for jaundice than in the late cord clamping group (RR 0.62 95% CI 0.41 to 0.96, with a LCER of < 5%, I^2 5%). This equates to 2.74% of infants in the early clamping group and 4.36% in the late clamping group, a risk difference of < 2% (95% CI -0.03 to 0.00) (Analysis 1.14). In a subgroup analysis, there were no clear differences in outcomes according to use and timing of uterotonic drugs.

Clinical jaundice

The number of infants with clinical jaundice was reported in six trials with 2098 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) (Analysis 1.15).

Polycythaemia

No difference between the early and late cord clamping groups was detected for polycythaemia in five trials reporting this outcome (RR 0.39 95% CI 0.12 to 1.27; 1025 infants) (Analysis 1.16).

Cord haemoglobin (g/dL)

The early cord clamping group showed higher concentrations of cord haemoglobin than did the late clamping group (MD 0.41 g/dL 95% CI 0.15 to 0.66, five trials, 696 infants) (Analysis 1.17).

Newborn haemoglobin (g/dL)

This outcome was reported for three trials with data for 671 infants. There were significantly lower infant haemoglobin concentrations at birth for babies in the in the early clamping group compared with those in the late clamping group (MD -2.17 g/dL 95% CI -4.06 to -0.28; random-effects model). This outcome showed very high heterogeneity (I^2 96%) between trials with a significant interaction test indicating a more pronounced effect in the uterotonic subgroup compared with the subgroup where use of uterotonic was not specified (Analysis 1.18).

Infant haemoglobin (g/dL)

- *at 24-48 hours*

In four trials, the early cord clamping groups showed significantly lower infant haemoglobin concentrations 24 hours after birth than the late clamping groups (MD -1.49 g/dL 95% CI -1.78 to -1.21; 884 infants) (Analysis 1.19).

- *three to six months*

Infant haemoglobin at three to six months was reported in six trials with 1115 infants. No statistically significant difference between early and late clamping was seen for all six trials combined (average MD -0.15 g/dL 95% CI -0.48 to 0.19) (Analysis 1.20). The discrepancy between trials manifested as extremely high statistical heterogeneity (I^2 84%).

- low haemoglobin at three to six months

In four trials, infant anaemia at four months did not reach a statistically significant difference between early and late clamping (RR 1.05 95% CI 0.79 to 1.39; 954 infants) (Analysis 1.21).

Infant haematocrit

- *haematocrit values at 24 hours; and at three to five months*

One trial with 180 infants reported haematocrit values for infants at 24 hours and at three to five months of age. Haematocrit at 24 hours was significantly higher in the late, compared with the early clamping group (MD -4.40% 95% CI -5.71 to -3.09) but this effect did not persist at three to five months (MD -0.40 95% CI -1.48 to 0.68; 160 infants) (Analysis 1.22).

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

When measured as a haematocrit threshold greater than 45% in a single study, 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) (Analysis 1.23).

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

In this same study, 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) (Analysis 1.24).

Infant iron deficiency at three to six months

Five trials with 1152 infants reported data on infant iron deficiency at three to six months in a way that allowed us to include results in meta- analysis.

Infants in the late clamping group were significantly less likely to have iron deficiency (average RR 2.65 95% CI 1.04 to 6.73; with a LCER ranging from 0.5% to 70%, I^2 82%) (Analysis 1.25). However, there was high heterogeneity for this outcome and differences in effect size may be partly explained by variation in the way iron deficiency was defined in trials as well as when it was measured. Andersson 2011 defined iron deficiency as two or more indicators outside reference ranges (low ferritin, low mean cell volume, low transferrin saturation, high transferrin receptors); Cernadas 2006 and Chaparro 2006 as ferritin < 9 μg/L; Al-Tawil 2012 as serum ferritin < 20 μg/L; and van Rheenen 2007 as zinc-protoporphyrin (ZPP) > 80 μmol/mol haem. These and other studies (Geethanath 1997; Gupta 2002) reported other findings relating to infant iron stores; some of these data were presented in ways that did not allow us to include results in data and analyses tables (e.g. results reported as geometric means) and we have set out findings in an additional table (Table 1).

Birthweight

Twelve trials reported mean birthweight in a way that allowed us to include data in meta-analysis. (In addition, Saigal 1972 reported means and ranges and as it is not possible to convert ranges to SDs, we have not included data from this study in the overall analysis). The results showed a decreased birthweight in babies in the early cord clamping arm with a mean difference in birthweight of -101.18 g (95% CI -157.59 to -44.76, 3139 infants). We used a random-effects model for this analysis in view of high heterogeneity (I^2 62%) (Analysis 1.26).

Not breastfed at discharge

Nine studies with a total of 2950 babies included data on breast-feeding; at discharge; Jahazi 2008; McDonald 1996; Nelson 1980 and Oxford Midwives 1991 at one month, Cernadas 2006 at two months, van Rheenen 2007 at three months, Geethanath 1997 and Gupta 2002 at four months, and Chaparro 2006 and van Rheenen 2007 at six months. Overall, there were no significant differences between the groups at any time point (Analysis 1.27).

Neonatal and child neurodevelopmental outcome

To date, one trial has reported longer-term developmental outcomes for babies. In Andersson 2011, no significant differences between early and late cord clamping were seen for infants at four months of age in parental responses to the Ages and Stages questionnaire (ASQ) - overall scores MD -1.40 95% CI -7.31 to 4.51; 365 infants. Four of the six ASQ components also showed no significant differences between groups with one (ASQ problem-solving) showing significantly higher (better) scores for the late clamping group and one (ASQ personal-social score) showing significantly higher (better) scores in the early clamping group (Analysis 1.28).

Neonatal and child infection

In the same trial (Andersson 2011), a range of symptoms that may be associated with infection were reported for 360 infants in the first four months of life. None of these symptoms showed significant differences between the early and late cord clamping groups (Analysis 1.29).

DISCUSSION

Summary of main results

In this updated version of the review we have included 15 trials (involving a total of 3911 women and infant pairs) carried out in a number of countries over a long timeframe.

There were no significant differences seen between early and late cord clamping groups for the primary maternal outcome of severe postpartum haemorrhage or for the secondary outcomes of postpartum haemorrhage of 500 mL or more or mean blood loss. No included trials reported on maternal death or severe maternal morbidity. Maternal haemoglobin values were not significantly different between women in the early and late cord clamping groups in the days after giving birth.

No significant difference between early and late cord clamping was seen for the primary outcome of neonatal mortality or for most other neonatal morbidity outcomes. There was a significant (101 g mean) birthweight increase seen with late, compared with early, cord clamping. However, significantly fewer infants in the early cord clamping group required phototherapy for jaundice than in the late cord clamping group. Haemoglobin concentration in infants at 24 to 48 hours was increased in the late cord clamping group. This difference in haemoglobin concentration was not seen at subsequent assessments. However, improvement in iron stores was significant (with infants in the early cord clamping over twice as likely (risk ratio (RR) 2.65 95% confidence interval (CI) 1.04,6.75) to be iron deficient at three to six months compared

with infants whose cord clamping was delayed. In the only trial to report longer-term neurodevelopmental outcomes so far, no overall differences between early and late clamping were identified at four months.

Overall completeness and applicability of evidence

Although reviews such as Hutton 2007 and van Rheenen 2006 have highlighted beneficial effects from delayed cord clamping compared with early cord clamping, maternal wellbeing has not been a major focus for reviews or trials of cord clamping. This is an important gap as 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 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.

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 this 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).

The World Health Organization 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 a "weak recommendation, low quality evidence" (Baker 2010; Stolzfus 2011; WHO 2012b. This recommendation is compatible with the evidence although this update of the review contains some additional data not considered by WHO 2012b, which increases the level of confidence in recommending later cord clamping.

Quality of the evidence

The overall methodological quality of the trials contributing data to the review was moderate or high. While none of the studies was assessed as being at high risk of bias for most domains, several trials

did not provide clear information on methods. Nine of the 15 included trials used methods to conceal allocation at the point of randomisation that we assessed as low risk of bias. Lack of blinding was a problem in all of the included studies; blinding women and clinical staff to randomised group is not feasible with this type of intervention. The impact of lack of blinding is difficult to judge. Knowledge of allocation could have affected other aspects of care and the assessment of many outcomes, particularly blood loss, could, in theory, have been unconsciously affected by people's beliefs. Haemoglobin assessment would usually be performed by a technician who would be blind to the trial allocation. Seven of the studies reported that an attempt was made to blind the collection of at least some of the outcome data to reduce detection bias (Al-Tawil 2012; Andersson 2011; Cernadas 2006; McDonald 1996; Oxford Midwives 1991; Nelson 1980; van Rheenen 2007). Although loss to follow-up was not always described, most of the outcomes related to the time close to birth when attrition was likely to have been low.

For most of the outcomes reported in the review, data were limited. For some outcomes event rates were low and even where we pooled data from several studies there was insufficient power to detect possible differences between groups. For some outcomes only a small number of studies contributed data, and this again, led to reduced confidence in the effect estimates. An added problem was the lack of consistency in the outcomes reported and the way outcomes were measured in different studies. For example, for infant anaemia and iron status, studies examined different outcomes, used different definitions or cut-off points, measured outcomes in different ways or at different time points. These differences meant that pooled estimates could not be obtained.

Some important outcomes were not reported in any of the included studies and so far, only one of the included studies has reported infant neurological outcomes or longer-term neurological development.

Potential biases in the review process

We are aware that there is the potential to introduce bias at every stage in the review process and we took steps to minimise bias. At least two review authors independently assessed each study for possible inclusion, and carried out data extraction and assessment of study quality for included studies. Assessing risk of bias is a matter of judgment rather than an exact science and it is possible that a different review team may have made different decisions. One of the review team was an author on one of the included trials (McDonald 1996) and was not involved in carrying out data extraction or assessing risk of bias for this trial.

Agreements and disagreements with other studies or reviews

A recent review of active management of the third stage of labour (including early cord clamping), showed a reduction in postpartum haemorrhage greater than 1000 mL although the outcomes for infants were less clear, and the authors recommended that the individual components of third-stage management should be examined separately (Begley 2011). Recent WHO guidelines recommend cord clamping between one to three minutes after the birth (WHO 2012b). While this review concentrated on term babies, it is of interest that a recently updated Cochrane review of early versus later cord clamping in preterm infants (Rabe 2012) also suggested that there may be benefits to the infant associated with later clamping. The conclusions of that review were that delaying clamping reduces the need for blood transfusion, risk of intraventricular haemorrhage and necrotising enterocolitis in this preterm population although effects on the mother and other important infant outcomes were not clear.

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. Clinical implications for improvement in iron stores would be enhanced if follow-up data were available for child development.

Implications for research

Future studies should have adequate power to be able to detect the true advantages and disadvantages of cord clamping on outcomes; they should also report fully details of methods to allow assessment of risk of bias. Future studies should compare maternal outcomes such as PPH, longer term (six to 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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Al-Tawil 2012

Methods	Randomised controlled trial, 2 arms with individual randomisation
Participants	Setting: 180 women giving birth at a hospital in Saudi Arabia between 2010-11 Inclusion criteria: Multigravid women who had received adequate antenatal care, with singleton, term pregnancy and without underlying medical disease of pregnancy complications and planning a normal vaginal delivery Exclusion criteria: Women who did not deliver vaginally, small for gestational age infants or with birthweight below 2500 g, neonates needing resuscitation or with respiratory difficulties, sepsis or congenital anomalies
Interventions	Early clamping: (90 women) immediate cord clamping (within 15 secs) Delayed clamping: (90 women) delayed cord clamping (estimated from the time of shoulder delivery) with cord clamping after 3 minutes. The baby was put on the mother's abdomen until the placenta was delivered. (If during the three minutes delay the infant showed any sign of compromise the cord was cut immediately to allow resuscitation.) Administration of uterotonic not clear.
Outcomes	Birthweight; At 24 hours post birth and 3-5 months: infant haemoglobin, haematocrit, MCV, transferrin saturation, ferritin, and (at 24 hours post birth only) serum bilirubin. At 3-5 months MCV < 73 fL, serum transferrin < 20 μg/L, transferring saturation < 10% and anaemia (haemoglobin < 10.5 g/dL)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	It was reported that the attending midwife opened a sealed envelope showing treatment allocation 20 minutes before the birth (it was not clear that all envelopes were accounted for and it appeared that there may have been post randomisation exclusions)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding women and staff not feasible although it was stated that neonatal assessments and laboratory assessments were carried out by staff blind to randomisation group

Al-Tawil 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	It was stated that 180 women were randomised and that data at 3-5 months were available for 160. The analysis does not appear to have been on an ITT basis. It was stated that randomisation occurred 20 minutes before delivery, however it seems likely that there were post randomisation exclusions as several exclusion criteria would be apparent at the birth (e. g. 18 infants requiring resuscitation were excluded)
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Low risk	Groups appeared comparable at baseline.

Andersson 2011

Methods	Randomised controlled trial: NCT01245296.
Participants	400 women in Sweden. Normal birth at term. Setting: Hospital in Halmstad, Sweden. Study conducted between April 2008 and September 2009 Inclusion criteria: Non-smoking, healthy women after normal pregnancy, singleton, term pregnancy, expected vaginal birth with cephalic presentation. Swedish speaking and living close enough to study hospital to attend for follow-up Exclusion criteria:serious congenital malformations, syndromes or other congenital diseases that could affect the outcome measures
Interventions	Early umbilical cord clamping (at or before 10 secs) versus delayed cord clamping (> 180 secs (3 minutes)) In both groups the midwife was instructed to hold the baby 20 cm below the vulva for 30 secs and then place the baby on the mother's abdomen. Oxytocin (10 IU) IV was administered immediately after clamping. The time to clamping was measured using a stopwatch Early clamping was the standard procedure before the study.
Outcomes	Postpartum haemorrhage; length of third stage of labour; maternal blood transfusion; umbilical arterial and venous blood gases; jaundice; iron stores in infants at 2-3 days of age and 4 months post birth, polycythaemia; neurodevelopment at 4 months (assessed by ASQ), immunoglobulin G at birth, 2-3 days, and 4 months, symptoms of infection during first 4 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation in blocks (random number generator in MS Excel)
Allocation concealment (selection bias)	Low risk	"When delivery was imminent (expected within 10 minutes), the midwife opened a sealed, numbered, opaque envelope containing the treatment allocation)."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Mother and midwife were not blinded. Doctors carrying out neonatal examinations and laboratory staff performing analyses were blind to group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were a small number of post-randomisation exclusions (18/400) however, for many outcomes there were missing data. For primary outcomes (haemoglobin and iron status at 4 months 347/400 were followed up (87%); loss to follow-up was similar in the two arms of the trial; neurodevelopmental outcomes were measured in a subset of infants at 4 months (180 in the early clamping group and 185 in the late clamping group)
Selective reporting (reporting bias)	Unclear risk	Unable to assess (assessment from published study report only).
Other bias	Unclear risk	Group characteristics appeared similar at baseline. It was stated that routine care was early clamping

Cernadas 2006

Methods	Randomised controlled trial.
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. 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 secs of birth). n = 93 [88/93 received the intervention - no cause given for 5 changes].

Cernadas 2006 *(Continued)*

2. Cord clamping at 1 minute 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 minutes 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 apnoea; 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers - stratified by hospital and then by mode of birth within each hospital. Variable length blocks were used
Allocation concealment (selection bias)	Low risk	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 (performance bias and detection bias) All outcomes	Unclear risk	Paediatricians assessing the outcomes were unaware of the assigned interventions. Nature of the intervention meant that others could not be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: primary outcome was not measured in: early 3/93; late 1 minute 1/91; late 3 minutes 0/92.

Cernadas 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.
Other bias	Unclear risk	More than a quarter of the women included had caesarean births. This may mean data from this study are affected by neonatal clinicians attending the delivery. In the past, babies delivered by caesarean were routinely admitted to special, or neonatal intensive care. In this study the number of caesarean births was balanced in the intervention and control groups so the impact of including data for these women is not clear

Chaparro 2006

Methods	Randomised controlled trial.
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 minutes 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of 4 generated by random digital generator in Microsoft Excel
Allocation concealment (selection bias)	Low risk	Numbered index cards with allocation were sealed in numbered opaque envelopes ordered sequentially
Blinding (performance bias and detection bias)	Unclear risk	No mention of blinding.

Chaparro 2006 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.
Other bias	Low risk	Other risk of bias not apparent.

Emhamed 2004

Methods	Randomised controlled trial.
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), polycythaemia, hyperviscosity and jaundice
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Emhamed 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Consecutive allocation of opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	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
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.
Other bias	Low risk	Other risk of bias not apparent.

Geethanath 1997

Methods	Randomised controlled trial.
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
Outcomes	Maternal: haemoglobin shortly after giving birth. Infant: cord blood at birth and venous blood sample at 3 months for ferritin and haemoglobin estimation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequences.

Geethanath 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	Allocation by opaque, sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Post randomisation exclusions were reported (presence of birth asphyxia, major congenital malformations) but no losses to follow-up are reported
Selective reporting (reporting bias)	Unclear risk	Not clear from paper.
Other bias	Low risk	No other obvious bias.

Gupta 2002

Methods	Randomisd controlled trial.
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. Post randomisation exclusions: 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequences.

Gupta 2002   (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation concealed by opaque sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Post randomisation exclusions: Infants who needed resuscitation at birth or who had major congenital malformations Losses to follow-up: at 3 months, 58 (57%) of the original 102 mother-infant pairs were available, 29 pairs in each group
Selective reporting (reporting bias)	Unclear risk	No explanation is offered for high level of attrition at 3 months so reporting bias is difficult to assess
Other bias	Low risk	No other obvious bias.

Jahazi 2008

Methods	Described as double-blind randomised controlled trial. A total of 64 women were allocated to either the early or delayed umbilical cord clamping arms via toss of a coin
Participants	Women with uncomplicated pregnancies, between 38 and 42 weeks gestation and anticipating a normal vaginal birth were deemed eligible for participation
Interventions	Immediately prior to birth women were randomised to receive either early cord clamping (30 secs) n = 30 women or delayed cord clamping (3 minutes) n = 34 women. Timing was observed by a midwife using a stopwatch from the time of complete birth of the baby. The infant was held supine at the level of the introitus. In the delayed cord clamping group the infant was placed on a table at the level of the introitus and wiped dry with a warm sterile towel. 1 mL of cord blood was collected immediately following cord clamping and 1 mL antecubital blood was collected from the infant at 2 hours and 18 hours post birth All women in the study received IM oxytocin (10 IU) following cord ligation. All infants were breastfed
Outcomes	Maternal: duration of the third stage of labour. Infant outcomes reported were: gestational age, birthweight, Apgars at 1 and 5 minutes, placental residual blood volume (PRCV)and estimated neonatal blood volume at birth (ENBV), haematocrit values at birth, 2 and 18 hours post birth It is mentioned in the article that clinical manifestations of polycythaemia were observed for at the time points listed for blood collection and at 5 days post birth but outcomes of those observations are not reported
Notes	Further information requested from authors regarding clarification of randomisation? (stated that the trial was double blinded) but description in the paper would indicate that this is inaccurate. Also, asked if the polycythaemia data were available in a table

Jahazi 2008 *(Continued)*

| | | format to enable the figures and comparisons of the individual components to be more accurately reported |

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Toss of coin to determine randomisation to one of two groups
Allocation concealment (selection bias)	Unclear risk	Further information requested from authors.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The authors have stated the study was double blinded but the description is not that of a blinded trial. Further information has been sought from the authors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More information has been requested from the authors related to the data for polycythaemia
Selective reporting (reporting bias)	Unclear risk	Infants with Apgars less than 7 at 1 or 5 minutes were excluded from analysis, Infants who were small (< 10th percentile) or large (> 90th percentile) for gestational age were excluded as were infants with a cord blood haematocrit of < 40 or > 65 and infants with congenital abnormalities
Other bias	Unclear risk	Not able to assess from data provided.

McDonald 1996

Methods	Randomised controlled trial.
Participants	All women attending the antenatal clinic at King Edward Memorial Hospital, Western Australia 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

McDonald 1996   (*Continued*)

	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 minutes 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 (i.e. not within 30 secs)
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 minutes and > 60 minutes); need for therapeutic uterotonics; evacuation of retained products; inversion of the uterus; length of hospital stay. Neonatal: Apgar score < 6 at 5 minutes; 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 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of computer-generated random numbers.

McDonald 1996 *(Continued)*

Allocation concealment (selection bias)	Low risk	Opaque, sealed, sequentially numbered envelopes kept at a central location in the delivery ward
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial could not be 'blind' as 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 objective, independent of observer bias and were carried out on women in the trial without knowledge of which intervention was used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	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)
Selective reporting (reporting bias)	Low risk	Further information on outcomes was available from the author
Other bias	Low risk	Not apparent.

Nelson 1980

Methods	Randomised controlled trial. Randomisation: "assigned randomly" - no further details provided
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 minute 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.

Nelson 1980 (*Continued*)

	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"assigned randomly" - no further details provided.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Women and care providers would be aware of allocation. 2nd observer blinded for Brazelton Neonatal Behavioural Assessment Scale, infant Bayley Scales of Infant Development assessed blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 1/55 (dropped out from conventional (early clamping) group
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.
Other bias	Low risk	Not apparent.

Oxford Midwives 1991

Methods	Randomised controlled trial.
Participants	554 women. Setting: large teaching hospital in Oxford, UK.
Interventions	Early clamping (as soon as possible after the birth) or late clamping (3 minutes 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

Oxford Midwives 1991 *(Continued)*

Notes	Data from 100 women recruited to pilot the trial design was subsequently included in the total of 554 women. It is not clear whether the pilot data was unblinded and therefore may have biased the larger trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generation by random-number tables (simple un-blocked and unstratified)
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were consecutively numbered and centrally stored in the delivery suite
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Women would be aware of allocation. None of the mid-wives involved in the postnatal care of women partici-pating in the trial was aware of the original trial alloca-tion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Protocol deviations: It is reported that 264/296 infants in the late cord clamping group received the actual man-agement allocated and 252/256 received the actual man-agement allocation. 32 deviations (19 cord around neck, 9 asphyxia,1 maternal emergency and 3 others) were re-ported. All protocol deviation data were included in the groups to which they were originally allocated for the purpose of analysis (ITT) Loss to follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Unclear risk	Data from 100 women recruited to pilot the trial design was subsequently included in the total of 554 women. It is not clear whether the pilot data was unblinded and therefore may have biased the larger trial

Philip 1973

Methods	Randomised controlled trial, 2-arm trial with individual randomisation
Participants	Setting: 57 women attending an Edinburgh (Scotland, UK) over a 6 month period in 1969 Inclusion criteria: Women with uncomplicated pregnancy and term infants with no evidence of blood group incompatibility Exclusion criteria: Not stated.

