Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (Review)

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[Intervention Review]

Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

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ABSTRACT

Background

Optimal timing for clamping the umbilical cord at preterm birth is unclear. Early clamping allows for immediate transfer of the infant to the neonatologist. Delaying clamping allows blood flow between the placenta, the umbilical cord and the baby to continue. The blood which transfers to the baby between birth and cord clamping is called placental transfusion. Placental transfusion may improve circulating volume at birth, which may in turn improve outcome for preterm infants.

Objectives

To assess the short- and long-term effects of early rather than delaying clamping or milking of the umbilical cord for infants born at less than 37 completed weeks' gestation, and their mothers.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group Trials Register (31 May 2011). We updated this search on 26 June 2012 and added the results to the awaiting classification section.

Selection criteria

Randomised controlled trials comparing early with delayed clamping of the umbilical cord and other strategies to influence placental transfusion for births before 37 completed weeks' gestation.

Data collection and analysis

Three review authors assessed eligibility and trial quality.

Main results

Fifteen studies (738 infants) were eligible for inclusion. Participants were between 24 and 36 weeks' gestation at birth. The maximum delay in cord clamping was 180 seconds. Delaying cord clamping was associated with fewer infants requiring transfusions for anaemia (seven trials, 392 infants; risk ratio (RR) 0.61, 95% confidence interval (CI) 0.46 to 0.81), less intraventricular haemorrhage (ultrasound diagnosis all grades) 10 trials, 539 infants (RR 0.59, 95% CI 0.41 to 0.85) and lower risk for necrotising enterocolitis (five trials, 241 infants, RR 0.62, 95% CI 0.43 to 0.90) compared with immediate clamping. However, the peak bilirubin concentration was higher for infants allocated to delayed cord clamping compared with immediate clamping (seven trials, 320 infants, mean difference 15.01 mmol/L, 95% CI 5.62 to 24.40). For most other outcomes (including the primary outcomes infant death, severe (grade three to four) intraventricular haemorrhage and periventricular leukomalacia) there were no clear differences identified between groups; but for many there was incomplete reporting and wide CIs. Outcome after discharge from hospital was reported for one small study; there were no significant differences between the groups in mean Bayley II scores at age seven months (corrected for gestation at birth (58 children)).

No studies reported outcomes for the women.

Authors' conclusions

Providing additional placental blood to the preterm baby by either delaying cord clamping for 30 to 120 seconds, rather than early clamping, seems to be associated with less need for transfusion, better circulatory stability, less intraventricular haemorrhage (all grades) and lower risk for necrotising enterocolitis. However, there were insufficient data for reliable conclusions about the comparative effects on any of the primary outcomes for this review.

PLAIN LANGUAGE SUMMARY

Early cord clamping versus delayed cord clamping or cord milking for preterm babies

In the womb, the baby's blood flows through the umbilical cord to and from the baby and the placenta bringing oxygen and nutrition to the baby from the mother's blood. If the umbilical cord is left unclamped for a short time after the birth, some of the blood from the placenta passes to the baby (this is called placental transfusion) to increase the baby's blood volume and help the flow of blood to the baby's important organs including the lungs. For many years now, standard care during the delivery of the placenta has been to clamp the cord immediately at birth. This review looks at delaying cord clamping to allow more placental transfusion compared with immediate cord clamping. The other intervention considered is "milking the cord" which means the caregiver holds the cord and squeezes blood down the cord into the baby. In this review we have included 15 randomised controlled trials with 738 babies born prematurely between 24 and 36 weeks' gestation by caesarean section or vaginal birth. These studies compared babies where the cord was clamped within a few seconds of the birth with those whose cords were clamped after a delay of at least 30 seconds. The maximum delay in cord clamping was 180 seconds. Providing babies with additional blood through delayed cord clamping or milking the cord before clamping appeared to help the babies to adjust to their new surroundings. Fewer babies needed transfusions for anaemia, the risk of bleeding in the brain (intraventricular haemorrhage) and the risk of necrotising enterocolitis (a severe infection in the bowel) were reduced. The trials had an unclear risk of bias and varied outcome definitions were used. Further studies are needed comparing methods of delivering placental blood to babies to see which has the most benefit.