Philip 1973 *(Continued)*

Interventions	Early clamping: immediately after the delivery of the baby's buttocks (usually achieved within 5 secs and never longer than 15 secs). N = 28 Delayed clamping: more than 10 secs after the doctor or midwife thought that the baby was breathing well (mean time 94 secs after birth). N = 29 In both groups the baby was placed approximately 15 cm below the perineum
Outcomes	Apgar score at 5 minutes, birthweight, cord blood hematocrit, bilirubin, haptoglobin, reticulocyte count and infant blood at 24 and 72 hours
Notes	For continuous outcomes mean and SE were reported. We calculated the SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described. "Infants were randomly selected for one of two methods of cord clamping"
Allocation concealment (selection bias)	Unclear risk	Not described. "Infants were randomly selected for one of two methods of cord clamping"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was not clear that all women randomised were accounted for. There were missing data for some outcomes and this was not balanced across groups.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.
Other bias	Low risk	No other bias apparent. Very little information was provided on study methods. Groups appeared comparable

Saigal 1972

Methods	Randomised controlled trial (no details of randomisation method)
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

Saigal 1972   (*Continued*)

	third percentile for gestational age)
Interventions	Immediate cord clamping - within 5 secs, median 2 secs (n = 15). Clamping at 1 minute - 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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"assigned prior to delivery according to a randomised study protocol" but no further details given
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up or deviation from protocol not reported.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.
Other bias	Unclear risk	Little information on study methods.

Spears 1966

Methods	Randomised controlled trial (no details of randomisation method)
Participants	379 women who gave birth vaginally to a term infant weighing greater than 2500 g at the Los Angeles County General Hospital USA
Interventions	Early cord clamping was defined as within 1 minute after birth (60% were clamped within 30 secs) (n = 192). Late cord clamping was defined as clamping as at 3 minutes 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.

Spears 1966 (*Continued*)

Notes	No maternal outcomes reported that were of relevance to this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated to early or late cord clamping group upon entering the delivery room.No further information
Allocation concealment (selection bias)	Unclear risk	No description of how the allocation process was decided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description of how or whether there was blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report: neonatal deaths not reportedly by group
Other bias	Unclear risk	Little information on study methods.

van Rheenen 2007

Methods	Randomised controlled trial.
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

van Rheenen 2007   *(Continued)*

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 = haemoglobin 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 μmol/mol haem for infants and adults. Iron-deficiency anaemia in mothers and infants = combination of ZPP above the cut-off level, together with haemoglobin more than 2 SD below the reference mean (and mean cell haemoglobin concentration below the cutoff level for 2-month follow-up)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes with unpredictable allocation code
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes with unpredictable allocation code
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"partially blinded" study; "one of the investigators… monitored the delivery procedure and was therefore not blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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)
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report only.

van Rheenen 2007 *(Continued)*

Other bias	Low risk	Not apparent.

ASQ: Ages and Stages Questionnaire
fL: femtolitre
IM: intramuscular
ITT: intention-to-treat
IUGR: intrauterine growth restriction
IV: intravenous
MCV: mean corpuscular volume
NICU: neonatal intensive care unit
PDA: patent ductus arteriosus
PPH: postpartum haemorrhage
rH: Rhesus
SD: standard deviation
SE: standard error
secs: seconds
ZPP: zinc protoporphyrin

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

Study	Reason for exclusion
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"
De Paco 2011	This was not a randomised trial, allocation to groups was alternate (quasi-randomised)
Duckman 1953	No mention of randomisation and allocation process not described
Dunn 1966	It was not clear that this was a randomised trial. It was stated that women were selected at random and then divided into two equal groups (i.e. random selection rather than random allocation)
Emmanouilides 1971	No mention of randomisation and allocation process not described

(Continued)

Erickson-Owens 2012	RCT compares early cord clamping with cord milking (not delayed cord clamping)
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
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
Lanzkowsky 1960	This was not a randomised trial. Women in labour were admitted alternately to two different labour wards
Linderkamp 1992	No mention of randomisation and allocation process not described
Navaneethakrishnan 2010	This was not a trial of early verus delayed cord clamping. In this study rhesus negative women in labour were randomised either to have immediate cord clamping and the cord remained clamped until placental delivery versus immediate cord clamping, then the cord was cut and unclamped on the maternal side to allow blood from the placenta to drain off. The purpose was to see whether this reduced feto-maternal transfusion to the rhesus negative mother. Analysis was not performed where the baby was also rhesus negative
Nelle 1996	No mention of randomisation and allocation process not described
Newton 1961	Quasi-randomised: allocation method by rotation.
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
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	It was not clear how many women were randomised to each group in this study comparing the Leboyer method with routine care. More than half of the sample were excluded post-randomisation. Women in the intervention group received a package of care which included delayed cord clamping along with other interventions and the impact of cord clamping is not clear
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
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	It was not clear that this was an RCT. No mention of random allocation to groups. Study concerned with effects of timing of cord clamping on systolic time intervals of the newborn infant

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Jaleel 2009

Methods	Not clear.
Participants	200 women admitted in labour to a hospital in Karachi.
Interventions	Group 1: umbilical cord clamped immediately after birth. Group 2: umbilical cord clamped after cessation of pulsation
Outcomes	Newborn haemoglobin and bilirubin.

Jaleel 2009 (*Continued*)

Notes	We are awaiting further information on the methods for this study; it was not clear that there was random allocation to groups. More than half of the sample were post-randomisation exclusions and the remaining sample did not appear to be random (for example 65% of the babies were male) It is stated that is a randomised trial but the authors also state: "447 deliveries were conducted in the Department. Problems were encountered as patients at Lyari General Hospital tend to leave early after normal deliveries and therefore, obtaining the second blood sample was difficult. Patients with incomplete data were excluded from the study. Finally, 200 patients were included, 100 in each group."

Li 2012

Methods	RCT.
Participants	158 mother-infant pairs.
Interventions	Early cord clamping (15 seconds) versus late cord clamping (1 minute)
Outcomes	Infant iron stores at 4 months.
Notes	Requires translation.

Nardozza 2012

Methods	RCT reported in brief abstract.
Participants	50 women giving birth in a hospital in Brazil (not clear).
Interventions	Immediate cord clamping versus spontaneous draining of the cord before clamping (not clear)
Outcomes	Fetal blood cells entering maternal circulation.
Notes	This study was reported in a brief abstract and there was insufficient information to allow us assess eligibility. We are awaiting publication of a full report of this trial

Ping 2010

Methods	Not clear. Trial registration with no information on study methods
Participants	All live births.
Interventions	Immediate (within 10 seconds of birth) umbilical cord clamping versus clamping after the cord has ceased pulsing
Outcomes	Infant haemoglobin at one month.
Notes	Hainan Medical College, China. Chief investigator Professor Hua Shao Ping. We will assess eligibility once findings are published

RCT: randomised controlled trial

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

Beal 2006

Trial name or title	Timing of cord clamping and neonatal haemoglobin - 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	

Hanson 2012

Trial name or title	Effect of delayed cord clamping on the haemoglobin levels of term newborn Aboriginal communities: A pilot randomised trial
Methods	Proposed pilot RCT.
Participants	72 Aboriginal women at 36-42 weeks' gestation with uncomplicated vaginal or caesarean birth
Interventions	Delayed cord clamping until pulsation ceases or after 3 minutes with baby held below the level of the placenta verus standard care (immediate cord clamping)
Outcomes	Infant haemoglobin at time of hospital discharge, neonatal morbidity, Apgar score at 5 minutes, neonatal death
Starting date	Starting date not clear. Proposed end date 29.02.12.
Contact information	melanie.hanson@menzies.edu.au
Notes	Proposed study reported in a brief conference abstract.

RCT: randomised controlled trial

D A T A   A N D   A N A L Y S E S

Comparison 1.   Early versus late cord clamping

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe PPH/blood loss 1000 mL or more	5	2066	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.65, 1.65]
1.1 Uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.46, 2.96]
1.2 Uterotonic at, or after, clamping	3	956	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.95]
1.3 Use of uterotonic not specified	2	630	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.29, 2.49]
2 Neonatal death	2	381	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.04, 3.41]
3 PPH/blood loss 500 mL or more	5	2260	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.94, 1.44]
3.1 Uterotonic before clamping	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.74, 1.67]
3.2 Uterotonic at, or after, clamping	3	956	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.90, 1.65]
3.3 Use of uterotonic not specified	1	272	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.73, 1.74]
4 Mean blood loss (mL)	2	1345	Mean Difference (IV, Fixed, 95% CI)	5.11 [-23.18, 33.39]
4.1 Uterotonic before clamping	1	480	Mean Difference (IV, Fixed, 95% CI)	22.0 [-40.16, 84.16]
4.2 Uterotonic at, or after, clamping	2	865	Mean Difference (IV, Fixed, 95% CI)	0.70 [-31.06, 32.46]
5 Maternal haemoglobin (g/dL) 24 to 72 hours postpartum	3	1128	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.30, 0.06]
5.1 Uterotonic before clamping	1	480	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.31, 0.31]
5.2 Uterotonic at, or after, clamping	1	483	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.42, 0.22]
5.3 Use of uterotonic not specified	2	165	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.60, 0.04]
6 Need for blood transfusion	2	1345	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.44, 2.37]
6.1 Uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.26, 9.20]
6.2 Uterotonic at, or after, clamping	2	865	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.35]
7 Need for manual removal of placenta	2	1515	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.78, 3.26]
7.1 Uterotonic before clamping	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.94, 5.01]
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 > 30 mins	2	1345	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.55, 2.52]

8.1 Uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	3.10 [0.32, 29.61]
8.2 Uterotonic at, or after, clamping	2	865	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.44, 2.29]
9 Length of third stage > 60 mins	2	1345	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.33, 3.74]
9.1 Uterotonic before clamping	1	480	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.34, 3.16]
9.2 Uterotonic at, or after clamping	2	865	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.09, 31.66]
10 Need for therapeutic uterotonics	1	963	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.74, 1.20]
10.1 Uterotonic before clamping	1	480	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.78, 1.55]
10.2 Uterotonic at, or after, clamping	1	483	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.14]
11 Apgar score < 7 at 5 mins	3	1399	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	2	540	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 Any admission to SCN or NICU	4	1675	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.31]
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	2	865	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.37, 1.46]
12.3 Use of uterotonic not specified	2	330	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.20, 1.60]
13 Respiratory distress	3	835	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.22, 2.19]
14 Jaundice requiring phototherapy	7	2324	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.41, 0.96]
14.1 Uterotonic before clamping	2	1032	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.32, 1.11]
14.2 Uterotonic at, or after, clamping	5	1112	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.35, 1.18]
14.3 Use of uterotonic not specified	1	180	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.74]
15 Clinical jaundice	6	2098	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.66, 1.07]
15.1 Uterotonic before clamping	2	1022	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.18]
15.2 Uterotonic at, or after, clamping	2	576	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.57, 1.31]
15.3 Use of uterotonic not specified	3	500	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.29, 1.39]
16 Polycythaemia	5	1025	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.12, 1.27]
16.1 Uterotonic at, or after, clamping	3	577	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.06, 2.48]
16.2 Use of uterotonic not specified	2	448	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.09, 1.80]

17 Cord haemoglobin (g/dL)	5	696	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.15, 0.66]
17.1 Uterotonic at, or after, clamping	3	531	Mean Difference (IV, Fixed, 95% CI)	0.48 [0.19, 0.76]
17.2 Use of uterotonic not specified	2	165	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.42, 0.71]
18 Newborn haemoglobin (g/dL)	3	671	Mean Difference (IV, Random, 95% CI)	-2.17 [-4.06, -0.28]
18.1 Uterotonic at, or after, clamping	1	45	Mean Difference (IV, Random, 95% CI)	-4.45 [-5.33, -3.57]
18.2 Use of uterotonic not specified	2	626	Mean Difference (IV, Random, 95% CI)	-1.07 [-2.03, -0.12]
19 Infant haemoglobin at 24-48 hours (g/dL)	4	884	Mean Difference (IV, Fixed, 95% CI)	-1.49 [-1.78, -1.21]
19.1 Uterotonic at, or after, clamping	2	426	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-1.75, -1.05]
19.2 Use of uterotonic not specified	2	458	Mean Difference (IV, Fixed, 95% CI)	-1.68 [-2.18, -1.19]
20 Infant haemoglobin at 3-6 months (g/dL)	6	1115	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.48, 0.19]
20.1 Uterotonic at, or after, clamping	2	434	Mean Difference (IV, Random, 95% CI)	0.03 [-0.17, 0.22]
20.2 Use of uterotonic not specified	4	681	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.79, 0.26]
21 Low infant haemoglobin at 3-6 months	4	954	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.79, 1.39]
21.1 Uterotonic at, or after, clamping	2	438	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.36]
21.2 Use of uterotonic not specified	2	516	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.74, 1.92]
22 Infant haematocrit (%)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 At 24 hours	1	180	Mean Difference (IV, Fixed, 95% CI)	-4.40 [-5.71, -3.09]
22.2 At 3-5 months	1	160	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.48, 0.68]
23 Low 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 Low 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 iron deficiency at 3-6 months	5	1152	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.04, 6.73]
25.1 Uterotonic at, or after, clamping	2	425	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.19, 40.19]
25.2 Use of uterotonic not specified	3	727	Risk Ratio (M-H, Random, 95% CI)	2.91 [1.18, 7.20]
26 Birthweight (g)	12	3139	Mean Difference (IV, Random, 95% CI)	-101.18 [-157.59, -44.76]
27 Not breastfeeding on discharge (or later)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
27.1 At discharge	4	1633	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.90, 1.36]
27.2 At 1 month	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.00, 1.20]

27.3 At 2 months	1	84	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.24]
27.4 At 3 months	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.36, 2.42]
27.5 At 4 months	2	391	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.04]
27.6 At 6 months	2	430	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.11]
28 Neurodevelopment at 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
28.1 ASQ total score	1	365	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-7.31, 4.51]
28.2 ASQ communication score	1	365	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.87, 1.27]
28.3 ASQ gross motor score	1	365	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.11, 0.91]
28.4 ASQ fine motor score	1	365	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.10, 1.30]
28.5 ASQ problem-solving score	1	365	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.38, -0.22]
28.6 ASQ personal-social score	1	365	Mean Difference (IV, Fixed, 95% CI)	2.30 [0.51, 4.09]
29 Symptoms of infection during first 4 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 Fever	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.31]
29.2 Diarrhoea	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.57, 2.19]
29.3 Loose stools	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.27]
29.4 Hard stools	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.28, 2.21]
29.5 Belly ache	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.81, 1.71]
29.6 Vomiting	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.79, 2.41]
29.7 Cough	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.72, 1.23]
29.8 Breathing difficulties	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.40, 1.60]
29.9 Rhinorrhea/runny nose	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.69, 1.28]
29.10 Nasal congestion	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.27]
29.11 Otitis	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 4.12]
29.12 Rash	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.60]
29.13 Crying	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.95, 1.96]
29.14 Tiredness	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.71, 1.93]
29.15 Visit to paediatrician	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.56, 1.23]
29.16 Visit to other doctor	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.60, 2.37]
29.17 Antibiotics	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.61, 3.02]
29.18 Admitted to hospital	1	360	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.67, 3.21]

Analysis 1.1. Comparison 1 Early versus late cord clamping, Outcome 1 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: 1 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	Risk Ratio M-H,Fixed,95% CI
1 Uterotonic before clamping				
McDonald 1996	9/236	8/244		1.16 [0.46, 2.96]
Subtotal (95% CI)	**236**	**244**		**1.16 [0.46, 2.96]**
Total events: 9 (early clamping), 8 (late clamping)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.32 (P = 0.75)				
2 Uterotonic at, or after, clamping				
Andersson 2011	14/189	9/193		1.59 [0.70, 3.58]
McDonald 1996	6/244	10/239		0.59 [0.22, 1.59]
van Rheenen 2007	0/45	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**478**	**478**		**1.06 [0.57, 1.95]**
Total events: 20 (early clamping), 19 (late clamping)				
Heterogeneity: Chi² = 2.30, df = 1 (P = 0.13); I² =56%				
Test for overall effect: Z = 0.18 (P = 0.86)				
3 Use of uterotonic not specified				
Cernadas 2006	3/90	8/182		0.76 [0.21, 2.79]
Chaparro 2006	2/171	2/187		1.09 [0.16, 7.68]
Subtotal (95% CI)	**261**	**369**		**0.85 [0.29, 2.49]**
Total events: 5 (early clamping), 10 (late clamping)				
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² =0.0%				
Test for overall effect: Z = 0.30 (P = 0.76)				
Total (95% CI)	**975**	**1091**		**1.04 [0.65, 1.65]**
Total events: 34 (early clamping), 37 (late clamping)				
Heterogeneity: Chi² = 2.59, df = 4 (P = 0.63); I² =0.0%				
Test for overall effect: Z = 0.15 (P = 0.88)				
Test for subgroup differences: Chi² = 0.20, df = 2 (P = 0.91), I² =0.0%				

```
           0.1   0.2   0.5   1    2    5   10
        Favours early clamp      Favours late clamp
```

Analysis 1.2. Comparison 1 Early versus late cord clamping, Outcome 2 Neonatal death.

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Cernadas 2006	0/92	0/184		0.0 [0.0, 0.0]
van Rheenen 2007	1/50	3/55		0.37 [0.04, 3.41]
Total (95% CI)	**142**	**239**		**0.37 [0.04, 3.41]**

Total events: 1 (early clamping), 3 (late clamping)

Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours early clamping   Favours late clamping

Analysis 1.3.   Comparison 1 Early versus late cord clamping, Outcome 3 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: 3 PPH/blood loss 500 mL or more

Study or subgroup	early clamping	late clamping	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
1 Uterotonic before clamping				
McDonald 1996	31/236	32/244		1.00 [0.63, 1.59]
Oxford Midwives 1991	12/256	9/296		1.54 [0.66, 3.60]
Subtotal (95% CI)	**492**	**540**		**1.11 [0.74, 1.67]**
Total events: 43 (early clamping), 41 (late clamping)				
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² =0.0%				
Test for overall effect: Z = 0.53 (P = 0.60)				
2 Uterotonic at, or after, clamping				
Andersson 2011	29/189	30/193		0.99 [0.62, 1.58]
McDonald 1996	48/244	33/239		1.42 [0.95, 2.14]
van Rheenen 2007	0/45	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**478**	**478**		**1.22 [0.90, 1.65]**
Total events: 77 (early clamping), 63 (late clamping)				
Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² =26%				
Test for overall effect: Z = 1.27 (P = 0.20)				
3 Use of uterotonic not specified				
Cernadas 2006	24/90	43/182		1.13 [0.73, 1.74]
Subtotal (95% CI)	**90**	**182**		**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)	**1060**	**1200**		**1.17 [0.94, 1.44]**
Total events: 144 (early clamping), 147 (late clamping)				
Heterogeneity: Chi² = 2.28, df = 4 (P = 0.68); I² =0.0%				
Test for overall effect: Z = 1.43 (P = 0.15)				
Test for subgroup differences: Chi² = 0.15, df = 2 (P = 0.93), I² =0.0%				

0.1   0.2   0.5   1   2   5   10

Favours early clamp   Favours late clamp

Analysis 1.4. Comparison 1 Early versus late cord clamping, Outcome 4 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: 4 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)		20.7 %	22.00 [-40.16, 84.16]
Subtotal (95% CI)	**236**		**244**			**20.7 %**	**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							
Andersson 2011 (1)	189	388 (193.5)	193	384 (193.5)		53.1 %	4.00 [-34.81, 42.81]
McDonald 1996	244	353 (278)	239	359 (338)		26.2 %	-6.00 [-61.25, 49.25]
Subtotal (95% CI)	**433**		**432**			**79.3 %**	**0.70 [-31.06, 32.46]**
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² =0.0%							
Test for overall effect: Z = 0.04 (P = 0.97)							
Total (95% CI)	**669**		**676**			**100.0 %**	**5.11 [-23.18, 33.39]**
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² =0.0%							
Test for overall effect: Z = 0.35 (P = 0.72)							
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² =0.0%							

```
        -100   -50    0    50   100
     Favours early clamp   Favours late clamp
```

(1) SD imputed from P value

Analysis 1.5. Comparison 1 Early versus late cord clamping, Outcome 5 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: 5 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: Chi² = 0.07, df = 1 (P = 0.80); I² =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: Chi² = 1.60, df = 3 (P = 0.66); I² =0.0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Test for subgroup differences: Chi² = 1.54, df = 2 (P = 0.46), I² =0.0%							

```
        -4    -2    0    2    4
    Favours late clamp    Favours early clamp
```

Analysis 1.6. Comparison I Early versus late cord clamping, Outcome 6 Need for blood transfusion.

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

Comparison: I Early versus late cord clamping

Outcome: 6 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
I Uterotonic before clamping					
McDonald 1996	3/236	2/244		18.9 %	1.55 [0.26, 9.20]
Subtotal (95% CI)	**236**	**244**		**18.9 %**	**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					
Andersson 2011	7/189	6/193		56.9 %	1.19 [0.41, 3.48]
McDonald 1996	0/244	2/239		24.2 %	0.20 [0.01, 4.06]
Subtotal (95% CI)	**433**	**432**		**81.1 %**	**0.89 [0.34, 2.35]**
Total events: 7 (early clamping), 8 (late clamping)					
Heterogeneity: Chi² = 1.24, df = I (P = 0.27); I² =19%					
Test for overall effect: Z = 0.23 (P = 0.82)					
Total (95% CI)	**669**	**676**		**100.0 %**	**1.02 [0.44, 2.37]**
Total events: 10 (early clamping), 10 (late clamping)					
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² =0.0%					
Test for overall effect: Z = 0.04 (P = 0.97)					
Test for subgroup differences: Chi² = 0.28, df = I (P = 0.59), I² =0.0%					

0.1 0.2 0.5 I 2 5 10

Favours early clamp   Favours late clamp

Analysis 1.7. Comparison 1 Early versus late cord clamping, Outcome 7 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: 7 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: Chi² = 0.51, df = 1 (P = 0.48); I² =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					
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: Chi² = 2.85, df = 2 (P = 0.24); I² =30%					
Test for overall effect: Z = 1.27 (P = 0.20)					
Test for subgroup differences: Chi² = 2.40, df = 1 (P = 0.12), I² =58%					

0.1 0.2   0.5   1   2   5   10

Favours early clamp   Favours late clamp

Analysis 1.8. Comparison 1 Early versus late cord clamping, Outcome 8 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: 8 Length of third stage > 30 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	3/236	1/244		8.2 %	3.10 [0.32, 29.61]
Subtotal (95% CI)	**236**	**244**		**8.2 %**	**3.10 [0.32, 29.61]**
Total events: 3 (early clamping), 1 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
2 Uterotonic at, or after, clamping					
Andersson 2011	9/189	7/193		58.0 %	1.31 [0.50, 3.45]
McDonald 1996	2/244	4/239		33.8 %	0.49 [0.09, 2.65]
Subtotal (95% CI)	**433**	**432**		**91.8 %**	**1.01 [0.44, 2.29]**
Total events: 11 (early clamping), 11 (late clamping)					
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² =0.0%					
Test for overall effect: Z = 0.02 (P = 0.98)					
Total (95% CI)	**669**	**676**		**100.0 %**	**1.18 [0.55, 2.52]**
Total events: 14 (early clamping), 12 (late clamping)					
Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² =0.0%					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² =0.0%					

0.1   0.2   0.5   1   2   5   10

Favours early clamp   Favours late clamp

Analysis 1.9. Comparison 1 Early versus late cord clamping, Outcome 9 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: 9 Length of third stage > 60 mins

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	6/236	6/244		52.1 %	1.03 [0.34, 3.16]
Subtotal (95% CI)	**236**	**244**		**52.1 %**	**1.03 [0.34, 3.16]**
Total events: 6 (early clamping), 6 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
2 Uterotonic at, or after clamping					
Andersson 2011	4/189	0/193		14.6 %	9.19 [0.50, 169.52]
McDonald 1996	2/244	4/239		33.3 %	0.49 [0.09, 2.65]
Subtotal (95% CI)	**433**	**432**		**47.9 %**	**1.68 [0.09, 31.66]**
Total events: 6 (early clamping), 4 (late clamping)					
Heterogeneity: Tau² = 3.13; Chi² = 3.12, df = 1 (P = 0.08); I² =68%					
Test for overall effect: Z = 0.35 (P = 0.73)					
Total (95% CI)	**669**	**676**		**100.0 %**	**1.11 [0.33, 3.74]**
Total events: 12 (early clamping), 10 (late clamping)					
Heterogeneity: Tau² = 0.41; Chi² = 3.04, df = 2 (P = 0.22); I² =34%					
Test for overall effect: Z = 0.17 (P = 0.87)					
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours early clamp   Favours late clamp

Analysis 1.10. Comparison I Early versus late cord clamping, Outcome 10 Need for therapeutic uterotonics.

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

Comparison: I Early versus late cord clamping

Outcome: 10 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
I 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: Chi² = 1.50, df = 1 (P = 0.22); I² =33%					
Test for overall effect: Z = 0.50 (P = 0.62)					
Test for subgroup differences: Chi² = 1.50, df = 1 (P = 0.22), I² =33%					

```
        0.1  0.2   0.5    I    2    5   10
          Favours early clamp   Favours late clamp
```

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	Risk Ratio M-H,Fixed,95% CI
1 Uterotonic before clamping				
McDonald 1996	5/236	3/244		1.72 [0.42, 7.13]
Subtotal (95% CI)	**236**	**244**		**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		1.96 [0.60, 6.42]
Philip 1973	0/28	0/29		0.0 [0.0, 0.0]
Subtotal (95% CI)	**272**	**268**		**1.96 [0.60, 6.42]**
Total events: 8 (early clamping), 4 (late clamping)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.11 (P = 0.27)				
3 Use of uterotonic not specified				
Spears 1966	17/192	17/187		0.97 [0.51, 1.85]
Subtotal (95% CI)	**192**	**187**		**0.97 [0.51, 1.85]**
Total events: 17 (early clamping), 17 (late clamping)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.08 (P = 0.94)				
Total (95% CI)	**700**	**699**		**1.23 [0.73, 2.07]**
Total events: 30 (early clamping), 24 (late clamping)				
Heterogeneity: Chi² = 1.32, df = 2 (P = 0.52); I² =0.0%				
Test for overall effect: Z = 0.78 (P = 0.43)				
Test for subgroup differences: Chi² = 1.31, df = 2 (P = 0.52), I² =0.0%				

0.1 0.2 0.5 1 2 5 10

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: 12 Any admission to SCN or NICU

Study or subgroup	early clamping	late clamping	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
1 Uterotonic before clamping					
McDonald 1996	7/236	5/244		14.4 %	1.45 [0.47, 4.50]
Subtotal (95% CI)	**236**	**244**		**14.4 %**	**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					
Andersson 2011	6/189	14/193		40.7 %	0.44 [0.17, 1.11]
McDonald 1996	8/244	5/239		14.8 %	1.57 [0.52, 4.72]
Subtotal (95% CI)	**433**	**432**		**55.6 %**	**0.74 [0.37, 1.46]**
Total events: 14 (early clamping), 19 (late clamping)					
Heterogeneity: Chi² = 2.99, df = 1 (P = 0.08); I² =67%					
Test for overall effect: Z = 0.87 (P = 0.38)					
3 Use of uterotonic not specified					
Cernadas 2006	4/93	13/183		25.7 %	0.61 [0.20, 1.81]
Nelson 1980	0/26	1/28		4.3 %	0.36 [0.02, 8.42]
Subtotal (95% CI)	**119**	**211**		**30.0 %**	**0.57 [0.20, 1.60]**
Total events: 4 (early clamping), 14 (late clamping)					
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² =0.0%					
Test for overall effect: Z = 1.07 (P = 0.28)					
Total (95% CI)	**788**	**887**		**100.0 %**	**0.79 [0.48, 1.31]**
Total events: 25 (early clamping), 38 (late clamping)					
Heterogeneity: Chi² = 4.58, df = 4 (P = 0.33); I² =13%					
Test for overall effect: Z = 0.92 (P = 0.36)					
Test for subgroup differences: Chi² = 1.52, df = 2 (P = 0.47), I² =0.0%					

0.1   0.2   0.5   1   2   5   10

Favours early clamp   Favours late clamp

Analysis 1.13. Comparison 1 Early versus late cord clamping, Outcome 13 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 Respiratory distress

Study or subgroup	early clamping	late clamping	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Al-Tawil 2012	0/90	0/90		0.0 [0.0, 0.0]
Cernadas 2006	4/184	6/92		0.33 [0.10, 1.15]
Spears 1966	25/192	22/187		1.11 [0.65, 1.89]
Total (95% CI)	**466**	**369**		**0.70 [0.22, 2.19]**

Total events: 29 (early clamping), 28 (late clamping)

Heterogeneity: Tau² = 0.48; Chi² = 3.03, df = 1 (P = 0.08); I² =67%

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours early clamping   Favours late clamping

Analysis 1.14.   Comparison I Early versus late cord clamping, Outcome 14 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: 14 Jaundice requiring phototherapy

Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Uterotonic before clamping				
McDonald 1996	12/236	16/244		0.78 [0.37, 1.60]
Oxford Midwives 1991	3/256	11/296		0.32 [0.09, 1.12]
Subtotal (95% CI)	**492**	**540**		**0.59 [0.32, 1.11]**
Total events: 15 (early clamping), 27 (late clamping)				
Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² =32%				
Test for overall effect: Z = 1.64 (P = 0.10)				
2 Uterotonic at, or after, clamping				
Andersson 2011	2/189	1/193		2.04 [0.19, 22.33]
Emhamed 2004	2/45	0/57		6.30 [0.31, 128.10]
McDonald 1996	10/244	21/239		0.47 [0.22, 0.97]
Nelson 1980	1/26	2/28		0.54 [0.05, 5.59]
van Rheenen 2007	0/45	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**549**	**563**		**0.64 [0.35, 1.18]**
Total events: 15 (early clamping), 24 (late clamping)				
Heterogeneity: Chi² = 3.86, df = 3 (P = 0.28); I² =22%				
Test for overall effect: Z = 1.42 (P = 0.16)				
3 Use of uterotonic not specified				
Al-Tawil 2012	1/90	1/90		1.00 [0.06, 15.74]
Subtotal (95% CI)	**90**	**90**		**1.00 [0.06, 15.74]**
Total events: 1 (early clamping), 1 (late clamping)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P = 1.0)				
Total (95% CI)	**1131**	**1193**		**0.62 [0.41, 0.96]**
Total events: 31 (early clamping), 52 (late clamping)				
Heterogeneity: Chi² = 5.41, df = 6 (P = 0.49); I² =0.0%				
Test for overall effect: Z = 2.14 (P = 0.032)				
Test for subgroup differences: Chi² = 0.14, df = 2 (P = 0.93), I² =0.0%				

0.5   0.7   1   1.5   2

Favours early clamp   Favours late clamp

Analysis 1.15.   Comparison 1 Early versus late cord clamping, Outcome 15 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: 15 Clinical jaundice

Study or subgroup	early clamping	late clamping	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
1 Uterotonic before clamping				
McDonald 1996	22/233	26/242		0.88 [0.51, 1.51]
Oxford Midwives 1991	35/251	49/296		0.84 [0.56, 1.26]
Subtotal (95% CI)	**484**	**538**		**0.86 [0.62, 1.18]**
Total events: 57 (early clamping), 75 (late clamping)				
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² =0.0%				
Test for overall effect: Z = 0.95 (P = 0.34)				
2 Uterotonic at, or after, clamping				
Emhamed 2004	14/45	15/57		1.18 [0.64, 2.19]
McDonald 1996	19/241	26/233		0.71 [0.40, 1.24]
Subtotal (95% CI)	**286**	**290**		**0.87 [0.57, 1.31]**
Total events: 33 (early clamping), 41 (late clamping)				
Heterogeneity: Chi² = 1.49, df = 1 (P = 0.22); I² =33%				
Test for overall effect: Z = 0.68 (P = 0.49)				
3 Use of uterotonic not specified				
Al-Tawil 2012	0/90	0/90		0.0 [0.0, 0.0]
Cernadas 2006	2/91	1/175		3.85 [0.35, 41.85]
Nelson 1980	5/26	12/28		0.45 [0.18, 1.10]
Subtotal (95% CI)	**207**	**293**		**0.64 [0.29, 1.39]**
Total events: 7 (early clamping), 13 (late clamping)				
Heterogeneity: Chi² = 2.77, df = 1 (P = 0.10); I² =64%				
Test for overall effect: Z = 1.12 (P = 0.26)				
Total (95% CI)	**977**	**1121**		**0.84 [0.66, 1.07]**
Total events: 97 (early clamping), 129 (late clamping)				
Heterogeneity: Chi² = 5.02, df = 5 (P = 0.41); I² =0%				
Test for overall effect: Z = 1.44 (P = 0.15)				
Test for subgroup differences: Chi² = 0.50, df = 2 (P = 0.78), I² =0.0%				

```
        0.1  0.2   0.5    1    2    5   10
        Favours early clamp    Favours late clamp
```

Analysis 1.16. Comparison 1 Early versus late cord clamping, Outcome 16 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: 16 Polycythaemia

Study or subgroup	early clamping	late clamping	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
1 Uterotonic at, or after, clamping				
Andersson 2011	0/189	0/193		0.0 [0.0, 0.0]
Emhamed 2004	0/46	3/58		0.18 [0.01, 3.39]
van Rheenen 2007	1/45	1/46		1.02 [0.07, 15.85]
Subtotal (95% CI)	**280**	**297**		**0.38 [0.06, 2.48]**
Total events: 1 (early clamping), 4 (late clamping)				
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² =0.0%				
Test for overall effect: Z = 1.01 (P = 0.31)				
2 Use of uterotonic not specified				
Al-Tawil 2012	0/90	0/90		0.0 [0.0, 0.0]
Cernadas 2006	2/89	10/179		0.40 [0.09, 1.80]
Subtotal (95% CI)	**179**	**269**		**0.40 [0.09, 1.80]**
Total events: 2 (early clamping), 10 (late clamping)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.19 (P = 0.23)				
Total (95% CI)	**459**	**566**		**0.39 [0.12, 1.27]**
Total events: 3 (early clamping), 14 (late clamping)				
Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² =0.0%				
Test for overall effect: Z = 1.56 (P = 0.12)				
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² =0.0%				

0.1 0.2 0.5 1 2 5 10

Favours early clamp   Favours late clamp

Analysis 1.17.   Comparison 1 Early versus late cord clamping, Outcome 17 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: 17 Cord haemoglobin (g/dL)

Study or subgroup	early clamping		late clamping		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
1 Uterotonic at, or after, clamping							
Andersson 2011	189	16.3 (1.6)	193	15.9 (1.8)		56.0 %	0.40 [0.06, 0.74]
Emhamed 2004	46	15.4 (1.4)	58	14.9 (1.7)		18.4 %	0.50 [-0.10, 1.10]
Saigal 1972	15	16.8 (1.7)	30	15.55 (2.1)		5.0 %	1.25 [0.11, 2.39]
Subtotal (95% CI)	**250**		**281**			**79.4 %**	**0.48 [0.19, 0.76]**
Heterogeneity: Chi² = 1.96, df = 2 (P = 0.38); I² =0.0%							
Test for overall effect: Z = 3.26 (P = 0.0011)							
2 Use of uterotonic not specified							
Geethanath 1997	48	16.1 (2.2)	59	15.5 (2.3)		8.9 %	0.60 [-0.26, 1.46]
Gupta 2002	29	13.9 (1.5)	29	14.1 (1.4)		11.7 %	-0.20 [-0.95, 0.55]
Subtotal (95% CI)	**77**		**88**			**20.6 %**	**0.15 [-0.42, 0.71]**
Heterogeneity: Chi² = 1.91, df = 1 (P = 0.17); I² =48%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Total (95% CI)	**327**		**369**			**100.0 %**	**0.41 [0.15, 0.66]**
Heterogeneity: Chi² = 4.92, df = 4 (P = 0.30); I² =19%							
Test for overall effect: Z = 3.13 (P = 0.0017)							
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.30), I² =5%							

```
                        -4    -2    0    2    4
                   Higher in late clamping    Higher in early clamping
```

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

Study or subgroup	early clamping		late clamping		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
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: Tau² = 0.40; Chi² = 6.52, df = 1 (P = 0.01); I² =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: Tau² = 2.69; Chi² = 56.40, df = 2 (P<0.00001); I² =96%							
Test for overall effect: Z = 2.25 (P = 0.025)							
Test for subgroup differences: Chi² = 26.15, df = 1 (P = 0.00), I² =96%							

```
            -10   -5    0    5    10
         Favours late clamp   Favours early clamp
```

Analysis 1.19. Comparison I Early versus late cord clamping, Outcome 19 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: 19 Infant haemoglobin at 24-48 hours (g/dL)

Study or subgroup	early clamping		late clamping		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Uterotonic at, or after, clamping							
Andersson 2011	160	17.5 (1.9)	162	18.9 (1.7)	■	52.7 %	-1.40 [-1.79, -1.01]
Emhamed 2004	46	17.1 (1.9)	58	18.5 (2.1)	■	13.8 %	-1.40 [-2.17, -0.63]
Subtotal (95% CI)	**206**		**220**		◆	**66.5 %**	**-1.40 [-1.75, -1.05]**
Heterogeneity: Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%							
Test for overall effect: Z = 7.82 (P < 0.00001)							
2 Use of uterotonic not specified							
Al-Tawil 2012	90	16.8 (2.9)	90	19.6 (3.8)	■	8.4 %	-2.80 [-3.79, -1.81]
Cernadas 2006	89	17.03 (2.3)	189	18.34 (2.18)	■	25.2 %	-1.31 [-1.88, -0.74]
Subtotal (95% CI)	**179**		**279**		◆	**33.5 %**	**-1.68 [-2.18, -1.19]**
Heterogeneity: Chi² = 6.56, df = 1 (P = 0.01); I² =85%							
Test for overall effect: Z = 6.68 (P < 0.00001)							
Total (95% CI)	**385**		**499**		◆	**100.0 %**	**-1.49 [-1.78, -1.21]**
Heterogeneity: Chi² = 7.39, df = 3 (P = 0.06); I² =59%							
Test for overall effect: Z = 10.25 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² =0.0%							

```
        -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: I Early versus late cord clamping

Outcome: 20 Infant haemoglobin at 3-6 months (g/dL)

Study or subgroup	early clamping		late clamping		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Uterotonic at, or after, clamping							
Andersson 2011 (1)	175	11.3 (0.7)	168	11.3 (0.8)		21.7 %	0.0 [-0.16, 0.16]
van Rheenen 2007 (2)	45	10.6 (1.5)	46	10.2 (2.1)		10.5 %	0.40 [-0.35, 1.15]
Subtotal (95% CI)	**220**		**214**			**32.2 %**	**0.03 [-0.17, 0.22]**
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.31); I² =5%							
Test for overall effect: Z = 0.26 (P = 0.79)							
2 Use of uterotonic not specified							
Al-Tawil 2012 (3)	78	11.6 (0.8)	82	12 (1.1)		19.3 %	-0.40 [-0.70, -0.10]
Chaparro 2006 (4)	171	12.7 (0.9)	185	12.7 (1.1)		20.9 %	0.0 [-0.21, 0.21]
Geethanath 1997 (5)	48	8.9 (1.6)	59	8.3 (2.1)		11.3 %	0.60 [-0.10, 1.30]
Gupta 2002 (6)	29	8.8 (0.8)	29	9.9 (0.9)		16.3 %	-1.10 [-1.54, -0.66]
Subtotal (95% CI)	**326**		**355**			**67.8 %**	**-0.26 [-0.79, 0.26]**
Heterogeneity: Tau² = 0.24; Chi² = 26.44, df = 3 (P<0.00001); I² =89%							
Test for overall effect: Z = 0.98 (P = 0.33)							
Total (95% CI)	**546**		**569**			**100.0 %**	**-0.15 [-0.48, 0.19]**
Heterogeneity: Tau² = 0.13; Chi² = 31.86, df = 5 (P<0.00001); I² =84%							
Test for overall effect: Z = 0.87 (P = 0.39)							
Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), I² =2%							