BACKGROUND

The comparative risks and benefits of early rather than later clamping of the umbilical cord for the preterm infant (fewer than 37 weeks' gestation) have been the subject of much debate, and the optimal timing to clamp the cord is unclear. Attempts to transfuse the baby from the placenta, by leaving the cord unclamped for longer at the time of birth, may conflict with a perceived need for immediate resuscitation, which usually takes place away from the mother.

The proportion of blood in the feto-placental circulation that resides in the placenta and cord varies with gestational age. In the second trimester of pregnancy the circulating blood volume can

be 100 to 120 mL/kg of body weight. Upto two-thirds of this amount can be distributed in the placenta at the time of delivery of a preterm infant.

The third stage of labour is the time between birth of the infant and delivery of the placenta. Cord clamping is part of active management of the third stage of labour, a package of care aimed at reducing the risk of postpartum haemorrhage for the women. The cord is usually clamped by applying two clamps. The cord is cut between the clamps, without blood loss for either the infant or the mother. Before the clamps are applied the infant can either be placed on the mother's abdomen (above the level of the placenta), between the mother's thighs (at the level of the placenta) or held below the level of the placenta. Blood flow from the placenta to the infant will depend on which position is used. Some birth attendants also 'milk' the cord towards the infant before clamping, as it can contain up to 20 mL of placental blood (Brune 2002). Whether additional blood actually passes to the infant as a result of this practice is unclear. Also, this milking of the cord is not a physiological transition. It is done with the aim of shortening the time for blood to transfer to the baby at birth, but this ignores a potential role of a slower placental transfusion which may be to facilitate transition from the fetal to the neonatal circulation. For preterm births, an alternative strategy is to provide initial care for the newborn at the bedside and so allow time for delayed cord clamping. There is no consensus about the definition of early or delayed cord clamping regarding the time intervals. Some authors prefer to use the term 'defer' rather than 'delay'.

Common complications and conditions of preterm babies born before 33 weeks' gestation include low blood pressure during the first days of life, the need for respiratory support due to immature lungs and the need for blood transfusions. Intraventricular haemorrhage (bleeding into the brain) and necrotising enterocolitis (severe infection of the bowel) can be life threatening events. These conditions inevitably add to the distress of the parents of these babies.

Suggested advantages of delaying clamping of the umbilical cord and subsequent increased placental transfusion include larger blood volume for the preterm baby, better adaption to extrauterine life; higher haemoglobin for the baby; less anaemia for the baby and better iron stores, less need for blood transfusion, less respiratory distress (Linderkamp 1978), and less requirement for respiratory support (Holland 1991; Hudson 1990; Kinmond 1993). Potential disadvantages include delay in resuscitation, hypothermia, polycythaemia, hyperbilirubinaemia needing treatment (Saigal 1972) and a possible risk of intraventricular haemorrhage (Hofmeyr 1988). If there are benefits for preterm infants in the first few days and weeks of life, it would also be important to assess whether these short-term benefits are reflected in improved long-term outcome.

There are different potential comparative effects of early rather then delayed cord clamping for term and preterm infants. For example, in term infants increasing placental transfusion by delaying cord clamping may increase respiratory morbidity after birth (Yao 1974). As a consequence the issue of timing of cord clamping is reviewed separately for preterm and term infants. There is a separate Cochrane review of this topic for term infants (McDonald 2008).

For developing countries, with limited resources and a high risk of transmitting infection through blood transfusion, the potential value of a reduced need for blood transfusion would be of particular interest. In more developed countries, 60% to 80% of preterm infants less than 32 completed weeks' gestation (Brune 2002; Ringer 1998) require transfusion, and strategies that might reduce this without risk would be desirable.