```
        -2    -1    0    1    2
```

Favours late clamp   Favours early clamp

(1) at 4 mo

(2) at 6 mo

(3) At 3-5 months

(4) at 6 mo

(5) at 3 mo

(6) at 3 mo

Analysis 1.21. Comparison 1 Early versus late cord clamping, Outcome 21 Low infant haemoglobin at 3-6 months.

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

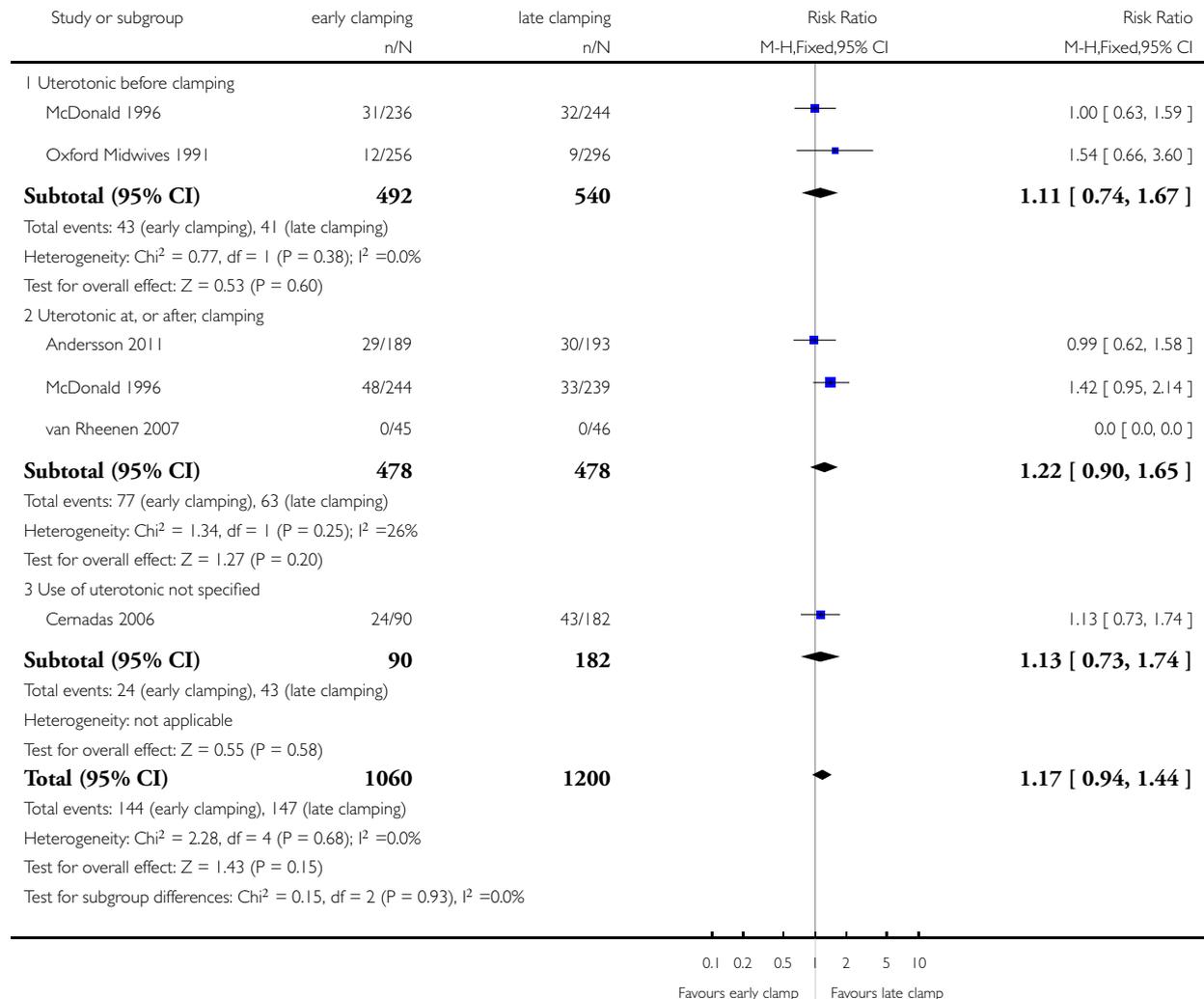Comparison: 1 Early versus late cord clamping

Outcome: 21 Low infant haemoglobin at 3-6 months
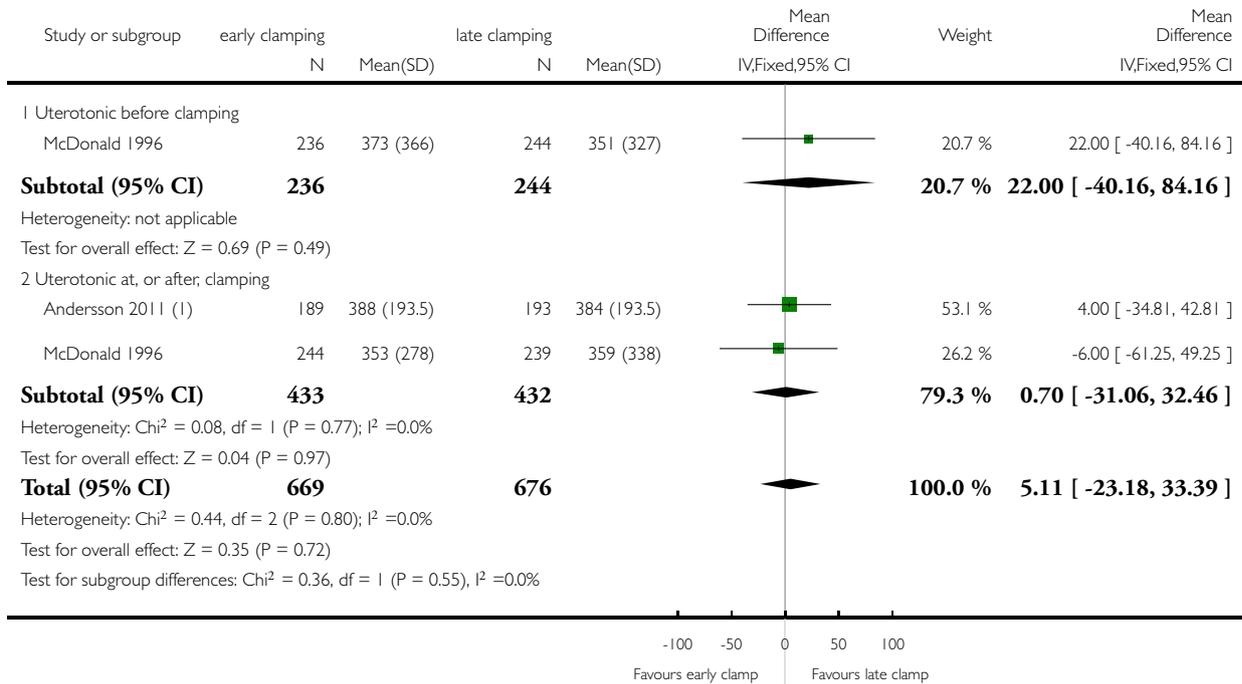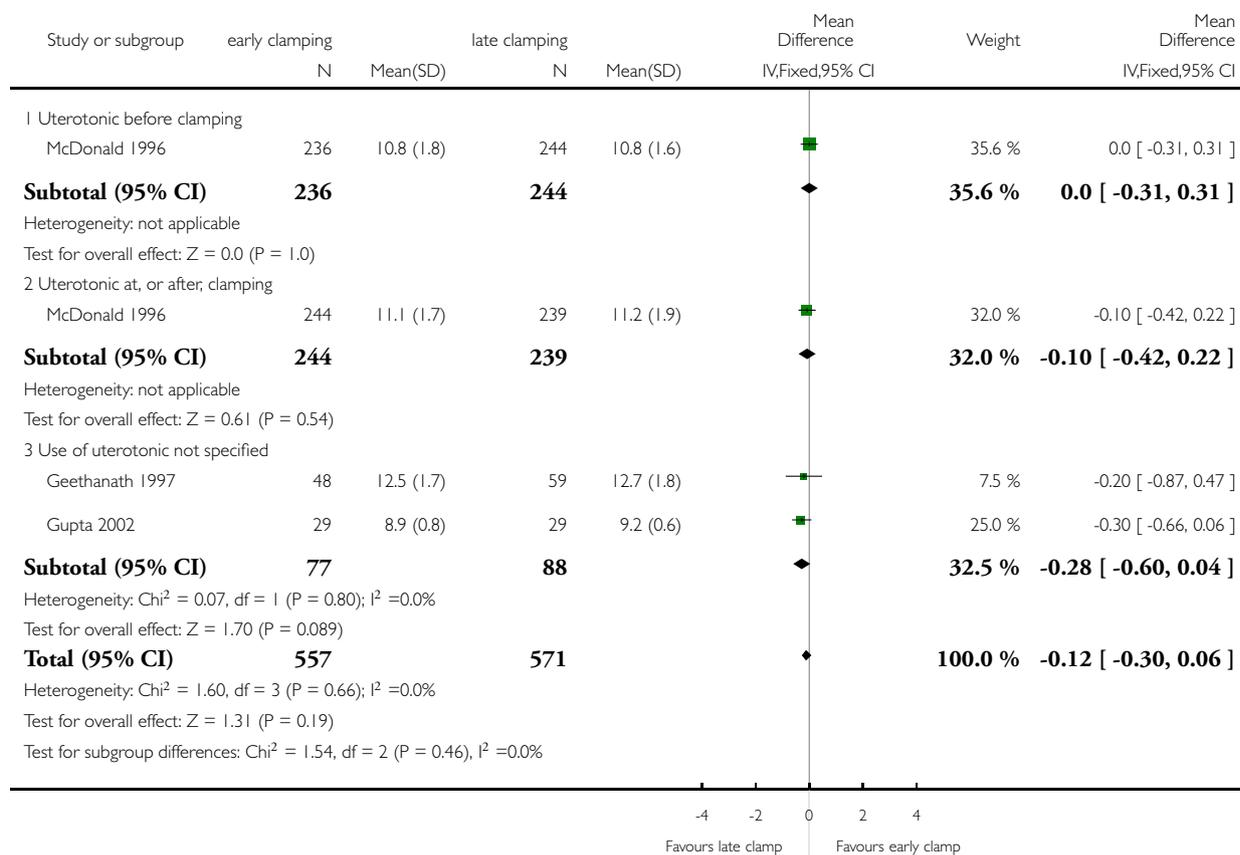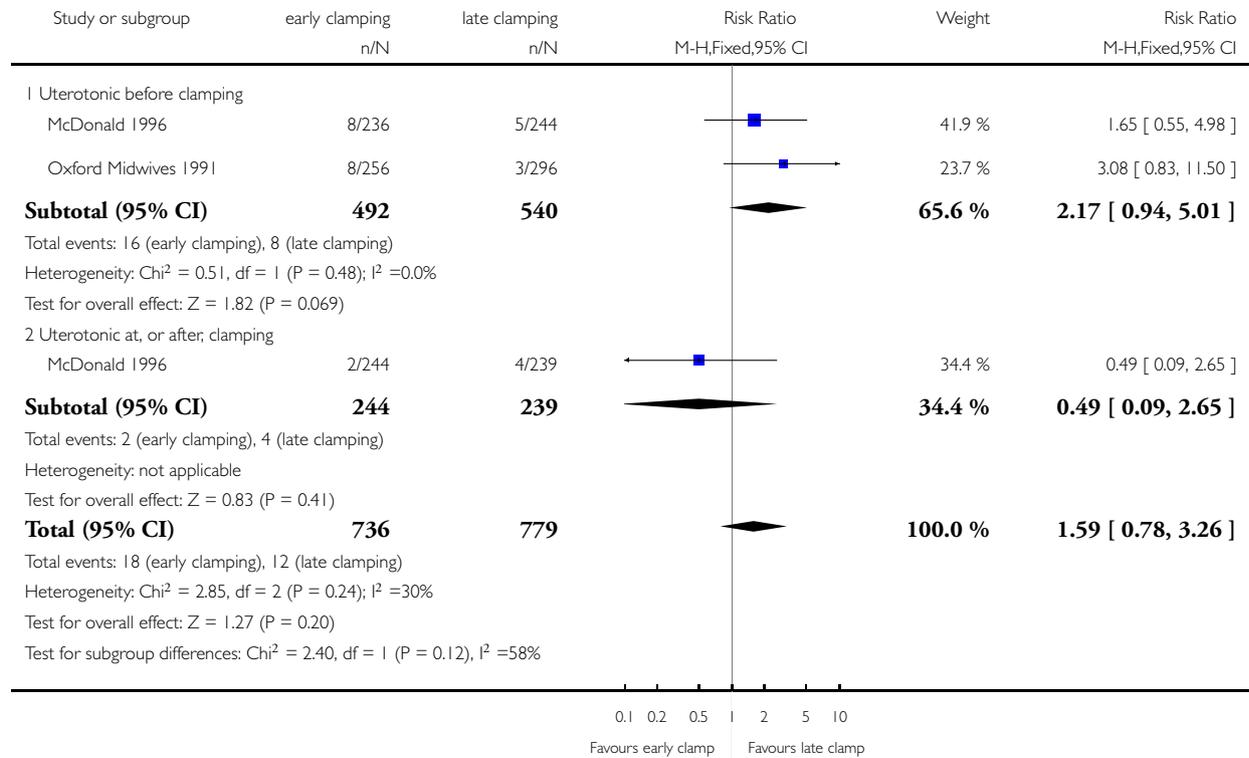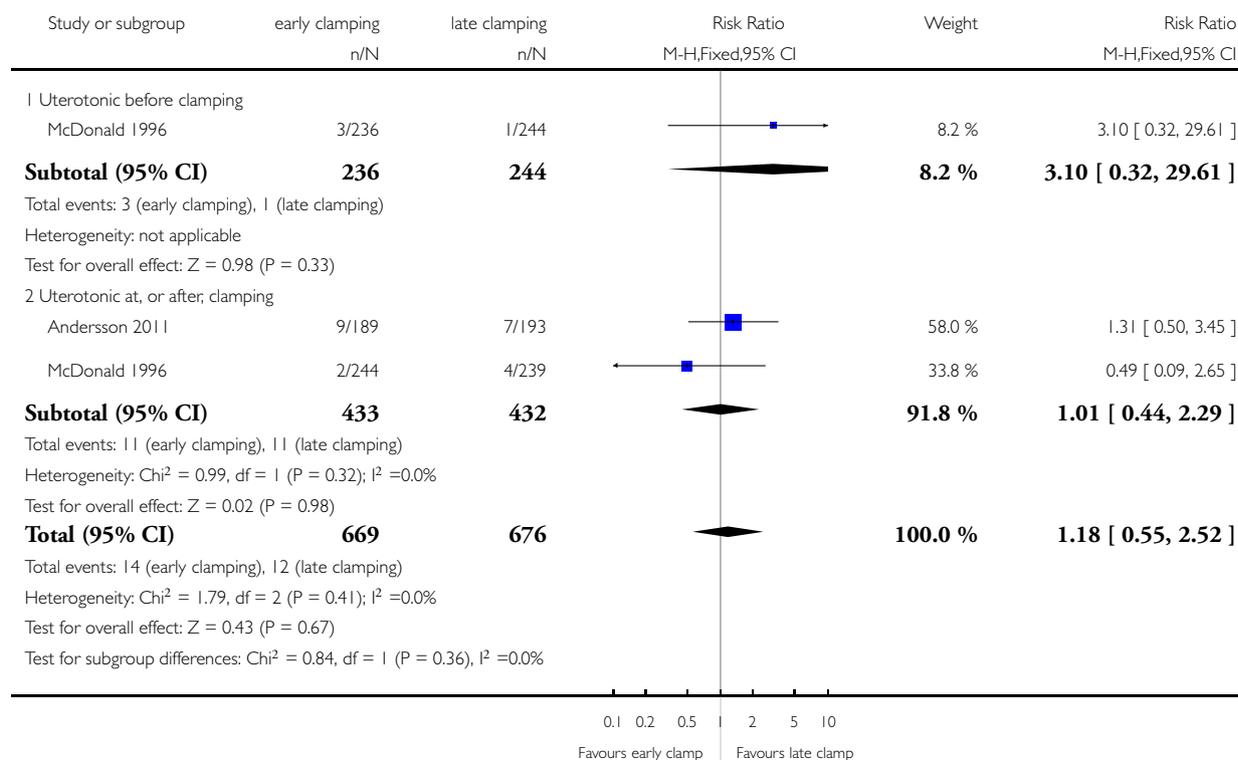
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Uterotonic at, or after, clamping					
Andersson 2011 (1)	21/175	21/172		29.9 %	0.98 [0.56, 1.73]
van Rheenen 2007 (2)	21/45	23/46		32.1 %	0.93 [0.61, 1.43]
Subtotal (95% CI)	**220**	**218**		**62.0 %**	**0.96 [0.67, 1.36]**
Total events: 42 (early clamping), 44 (late clamping)					
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² =0.0%					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 Use of uterotonic not specified					
Al-Tawil 2012 (3)	5/78	4/82		5.5 %	1.31 [0.37, 4.72]
Chaparro 2006 (4)	26/171	24/185		32.5 %	1.17 [0.70, 1.96]
Subtotal (95% CI)	**249**	**267**		**38.0 %**	**1.19 [0.74, 1.92]**
Total events: 31 (early clamping), 28 (late clamping)					
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² =0.0%					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	**469**	**485**		**100.0 %**	**1.05 [0.79, 1.39]**
Total events: 73 (early clamping), 72 (late clamping)					
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² =0.0%					
Test for overall effect: Z = 0.31 (P = 0.75)					
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours early clamp   Favours late clamp

(1) Hb < 10.5 g/dl at 4 mo

(2) Hb < 10.3 g/dl at 6 mo

(3) Hb < 10.5 g/dl at 3-5 mo

(4) Hb < 11.7 g/dl at 4-6 mo

Analysis 1.22.   Comparison 1 Early versus late cord clamping, Outcome 22 Infant haematocrit (%).

Comparison: 1 Early versus late cord clamping

Outcome: 22 Infant haematocrit (%)

Study or subgroup	early clamping		late clamping		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 At 24 hours							
Al-Tawil 2012	90	51.4 (3.8)	90	55.8 (5.1)		100.0 %	-4.40 [-5.71, -3.09]
Subtotal (95% CI)	**90**		**90**			**100.0 %**	**-4.40 [-5.71, -3.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.56 (P < 0.00001)							
2 At 3-5 months							
Al-Tawil 2012	78	33 (3.4)	82	33.4 (3.6)		100.0 %	-0.40 [-1.48, 0.68]
Subtotal (95% CI)	**78**		**82**			**100.0 %**	**-0.40 [-1.48, 0.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
Test for subgroup differences: Chi² = 21.17, df = 1 (P = 0.00), I² =95%							

```
        -10    -5    0    5    10
        Favours late      Favours early
```
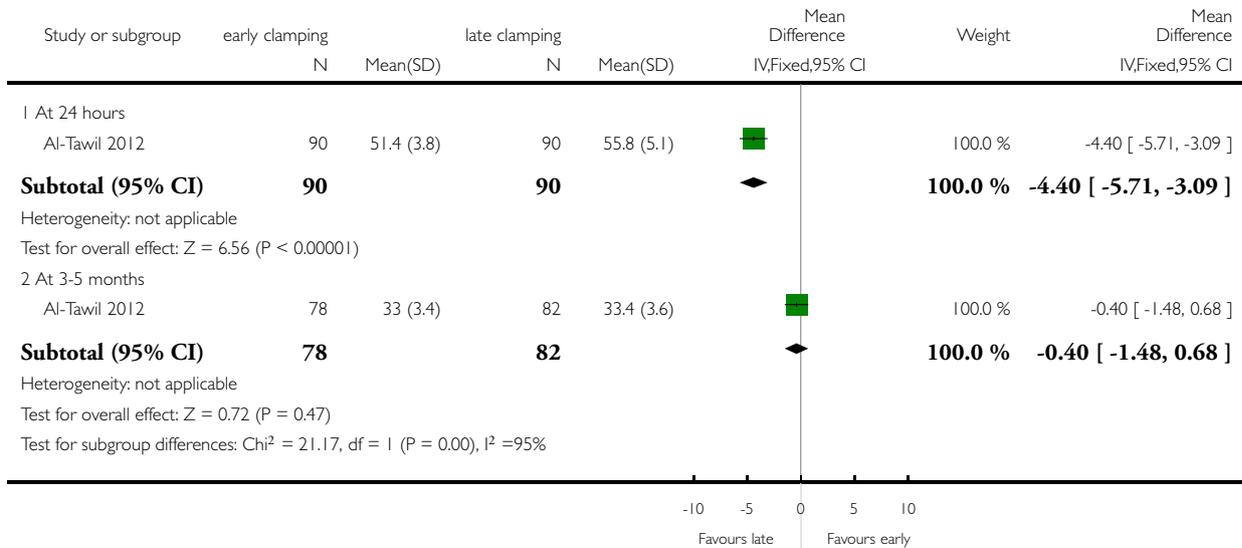
Analysis 1.23.   Comparison 1 Early versus late cord clamping, Outcome 23 Low infant haematocrit (< 45% at 6 hours).

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

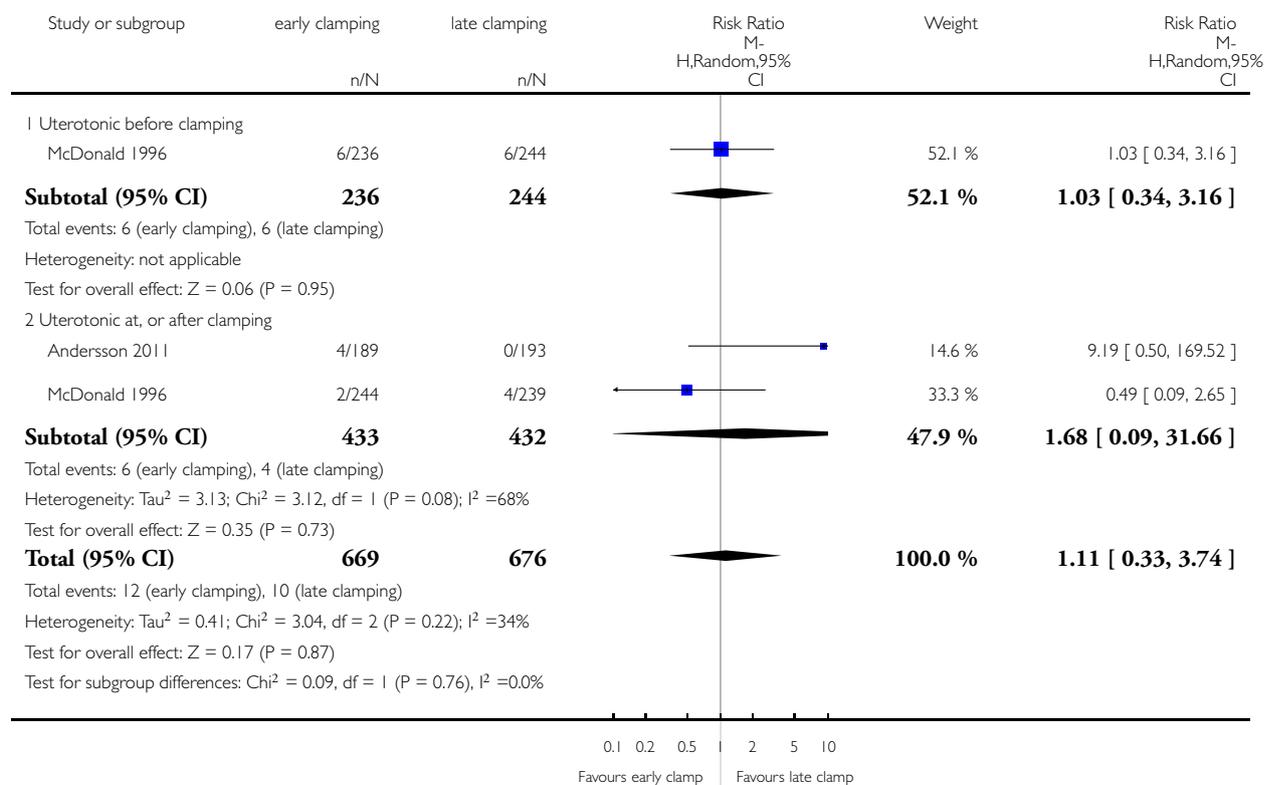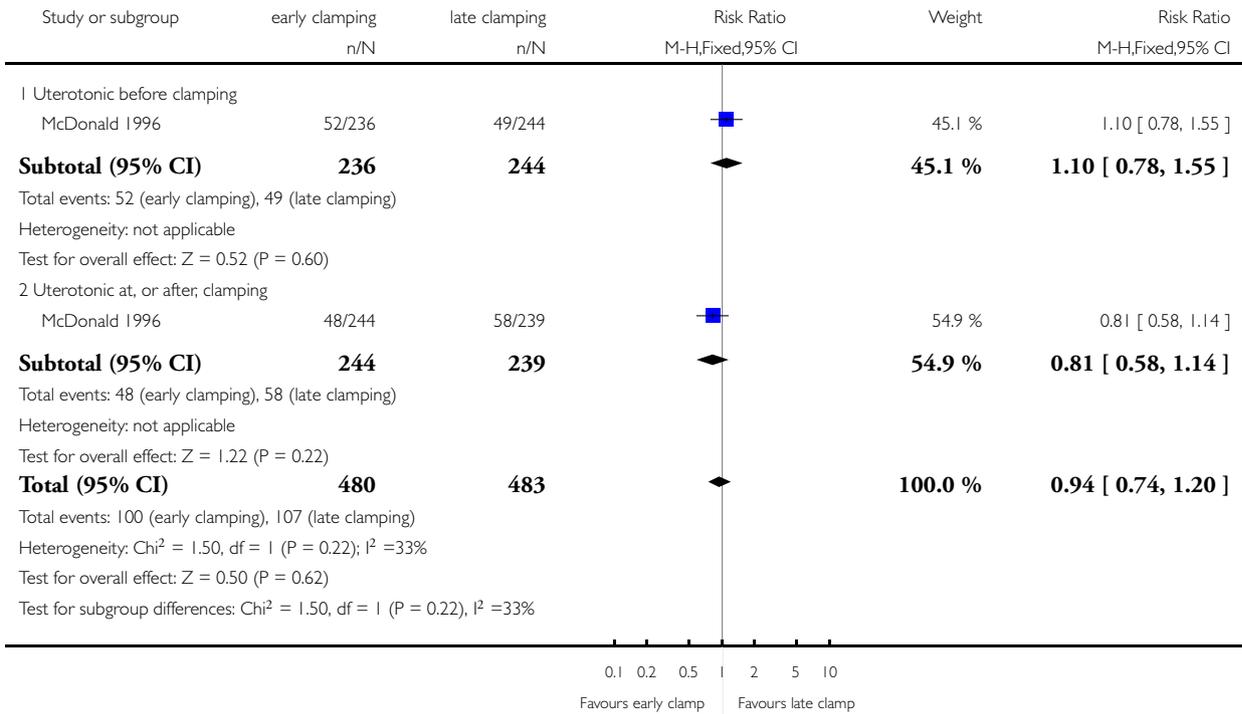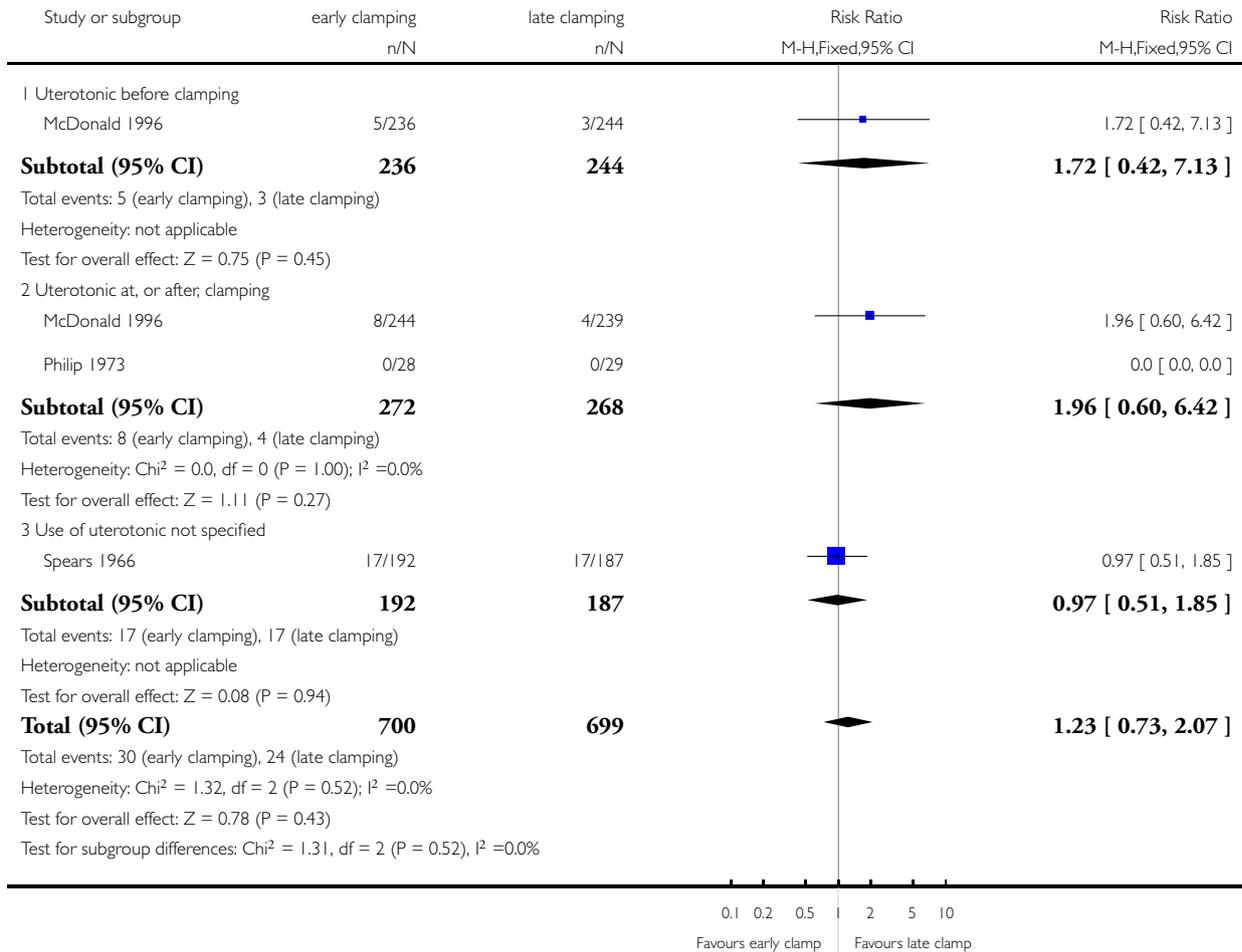Comparison: 1 Early versus late cord clamping

Outcome: 23 Low infant haematocrit (< 45% at 6 hours)

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					
Cernadas 2006	8/90	1/182		100.0 %	16.18 [2.05, 127.37]
Total (95% CI)	**90**	**182**		**100.0 %**	**16.18 [2.05, 127.37]**
Total events: 8 (early clamping), 1 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0082)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100

Favours early clamp   Favours late clamp

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

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

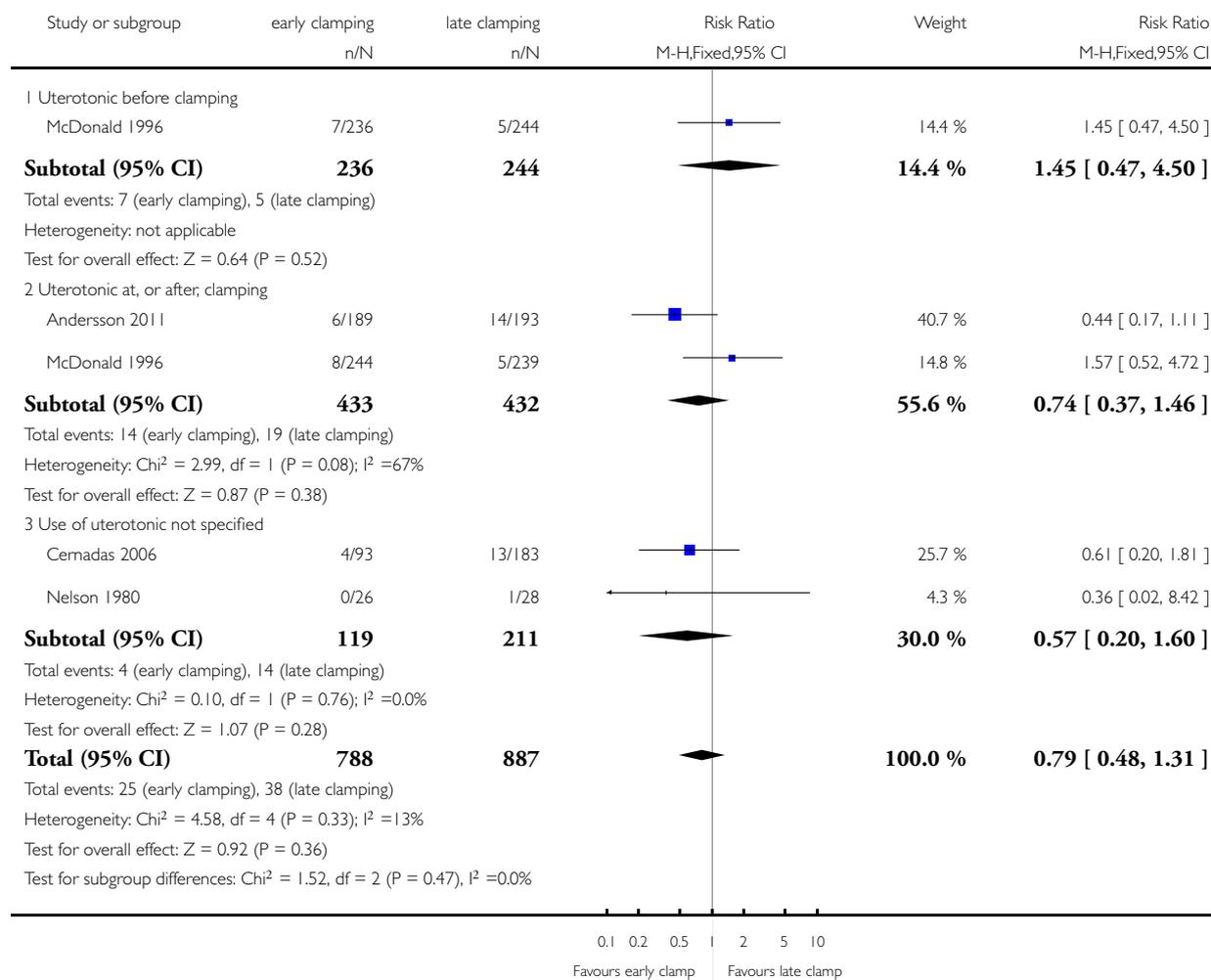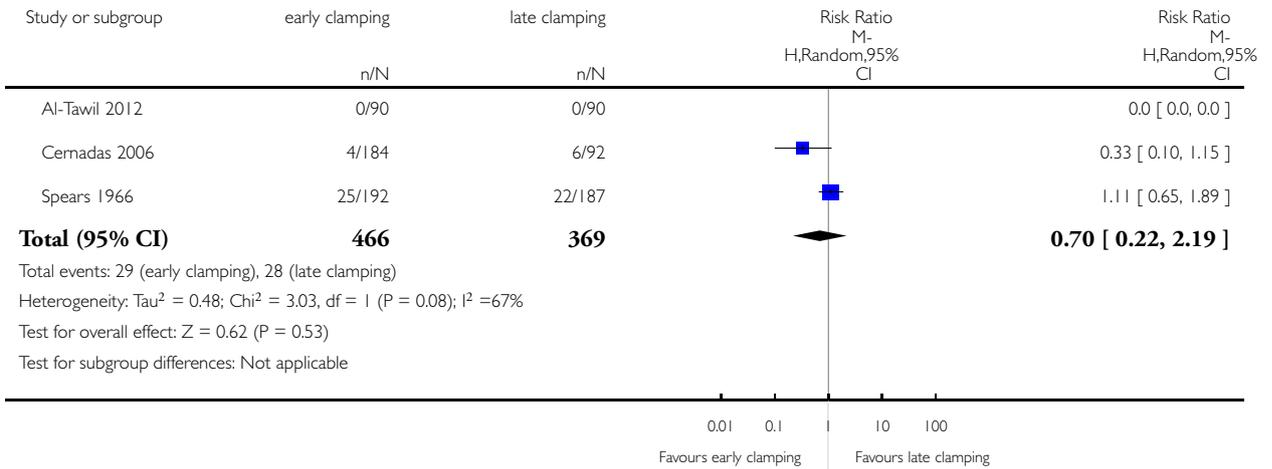Comparison: 1 Early versus late cord clamping

Outcome: 24 Low infant haematocrit (< 45% at 24-48 hours)

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					
Cernadas 2006	15/89	5/179		100.0 %	6.03 [2.27, 16.07]
Total (95% CI)	**89**	**179**		**100.0 %**	**6.03 [2.27, 16.07]**
Total events: 15 (early clamping), 5 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.60 (P = 0.00032)					
Test for subgroup differences: Not applicable					

0.1   0.2   0.5   1   2   5   10

Favours early clamp   Favours late clamp

Analysis 1.25.   Comparison 1 Early versus late cord clamping, Outcome 25 Infant iron deficiency at 3-6 months.

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

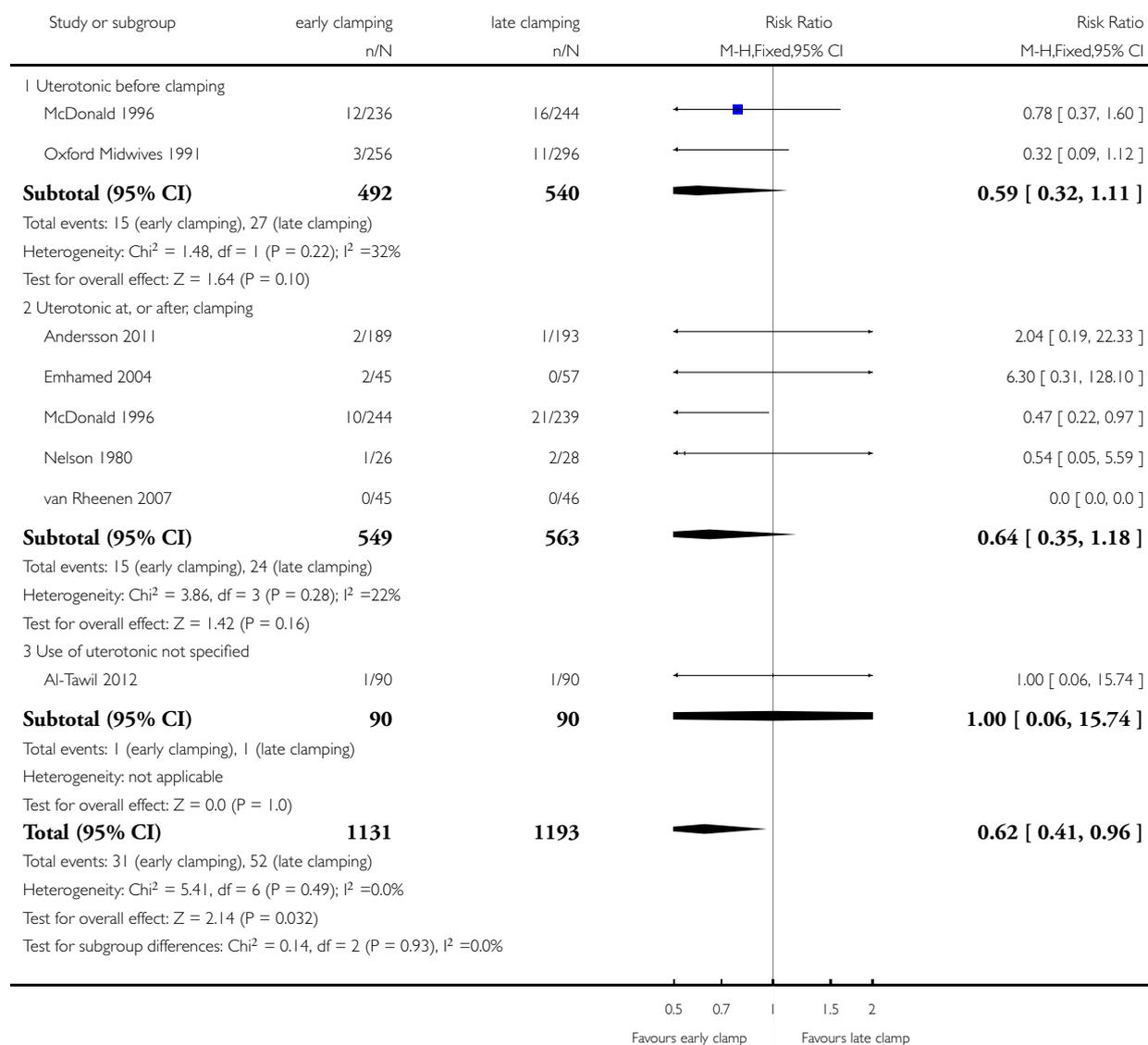Comparison: 1 Early versus late cord clamping

Outcome: 25 Infant iron deficiency at 3-6 months

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 at, or after, clamping					
Andersson 2011 (1)	10/175	1/172		12.0 %	9.83 [1.27, 75.95]
van Rheenen 2007 (2)	28/39	27/39		27.7 %	1.04 [0.78, 1.38]
Subtotal (95% CI)	**214**	**211**		**39.7 %**	**2.73 [0.19, 40.19]**
Total events: 38 (early clamping), 28 (late clamping)					
Heterogeneity: Tau² = 3.28; Chi² = 6.92, df = 1 (P = 0.01); I² =86%					
Test for overall effect: Z = 0.73 (P = 0.46)					
2 Use of uterotonic not specified					
Al-Tawil 2012 (3)	12/78	2/82		16.7 %	6.31 [1.46, 27.28]
Cernadas 2006 (4)	13/86	16/166		24.7 %	1.57 [0.79, 3.11]
Chaparro 2006 (5)	12/154	3/161		18.9 %	4.18 [1.20, 14.53]
Subtotal (95% CI)	**318**	**409**		**60.3 %**	**2.91 [1.18, 7.20]**
Total events: 37 (early clamping), 21 (late clamping)					
Heterogeneity: Tau² = 0.33; Chi² = 4.11, df = 2 (P = 0.13); I² =51%					
Test for overall effect: Z = 2.31 (P = 0.021)					
Total (95% CI)	**532**	**620**		**100.0 %**	**2.65 [1.04, 6.73]**
Total events: 75 (early clamping), 49 (late clamping)					
Heterogeneity: Tau² = 0.80; Chi² = 21.94, df = 4 (P = 0.00021); I² =82%					
Test for overall effect: Z = 2.05 (P = 0.041)					
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² =0.0%					

0.01   0.1   1   10   100

Favours early   Favours late

(1) 2 or more of low ferritin, MCV, transferrin saturation or high transferrin receptors at 4 mo

(2) ZPP > 80   mol/mol haem

(3) serum ferritin < 20   g/l

(4) ferritin < 9   g/l at 6 mo

(5) ferritin < 9   g/l at 4-6 mo

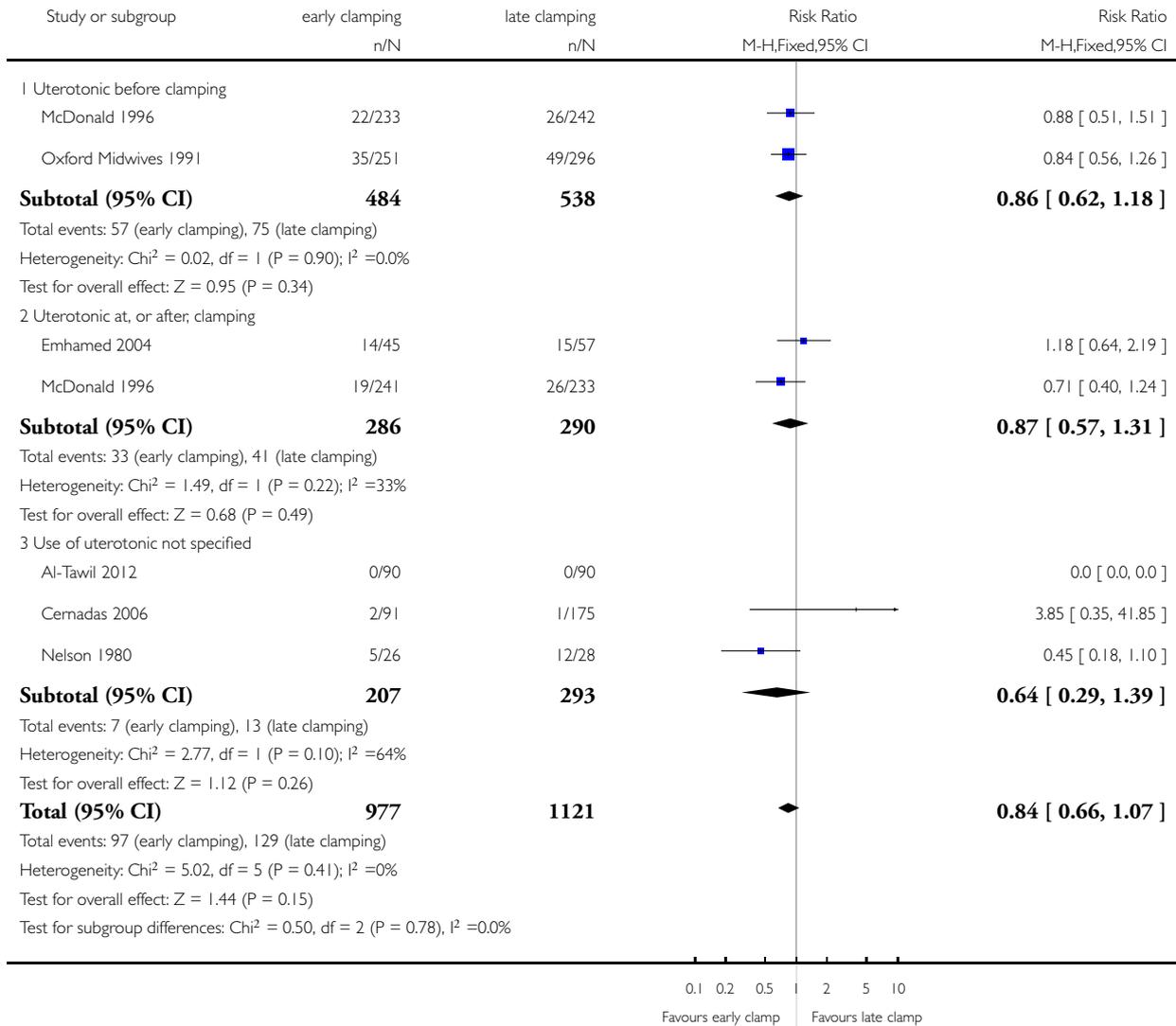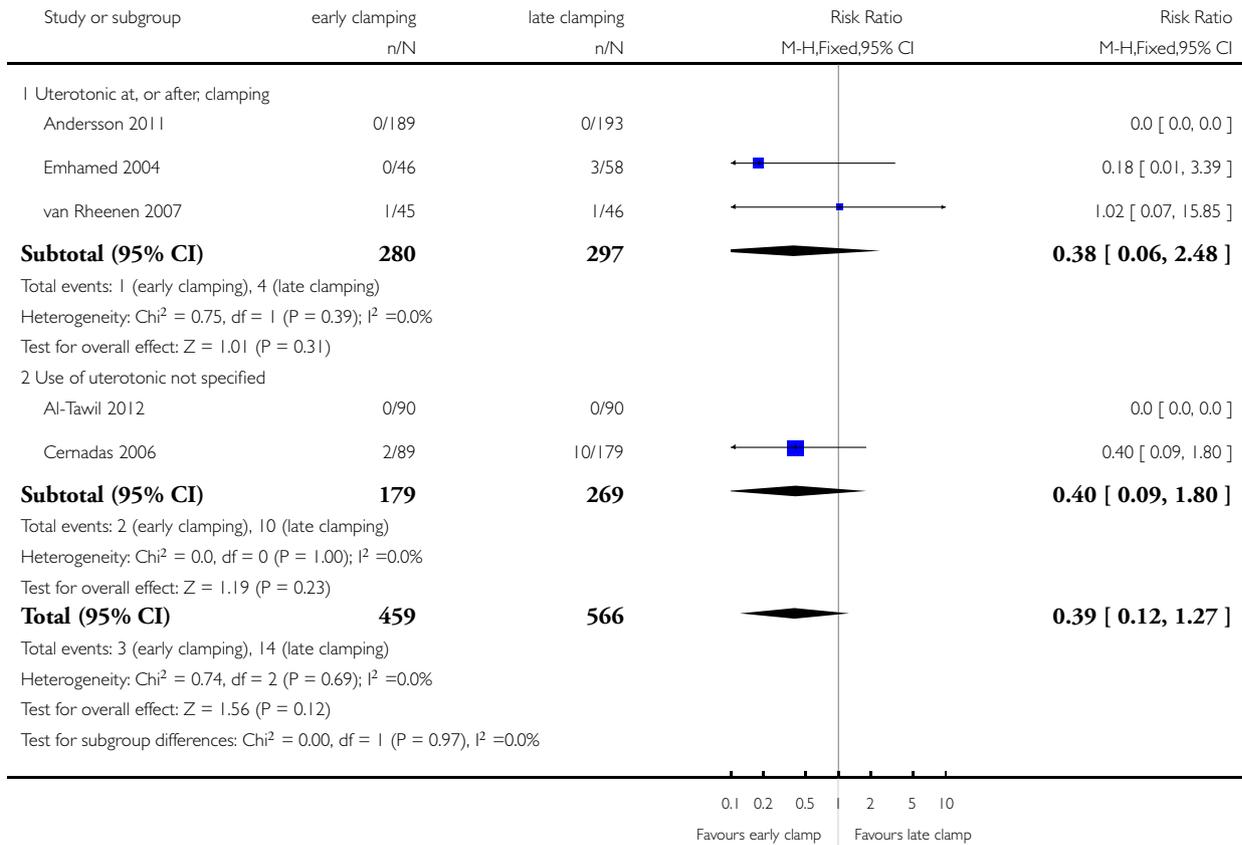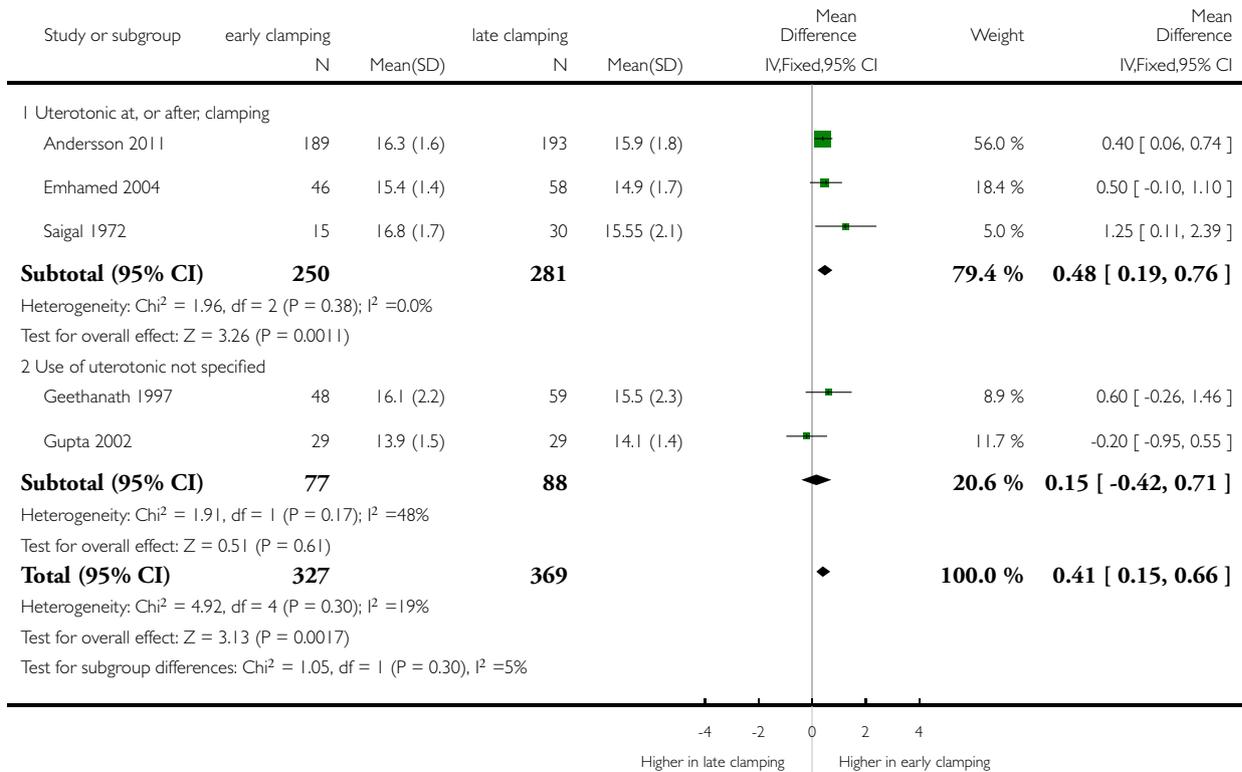### Analysis 1.26.   Comparison 1 Early versus late cord clamping, Outcome 26 Birthweight (g).

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

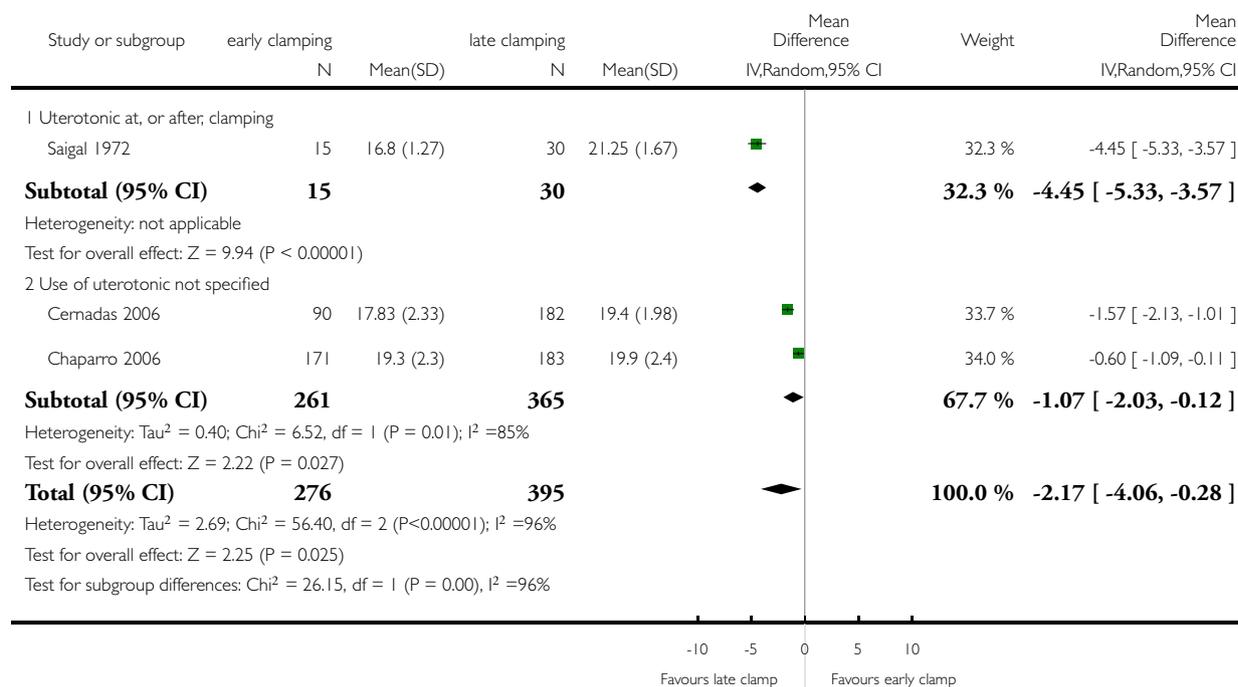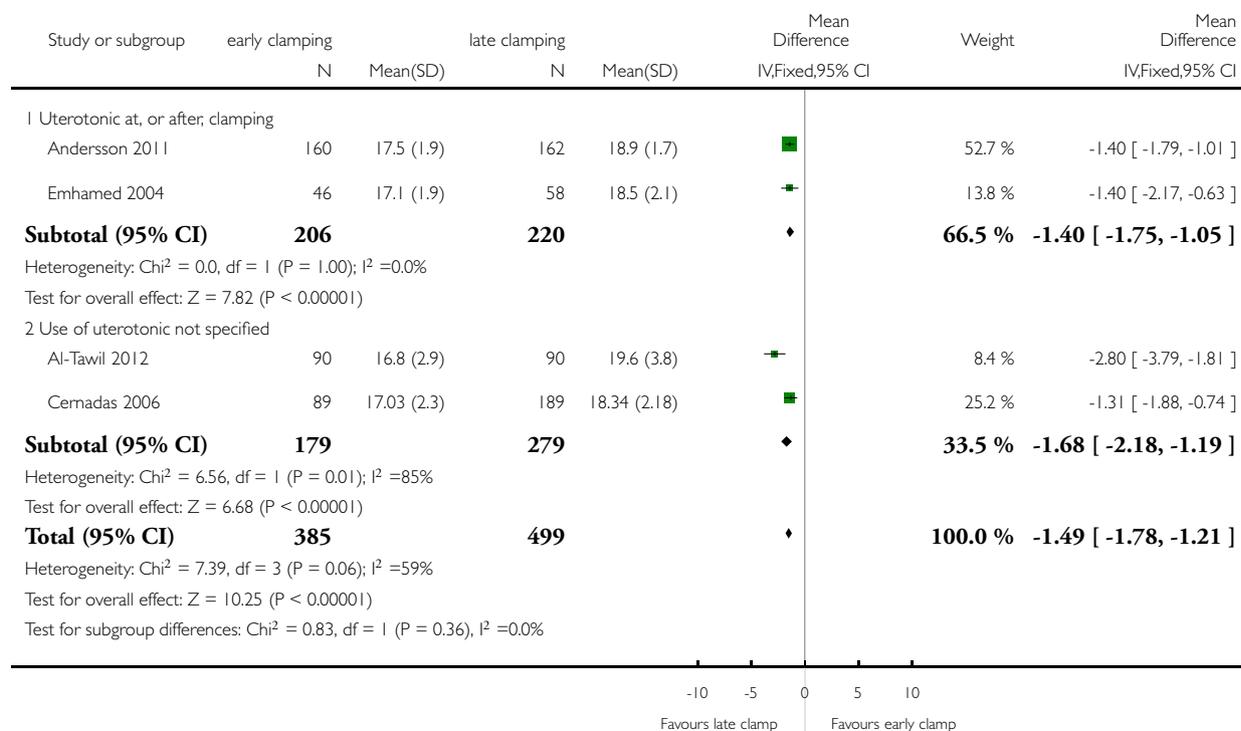Comparison: 1 Early versus late cord clamping

Outcome: 26 Birthweight (g)

Study or subgroup	early clamping		late clamping		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
Al-Tawil 2012	90	3110.6 (540.8)	90	3348 (390.8)		8.1 %	-237.40 [-375.25, -99.55]
Andersson 2011	189	3533 (486)	193	3629 (460)		10.9 %	-96.00 [-190.93, -1.07]
Cernadas 2006	93	3390 (395)	183	3422 (372)		10.8 %	-32.00 [-128.69, 64.69]
Chaparro 2006	171	3196 (362)	187	3318 (369)		12.3 %	-122.00 [-197.77, -46.23]
Emhamed 2004	46	3428 (424)	58	3390 (421)		6.8 %	38.00 [-125.56, 201.56]
Gupta 2002	29	2707 (417)	29	2744 (408)		4.9 %	-37.00 [-249.33, 175.33]
Jahazi 2008	30	3009 (573)	34	3272 (329)		4.3 %	-263.00 [-495.96, -30.04]
McDonald 1996	480	3374 (493)	483	3416 (495)		13.3 %	-42.00 [-104.40, 20.40]
Nelson 1980	26	3489 (453)	28	3437 (439)		4.1 %	52.00 [-186.24, 290.24]
Oxford Midwives 1991	256	3406 (441)	296	3432 (445)		12.4 %	-26.00 [-100.08, 48.08]
Philip 1973	28	3543 (534)	29	3850 (452)		3.7 %	-307.00 [-564.26, -49.74]
van Rheenen 2007	45	3119 (328)	46	3412 (326)		8.3 %	-293.00 [-427.38, -158.62]
Total (95% CI)	**1483**		**1656**			**100.0 %**	**-101.18 [-157.59, -44.76]**

Heterogeneity: Tau² = 5235.09; Chi² = 29.01, df = 11 (P = 0.002); I² =62%

Test for overall effect: Z = 3.51 (P = 0.00044)

Test for subgroup differences: Not applicable

-200   -100   0   100   200

Analysis 1.27. Comparison I Early versus late cord clamping, Outcome 27 Not breastfeeding on discharge (or later).

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

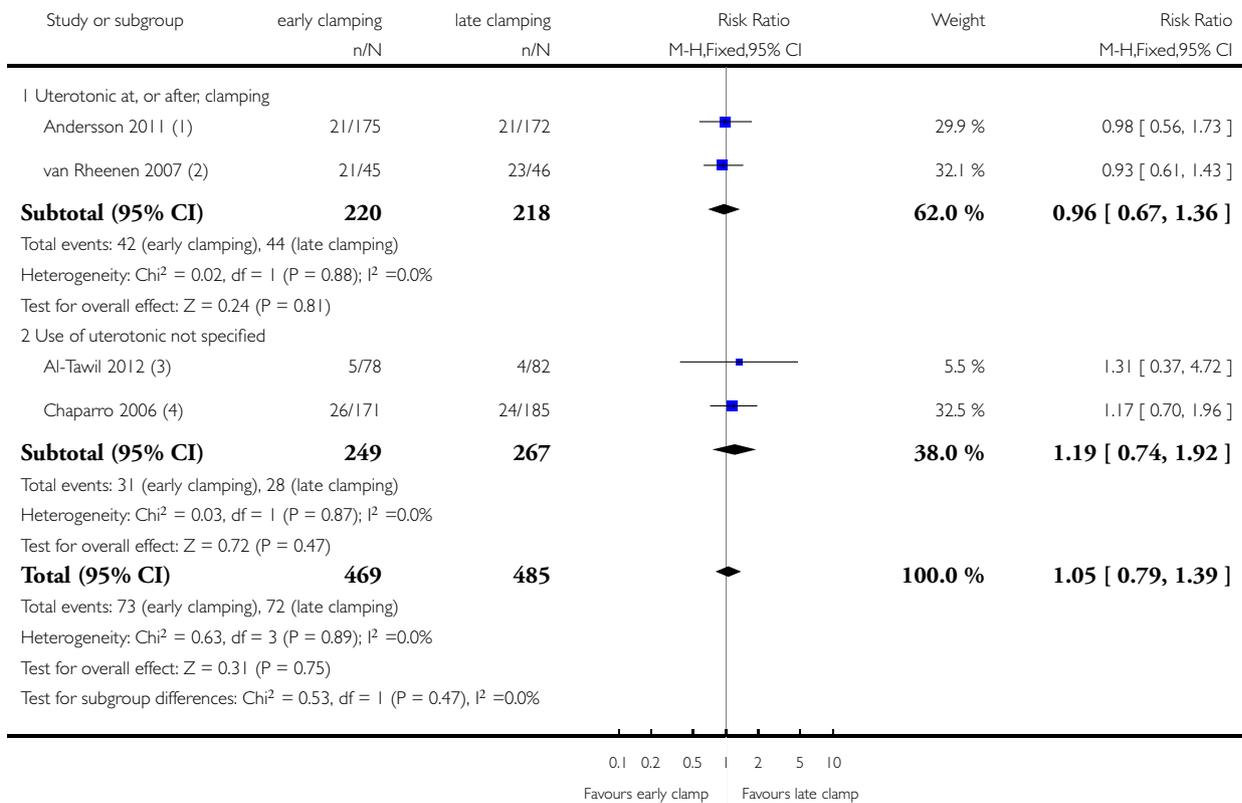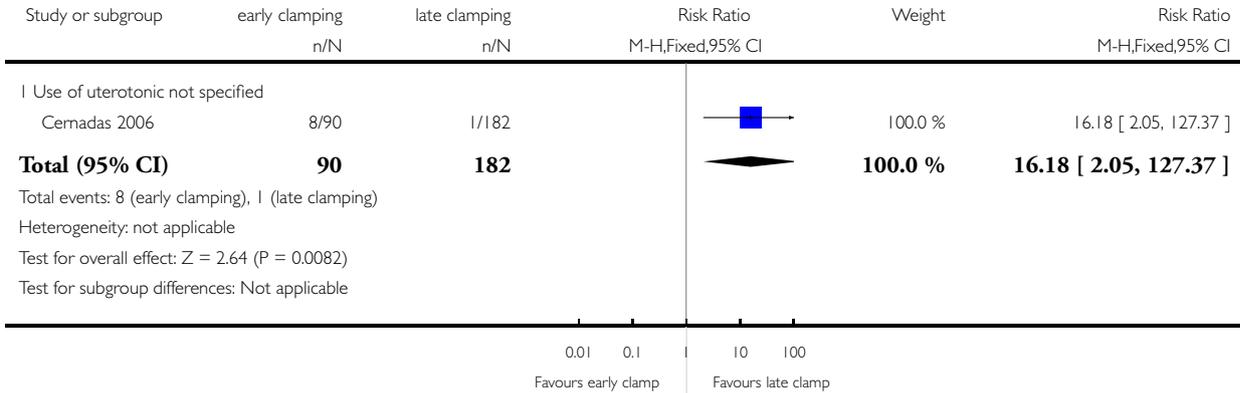Comparison: I Early versus late cord clamping

Outcome: 27 Not breastfeeding on discharge (or later)
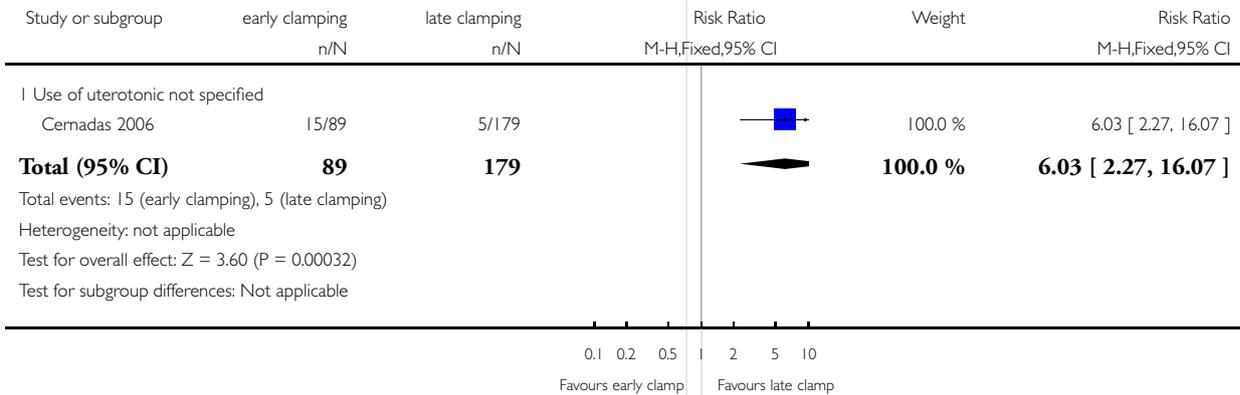
Study or subgroup	early clamping n/N	late clamping n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
I At discharge				
Jahazi 2008	0/30	0/34		0.0 [0.0, 0.0]
McDonald 1996	48/480	49/483		0.99 [0.68, 1.44]
Nelson 1980	2/26	1/28		2.15 [0.21, 22.37]
Oxford Midwives 1991	90/256	89/296		1.17 [0.92, 1.49]
Subtotal (95% CI)	**792**	**841**		**1.11 [0.90, 1.36]**
Total events: 140 (early clamping), 139 (late clamping)				
Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² =0.0%				
Test for overall effect: Z = 0.99 (P = 0.32)				
2 At I month				
Cernadas 2006	82/90	148/178		1.10 [1.00, 1.20]
Subtotal (95% CI)	**90**	**178**		**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)				
3 At 2 months				
van Rheenen 2007	0/41	2/43		0.21 [0.01, 4.24]
Subtotal (95% CI)	**41**	**43**		**0.21 [0.01, 4.24]**
Total events: 0 (early clamping), 2 (late clamping)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.02 (P = 0.31)				
4 At 3 months				
Geethanath 1997	4/40	3/46		1.53 [0.36, 6.44]
Gupta 2002	3/29	5/29		0.60 [0.16, 2.28]
Subtotal (95% CI)	**69**	**75**		**0.93 [0.36, 2.42]**
Total events: 7 (early clamping), 8 (late clamping)				
Heterogeneity: Chi² = 0.88, df = I (P = 0.35); I² =0.0%				
Test for overall effect: Z = 0.14 (P = 0.89)				
5 At 4 months				
Chaparro 2006	87/147	98/166		1.00 [0.83, 1.21]
van Rheenen 2007	15/39	30/39		0.50 [0.32, 0.77]

0.1 0.2 0.5 I 2 5 10

Favours late clamp   Favours early clamp

(*Continued* . . .)

Study or subgroup	early clamping	late clamping	Risk Ratio	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
Subtotal (95% CI)	**186**	**205**		**0.88 [0.74, 1.04]**

Total events: 102 (early clamping), 128 (late clamping)

Heterogeneity: Chi² = 8.48, df = 1 (P = 0.004); I² =88%

Test for overall effect: Z = 1.50 (P = 0.13)

6 At 6 months

Chaparro 2006	116/171	127/187		1.00 [0.87, 1.15]
van Rheenen 2007	36/37	35/35		0.97 [0.90, 1.05]
Subtotal (95% CI)	**208**	**222**		**0.99 [0.89, 1.11]**

Total events: 152 (early clamping), 162 (late clamping)

Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² =0.0%

Test for overall effect: Z = 0.12 (P = 0.90)

Test for subgroup differences: Chi² = 7.14, df = 5 (P = 0.21), I² =30%

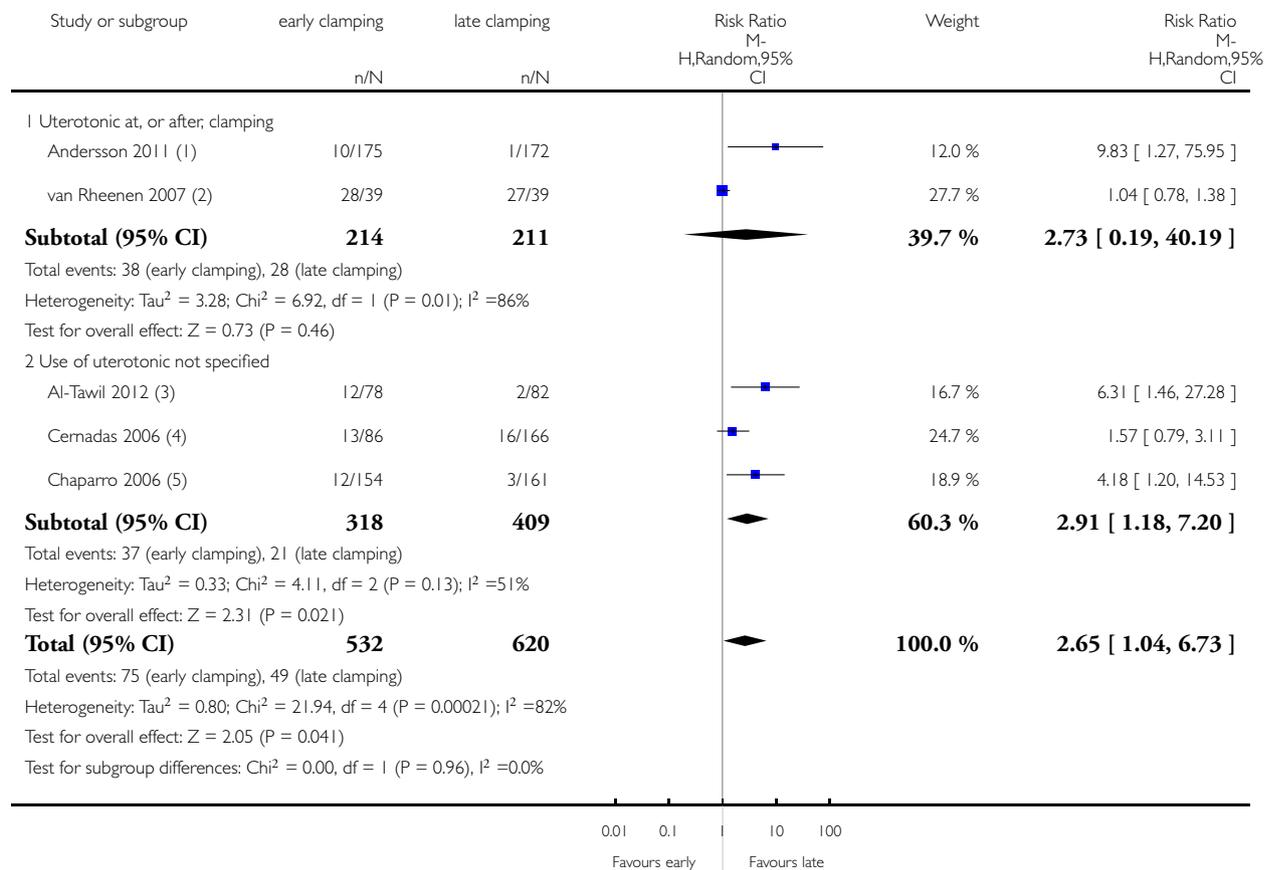0.1 0.2 0.5 1 2 5 10

Favours late clamp   Favours early clamp

Analysis 1.28.   Comparison 1 Early versus late cord clamping, Outcome 28 Neurodevelopment 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: 28 Neurodevelopment at 4 months

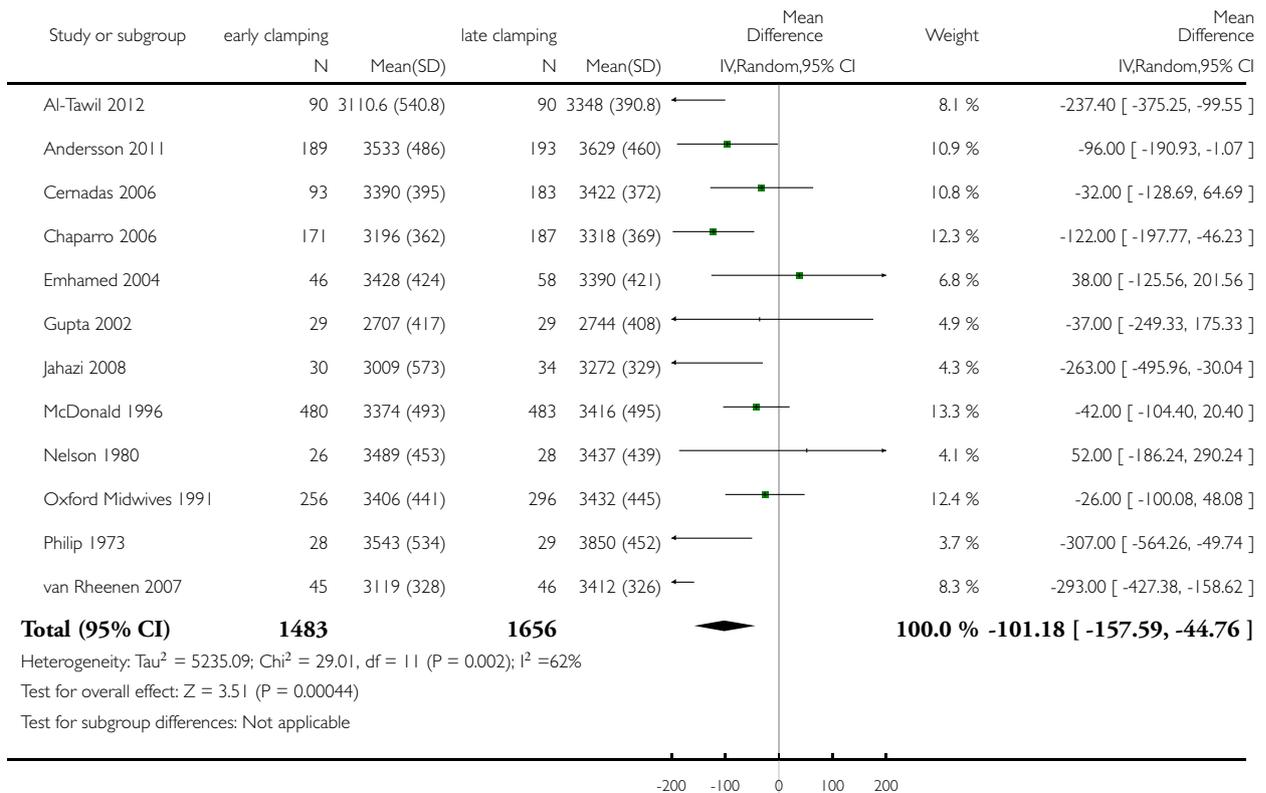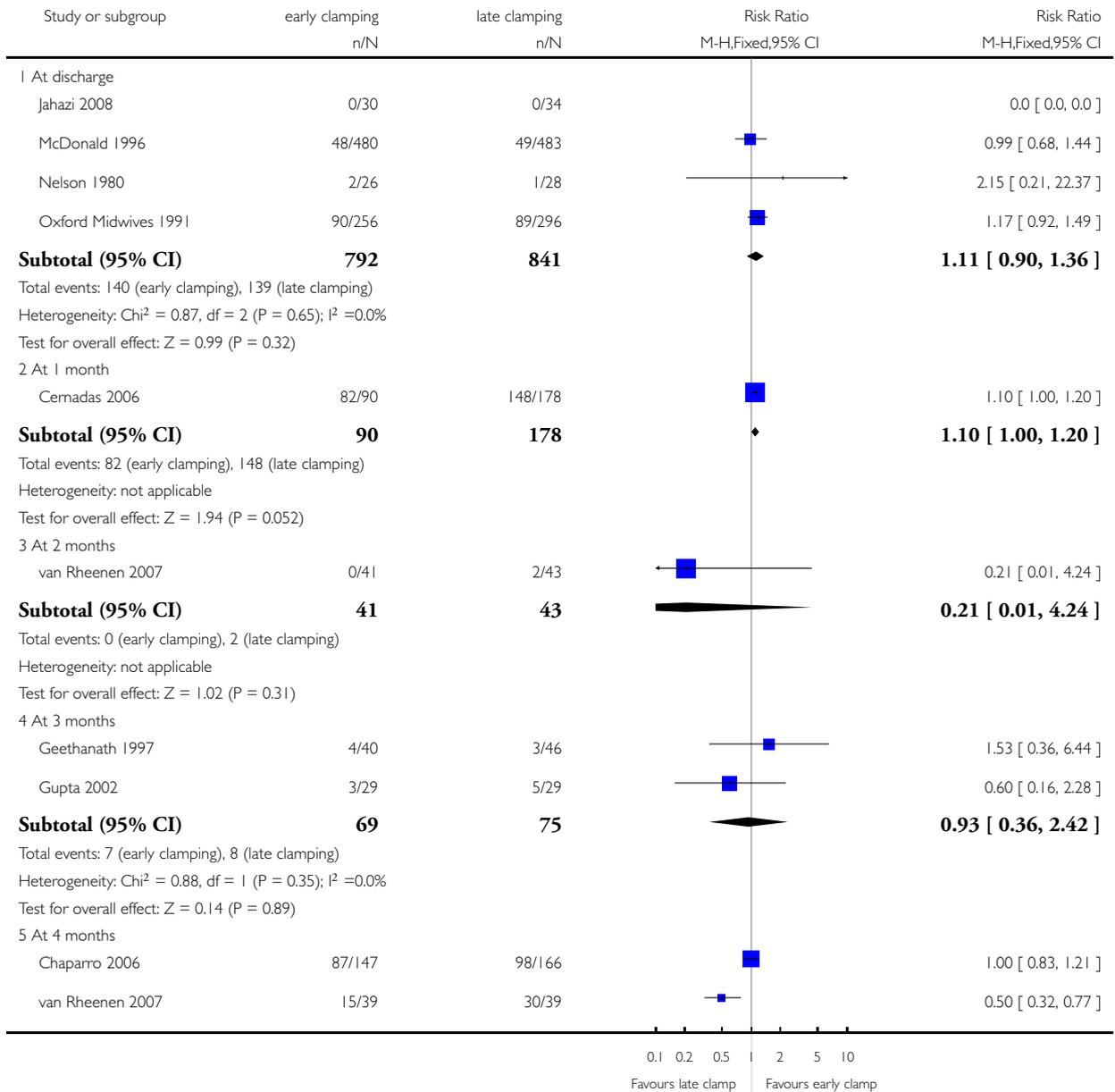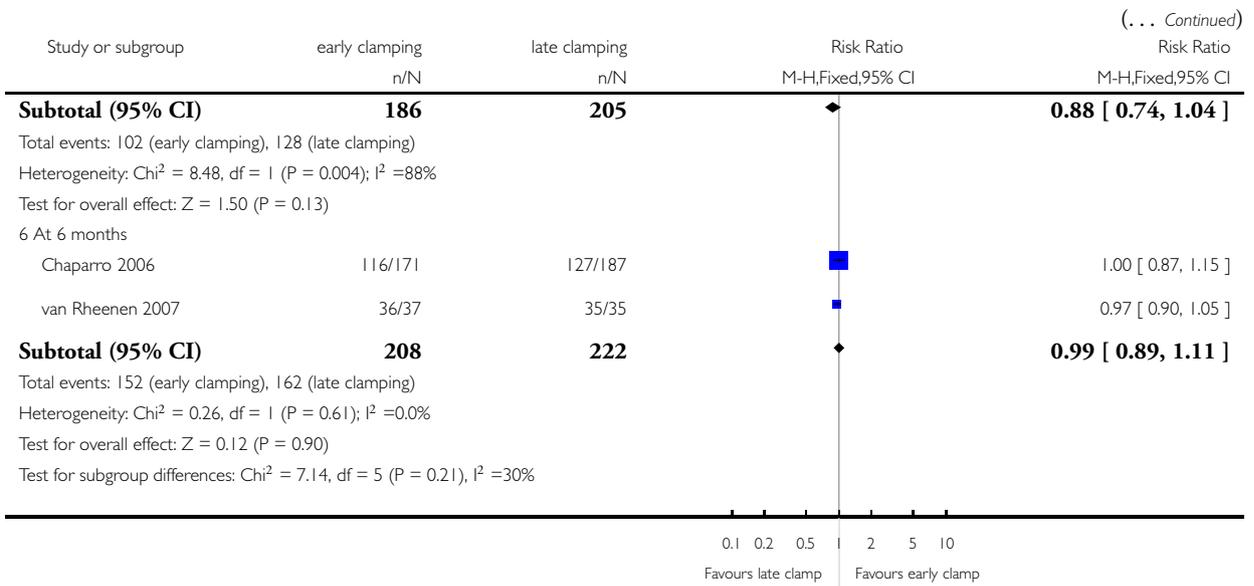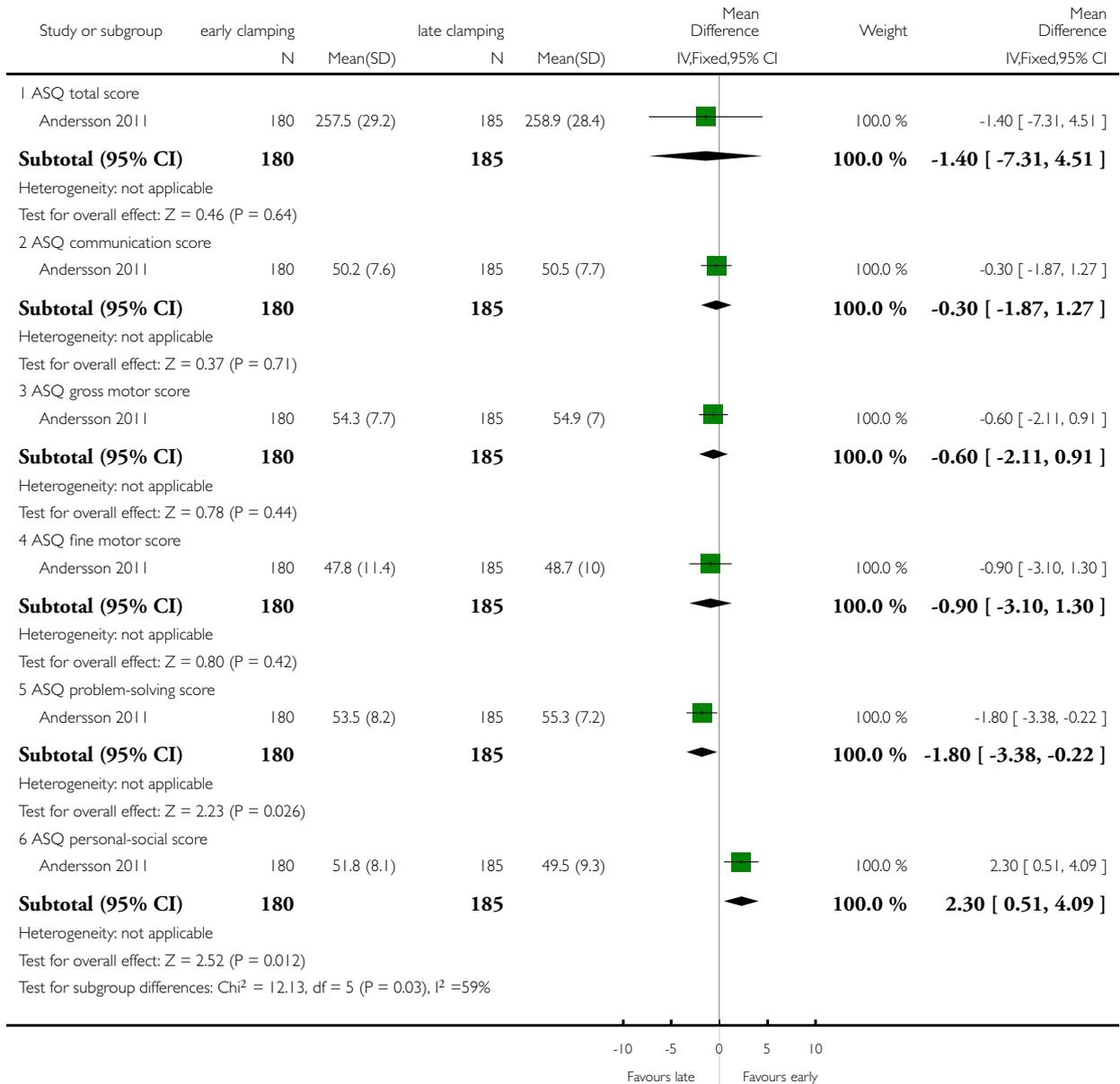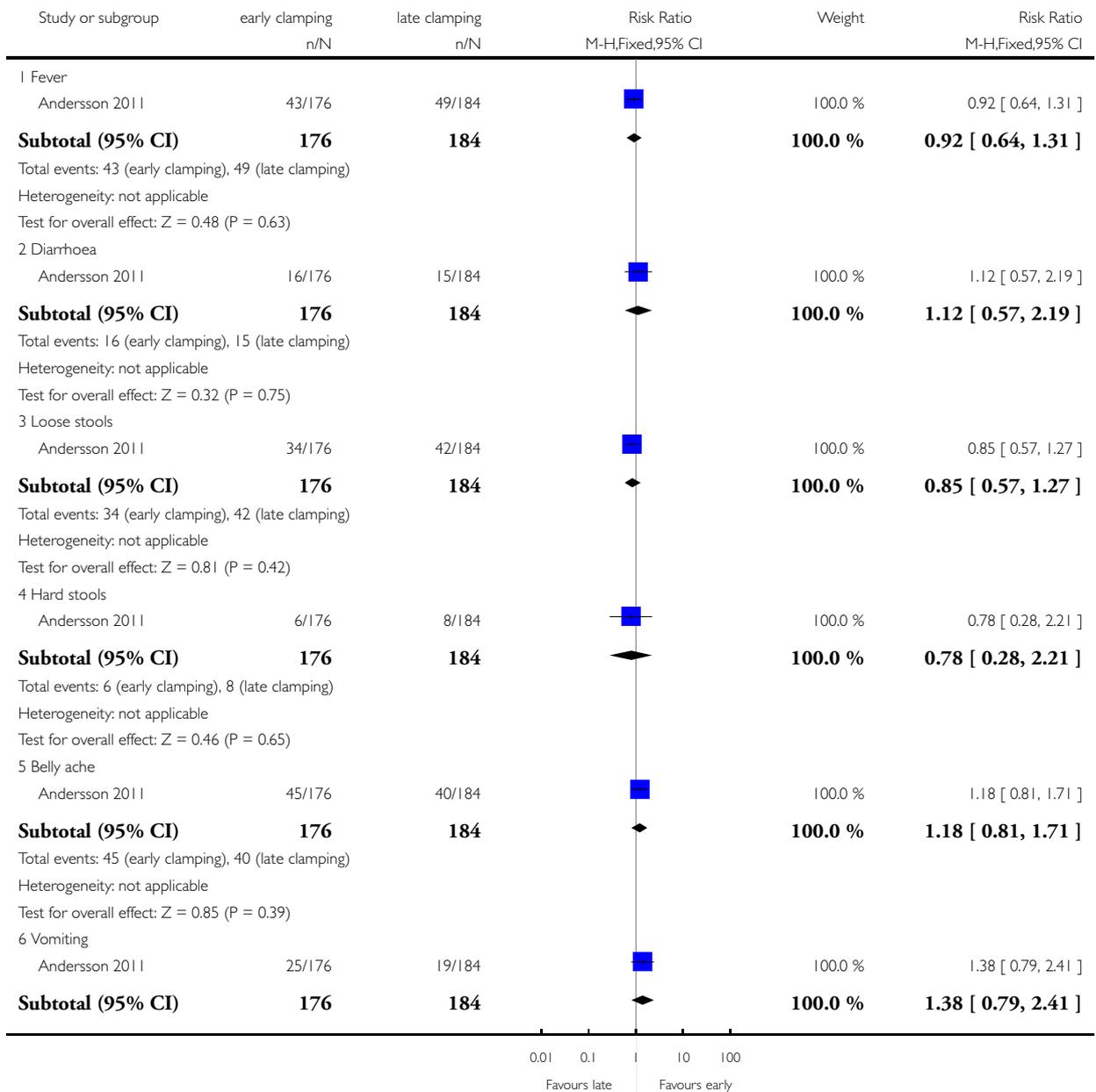| Study or subgroup	early clamping		late clamping		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
1 ASQ total score							
Andersson 2011	180	257.5 (29.2)	185	258.9 (28.4)		100.0 %	-1.40 [-7.31, 4.51]
Subtotal (95% CI)	**180**		**185**			**100.0 %**	**-1.40 [-7.31, 4.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.46 (P = 0.64)							
2 ASQ communication score							
Andersson 2011	180	50.2 (7.6)	185	50.5 (7.7)		100.0 %	-0.30 [-1.87, 1.27]
Subtotal (95% CI)	**180**		**185**			**100.0 %**	**-0.30 [-1.87, 1.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
3 ASQ gross motor score							
Andersson 2011	180	54.3 (7.7)	185	54.9 (7)		100.0 %	-0.60 [-2.11, 0.91]
Subtotal (95% CI)	**180**		**185**			**100.0 %**	**-0.60 [-2.11, 0.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.78 (P = 0.44)							
4 ASQ fine motor score							
Andersson 2011	180	47.8 (11.4)	185	48.7 (10)		100.0 %	-0.90 [-3.10, 1.30]
Subtotal (95% CI)	**180**		**185**			**100.0 %**	**-0.90 [-3.10, 1.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.80 (P = 0.42)							
5 ASQ problem-solving score							
Andersson 2011	180	53.5 (8.2)	185	55.3 (7.2)		100.0 %	-1.80 [-3.38, -0.22]
Subtotal (95% CI)	**180**		**185**			**100.0 %**	**-1.80 [-3.38, -0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.23 (P = 0.026)							
6 ASQ personal-social score							
Andersson 2011	180	51.8 (8.1)	185	49.5 (9.3)		100.0 %	2.30 [0.51, 4.09]
Subtotal (95% CI)	**180**		**185**			**100.0 %**	**2.30 [0.51, 4.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.52 (P = 0.012)							

Test for subgroup differences: Chi^2 = 12.13, df = 5 (P = 0.03), I^2 =59%

```
         -10    -5     0     5     10
            Favours late    Favours early
```

Analysis 1.29. Comparison I Early versus late cord clamping, Outcome 29 Symptoms of infection during first 4 months.
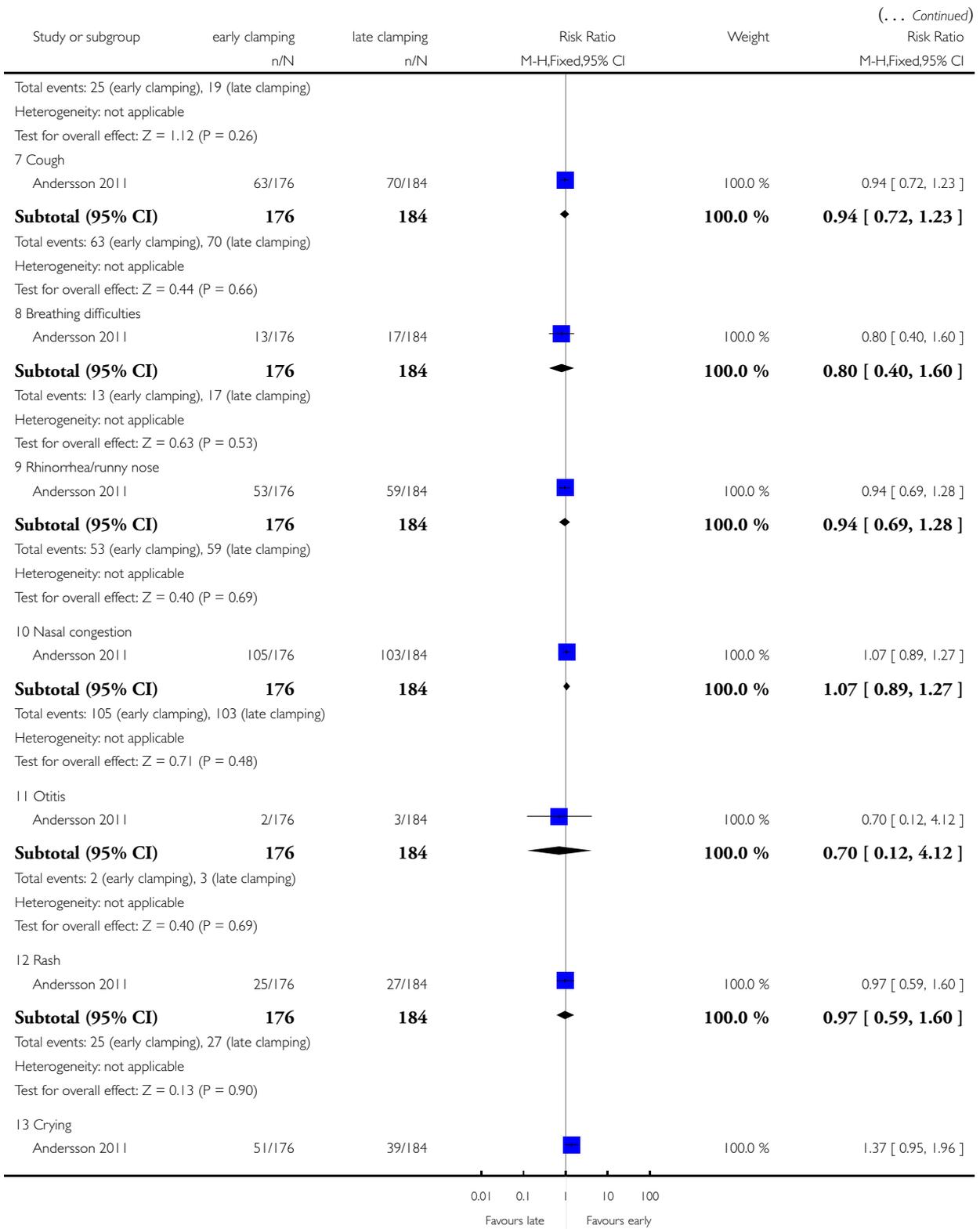
Review: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

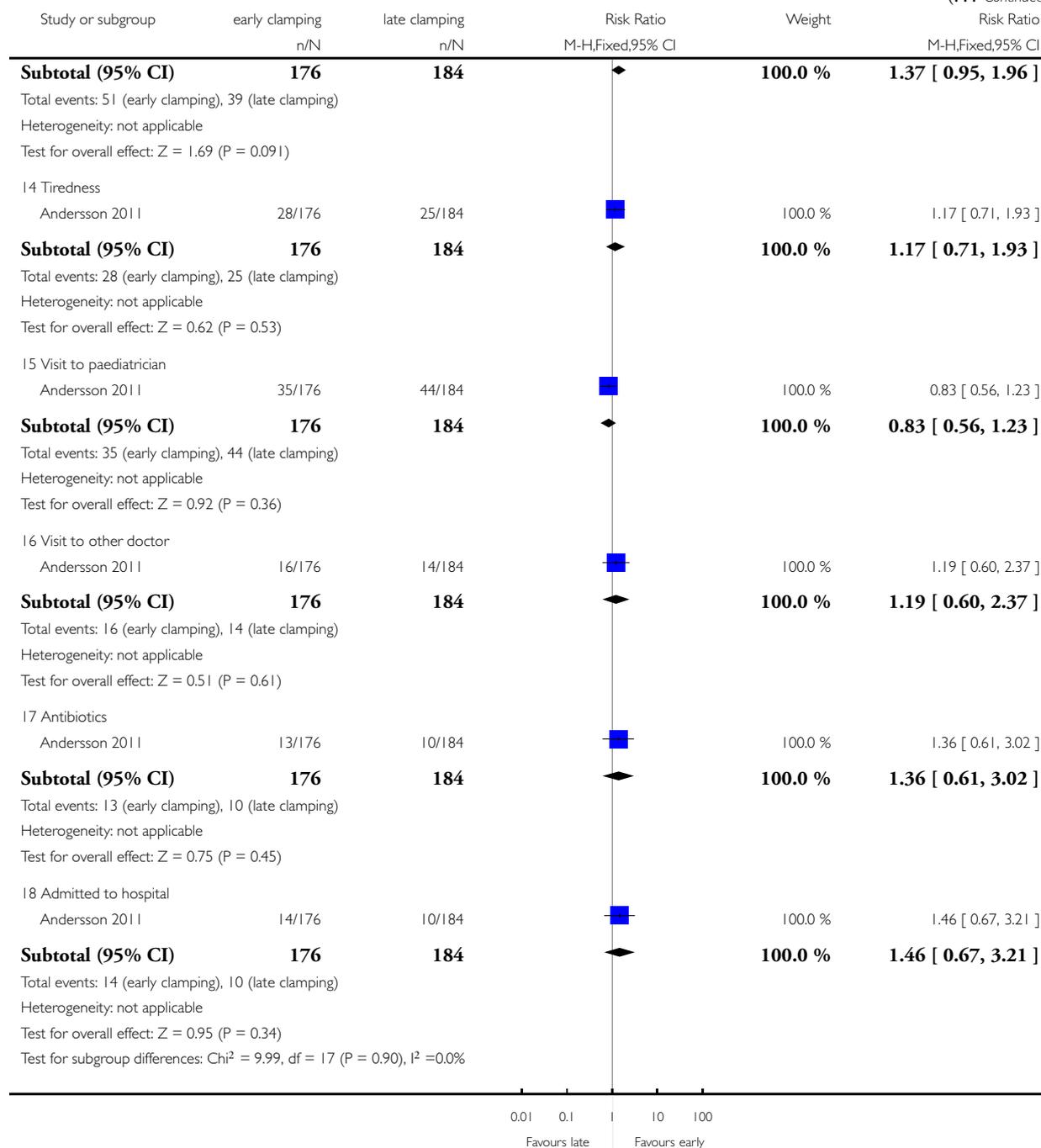Comparison: I Early versus late cord clamping

Outcome: 29 Symptoms of infection during first 4 months

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
I Fever					
Andersson 2011	43/176	49/184		100.0 %	0.92 [0.64, 1.31]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**0.92 [0.64, 1.31]**
Total events: 43 (early clamping), 49 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
2 Diarrhoea					
Andersson 2011	16/176	15/184		100.0 %	1.12 [0.57, 2.19]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.12 [0.57, 2.19]**
Total events: 16 (early clamping), 15 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
3 Loose stools					
Andersson 2011	34/176	42/184		100.0 %	0.85 [0.57, 1.27]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**0.85 [0.57, 1.27]**
Total events: 34 (early clamping), 42 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.81 (P = 0.42)					
4 Hard stools					
Andersson 2011	6/176	8/184		100.0 %	0.78 [0.28, 2.21]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**0.78 [0.28, 2.21]**
Total events: 6 (early clamping), 8 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
5 Belly ache					
Andersson 2011	45/176	40/184		100.0 %	1.18 [0.81, 1.71]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.18 [0.81, 1.71]**
Total events: 45 (early clamping), 40 (late clamping)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
6 Vomiting					
Andersson 2011	25/176	19/184		100.0 %	1.38 [0.79, 2.41]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.38 [0.79, 2.41]**

```
        0.01   0.1    I    10   100
          Favours late    Favours early
```

(*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: 25 (early clamping), 19 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 1.12 (P = 0.26)

7 Cough

| Andersson 2011 | 63/176 | 70/184 | | 100.0 % | 0.94 [0.72, 1.23] |
| **Subtotal (95% CI)** | **176** | **184** | | **100.0 %** | **0.94 [0.72, 1.23]** |

Total events: 63 (early clamping), 70 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

8 Breathing difficulties

| Andersson 2011 | 13/176 | 17/184 | | 100.0 % | 0.80 [0.40, 1.60] |
| **Subtotal (95% CI)** | **176** | **184** | | **100.0 %** | **0.80 [0.40, 1.60]** |

Total events: 13 (early clamping), 17 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

9 Rhinorrhea/runny nose

| Andersson 2011 | 53/176 | 59/184 | | 100.0 % | 0.94 [0.69, 1.28] |
| **Subtotal (95% CI)** | **176** | **184** | | **100.0 %** | **0.94 [0.69, 1.28]** |

Total events: 53 (early clamping), 59 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

10 Nasal congestion

| Andersson 2011 | 105/176 | 103/184 | | 100.0 % | 1.07 [0.89, 1.27] |
| **Subtotal (95% CI)** | **176** | **184** | | **100.0 %** | **1.07 [0.89, 1.27]** |

Total events: 105 (early clamping), 103 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.71 (P = 0.48)

11 Otitis

| Andersson 2011 | 2/176 | 3/184 | | 100.0 % | 0.70 [0.12, 4.12] |
| **Subtotal (95% CI)** | **176** | **184** | | **100.0 %** | **0.70 [0.12, 4.12]** |

Total events: 2 (early clamping), 3 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

12 Rash

| Andersson 2011 | 25/176 | 27/184 | | 100.0 % | 0.97 [0.59, 1.60] |
| **Subtotal (95% CI)** | **176** | **184** | | **100.0 %** | **0.97 [0.59, 1.60]** |

Total events: 25 (early clamping), 27 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.13 (P = 0.90)

13 Crying

| Andersson 2011 | 51/176 | 39/184 | | 100.0 % | 1.37 [0.95, 1.96] |

0.01　0.1　1　10　100

Favours late　　Favours early

(*Continued* . . .)

Study or subgroup	early clamping	late clamping	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.37 [0.95, 1.96]**

Total events: 51 (early clamping), 39 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 1.69 (P = 0.091)

14 Tiredness					
Andersson 2011	28/176	25/184		100.0 %	1.17 [0.71, 1.93]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.17 [0.71, 1.93]**

Total events: 28 (early clamping), 25 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.53)

15 Visit to paediatrician					
Andersson 2011	35/176	44/184		100.0 %	0.83 [0.56, 1.23]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**0.83 [0.56, 1.23]**

Total events: 35 (early clamping), 44 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

16 Visit to other doctor					
Andersson 2011	16/176	14/184		100.0 %	1.19 [0.60, 2.37]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.19 [0.60, 2.37]**

Total events: 16 (early clamping), 14 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)

17 Antibiotics					
Andersson 2011	13/176	10/184		100.0 %	1.36 [0.61, 3.02]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.36 [0.61, 3.02]**

Total events: 13 (early clamping), 10 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.75 (P = 0.45)

18 Admitted to hospital					
Andersson 2011	14/176	10/184		100.0 %	1.46 [0.67, 3.21]
Subtotal (95% CI)	**176**	**184**		**100.0 %**	**1.46 [0.67, 3.21]**

Total events: 14 (early clamping), 10 (late clamping)

Heterogeneity: not applicable

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Chi^2 = 9.99, df = 17 (P = 0.90), I^2 =0.0%

```
        0.01   0.1    1    10   100
            Favours late   Favours early
```

ADDITIONAL TABLES

Table 1. Infant iron deficiency and ferritin at 3-6 months

STUDY	Iron deficiency	Ferritin
Al-Tawil 2012	Data collected at 3-5 months Mean cell volume < 73 fL Early clamping group 4/78 Late clamping group 2/82 P = 0.43 Transferrin saturation levels below 10% Early clamping group 11/78 Late clamping group 8/82 P = 0.62	At 3-5 months. Defined as serum ferritin < 20 µg/L Early clamping group 12/78 Late clamping group 2/82 P <0.001 Also reported mean (SD) ferritin Early clamping group (n = 78) mean 228 (SD 147) Late clamping group (n = 82) mean 430 (SD 132) P <0.001
Andersson 2011	Defined as 2 or more indicators outside reference ranges (low ferritin, low mean cell volume, low transferrin saturation, high transferrin receptors) At 4 months Early clamping group 10/175 Late clamping group 1/172 P = 0.01 Also reported mean iron (µmol/L) At 4 months Early clamping group (n = 175) 9.3 (SD 2.9) Late clamping group (n = 172) 10.2 (SD 3.0) P = 0.007	Geometric mean and range At 4 months Early (n = 175) 81 (6-670) Late (n = 168) 117 (20-880) P < 0.001
Cernadas 2006	Iron deficiency anaemia at 6 months (defined as Hb < 10.5 g/dL and ferritin < 9 µg/L) 15 second group 6/86 1-minute group 3/84 3-minute group 2/84	Ferritin < 9 µg/L at 6 months 15 second 13/86 1 minute 10/83 3 minutes 6/83 Ferritin geometric mean at 6 months 15 seconds (n = 86) 20.9 (SD 26.3) 1 minute (n = 83) 25.5 (SD 26.0) 3 minute (n = 83) 33.2 SD 36.8)
Chaparro 2006	Iron deficiency at 4-6 months (defined as ferritin < 9 µg/L) Early clamping 12/154 Late clamping 3/ 161 P = 0.02	Ferritin µg/L at 4-6 months. Mean and SD Early clamping (n = 154) 34.9 (32.2) Late clamping (n = 161) 46.7 (37.7) P = 0.001
Geethanath 1997	Not reported	Ferritin µg/mL geometric mean at 3 months (dispersion statistic not clear) Early clamping group (n = 48) 55.7 (3.7) Late clamping group (n = 59) 73.6 (3.1) Difference not significant.

Table 1. Infant iron deficiency and ferritin at 3-6 months *(Continued)*

Gupta 2002	Not reported	Ferritin µg/L geometric mean, median and range at 3 months. Early clamping (n = 29) geometric mean 73.04, median and range 80 (15 to 180) Late clamping (n = 29) geometric mean 118.39, median and range 105 (30 to 500) P = 0.02
van Rheenen 2007	Iron deficiency anaemia (defined as zinc-protoporphyrin (ZPP) >80 µmol/mol haem and Hb < 10.3) At 4 months Immediate clamping 14/39 Delayed clamping 6/39 NS At 6 months Immediate clamping 17/37 Delayed clamping 17/35 NS Iron deficiency (ZPP > 80 µmol/mol haem) At 4 months Delayed clamping 27/39 Immediate clamping 28/39 NS At 6 months Delayed clamping 27/35 Immediate clamping 28/37 NS	

fL: femtolitre
Hb: haemoglobin
SD: standard deviation

FEEDBACK

Erickson-Owens and Mercer, 21 April 2008

Summary

First we would like to thank Susan J McDonald 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 (McDonald) in Australia. When that one trial is removed from data (offered in Analysis 1.14) 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 McDonald 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 McDonald study or simply more infants receiving phototherapy? What were peak bilirubin levels? The use of phototherapy does not necessarily 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 McDonald 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.

(Feedback received from Judith S Mercer, PhD, CNM, FACNM and Debra A Erickson-Owens, PhD(c), CNM)

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 an increase in jaundice. The authors recognise that interpretation of the clinical relevance of this for infants may vary. 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, while it is possible that lack of blinding may have had an influence, we think that it is unlikely since women were not explicitly informed of their allocation at the time of birth. In the period that most of these trials were conducted, in many units, the midwives at the birth would not be the midwives providing postnatal care. In the McDonald study, midwives and other clinicians providing postnatal care were not aware of allocations to groups, or even that a particular infant had participated in the study. Furthermore, the decision to place a baby under phototherapy has many objective elements and criteria. We did include a brief mention of blinding of outcome assessment in the text of the review, but have added 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 four 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

All infants from the Cernadas study (including the 90 infants clamped at three minutes) have been included in the clinical jaundice outcome. We feel that we have given appropriate weight to the favourable results for six-month anaemia and iron levels, pointing this out in the Results, Discussion, Authors' conclusions and Abstract.

Potential risks 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 Authors' 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 when we update the review.

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. (Feedback from Eileen Nicole Simon, PhD, RN)

Reply

Many of the comments in Simon's feedback are outside the scope of this Cochrane review. However, responses to some specific issues follow:

Delayed clamping regarded as novel

Cochrane reviews are often done when there is variation in practice, as is the case here. For example, in the Background of the review we cite such documented variation which indicates widespread use of both delayed and immediate cord clamping, and we make no judgement about the novelty or otherwise of either technique.

Infant loses 30% of blood volume, does not gain 30%

Our phrasing in the background is about transfer of fetal blood. In order to clarify further, we have added "compared with immediate cord clamping" after "This placental transfusion can provide the infant with an additional 30% more blood volume and up to 60% more red blood cells".

Increased bilirubin levels are insufficient justification for promoting continued use of the obstetric clamp

Firstly our review does not promote the continued use of clamping; in fact, it is more the reverse. However, we do note that increased levels of jaundice may be associated with delayed cord clamping, which is the responsible course of action.

Evidence from animal studies should suffice

This is not the place for a detailed discussion of the pros and cons of using data from animal studies, except to say that most clinicians and researchers would be very cautious about extrapolating to humans, especially human infants.

Saigal 1972**influenced adopting immediate cord clamping as a standard protocol**

This may well be so, but the Saigal study did not contribute data to the outcome of jaundice in this review (as they reported only the biochemical outcome of bilirubin levels and not jaundice). The fundamental purpose of systematic reviews is to show the consolidated evidence of benefits and harms of particular actions, not to rely on single studies or opinion.

Contributors

Feedback from Eileen Nicole Simon, PhD, RN
Reply from Susan J McDonald and Philippa Middleton

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 versus 2/33 ICC babies exposed to oxytocin required phototherapy for jaundice, and 6/222 DCC versus 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 versus 256 ICC.
- A large number of protocol deviations in the DCC arm (32 versus 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

The actual influence of infants exposed to synthetic oxytocins in the Oxford Midwives study is minimal; a re-analysis omitting these infants changes the overall risk ratio (of the pooled studies) from 0.59 95% CI to 0.38 to 0.92; to 0.59 95% CI 0.37 to 0.95.

While it is possible that lack of blinding may have had an influence, we think that it is unlikely, since women were not explicitly informed of their allocation at the time of the birth. In the period that most of these trials were conducted, midwives present at the birth would not be the midwives providing postnatal care. In the McDonald Study, postnatal ward staff were not aware of allocations to groups, or even that a particular infant had participated in the study. Furthermore, the decision to place a baby under phototherapy has many objective elements and criteria.

We agree that the study authors did not explain the reasonably large discrepancy in numbers randomised to delayed and immediate cord clamping (296 versus 256) but do not have the information to assess any impact of this on the trial's reported results.

Some protocol deviations are to be expected with the nature of these interventions; particularly for delayed cord clamping where immediate cord clamping may have to be carried out in some cases. The study authors analysed these deviations correctly (in the groups to which the mothers were originally randomised). However, an additional 'as treated' analysis would have been informative.

Small numbers of events usually are associated with less precision, so it is interesting to see that the pooled result reached statistical significance with these small numbers.

The McDonald trial is a thesis, available from the Cochrane Pregnancy and Childbirth Group or from Professor McDonald. A journal manuscript is being prepared.

Contributors

Feedback from Dr Sarah J Buckley
Reply from Susan J McDonald and Philippa Middleton

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

Thank you for pointing out this omission. Approximately half of the studies did report birthweight. We will add birthweight to the next revision of the review. A preliminary assessment of the available data reveals no statistically significant difference between the late and early cord clamping arms

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; particularly when there is a suite of trials and a way to answer the question. I do know of some who are suspicious as to why the weight data are as yet unpublished.

As birthweight will undoubtedly have been recorded in the trials, lets report it here!

(Feedback from Sam Oddie)

Reply

The question of the amount of transfusion cannot be answered in a satisfactory amount of detail through the randomised trials we have included in this review. This would require another prospective study of comparing birthweights with timing of clamping.

Contributors

Feedback from Sam Oddie
Reply from Susan J McDonald and Philippa Middleton

W H A T ' S N E W

Last assessed as up-to-date: 14 March 2013.

Date	Event	Description
14 March 2013	New citation required and conclusions have changed	There is increased evidence that infant iron stores are improved with late cord clamping
13 February 2013	New search has been performed	The review has been updated. A new search was carried out in February 2013. In this version of the review we have included four new trials making a total of 15 included and 37 excluded trials

H I S T O R Y

Protocol first published: Issue 1, 2003

Review first published: Issue 2, 2008

Date	Event	Description
27 May 2008	Feedback has been incorporated	We have replied to feedback from DA Erickson-Owens and JS Mercer, Eileen Simon, SJ Buckley and S Oddie
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, Philippa Middleton and Therese Dowswell wrote the review, carried out data extraction, set up the analysis and edited drafts. Peter Morris provided feedback and paediatric expertise to 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.

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Internal sources

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

External sources

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- NIHR, UK.

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- National Health and Medical Research Council (NHMRC), 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 that 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.

In 2013 the review includes restructured primary and secondary outcome criteria and we have now included birthweight and symptoms of infection in infants as secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Umbilical Cord; 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

MeSH check words

Female; Humans; Pregnancy