This review will be of interest to obstetricians, midwives, neonatologists as well as pregnant women and their partners.

OBJECTIVES

To assess the short- and long-term effects of early rather than delayed clamping of the umbilical cord for births before 37 completed weeks' gestation. A secondary objective is to assess the effect of positioning the baby above or below the introitus at birth, and the effect of milking the umbilical cord.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials including cluster-randomised trials. Quasi-randomised trials were not included.

Types of participants

Preterm infants born before 37 completed weeks' gestation and their mothers.

Types of interventions

Immediate cord clamping versus delayed clamping (after 30 seconds or more). This could be with or without oxytocin, with or without the baby held above or below the level of the placenta, and with or without milking of the cord towards the infant. In this version of the review we have also considered studies examining cord milking with clamping earlier than 30 seconds.

Types of outcome measures

Primary outcomes

For the baby

1. Death of the baby: before discharge from hospital, after discharge from hospital, total.
2. Death or neurosensory disability at age two to three years.
3. Intraventricular haemorrhage (IVH) - ultrasound diagnosis grade three and four.
4. Periventricular leukomalacia.

For the mother

1. Postpartum haemorrhage (blood loss greater than 500 mL).

Secondary outcomes

For the baby

Condition at birth

1. Requirement for resuscitation.
2. Apgar score at one, five and 10 minutes.
3. Hypothermia during first hour of life or on admission to labour ward.

Respiratory

1. Respiratory distress syndrome (assessed by clinical signs, oxygen requirement, respiratory support, chest x-ray) during first 36 hours of life.
2. Use of exogenous surfactant.
3. Days of oxygen dependency.
4. Oxygen dependency at 28 days after birth.
5. Oxygen dependency at equivalent of 36 completed weeks' gestational age.
6. Chronic lung disease (Northway Stage two, three or four).

Cardiovascular

1. Volume (colloid, sodium chloride 0.9%, blood transfusion) administration for hypotension during the first 24 hours of life.
2. Inotropic support for hypotension during the first 24 hours of life.
3. Treatment for patent ductus arteriosus.

Haematological

1. Anaemia, number or volume of blood transfusions.
2. Treatment for hyperbilirubinaemia with phototherapy.
3. Treatment for hyperbilirubinaemia with blood exchange transfusion.
4. Blood counts at six and 12 months of age (haemoglobin and ferritin).

Central nervous system

1. IVH all grades.

Gastrointestinal

1. Necrotising enterocolitis.

Other

1. Length of hospital stay.

For the mother

1. Death.
2. Manual removal of the placenta.
3. Effects on Rhesus-isoimmunisation.
4. Psychological well-being.
5. Bonding to the infant.
6. Anxieties.
7. Mother's views.

For the father

1. Psychological well-being.
2. Bonding to the infant.
3. Anxieties.
4. Father's views.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (31 May 2011). We updated this search on 26 June 2012 and added the results to Studies awaiting classification.

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.

For details of additional searching carried out in the previous version of the review, please see Appendix 1.

Data collection and analysis

For the methods used to assess the trials identified in the previous version of this review, *see* Appendix 2.

For this update we used the following methods when assessing the trials identified by the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. We entered data into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion, or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We have described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should 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 allocation to interventions prior to assignment and have assessed whether intervention 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 of participants and personnel (checking for possible performance and detection bias)

Blinding participants and staff to the types of interventions considered in this review may not be feasible, but it may be possible to blind outcome assessors for at least some of the outcomes reported. We have described for each included study the methods used, if any, to achieve blinding. We considered studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We have described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We have stated whether attrition and exclusions were reported and 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. Where sufficient information was reported, or was supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We have described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

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 could not be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We have described for each included study any important concerns we have 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 whether there is 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 *Handbook* (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 the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

Had we found any, we would have included cluster-randomised trials in the analyses along with individually-randomised trials. If in future updates we do include cluster-randomised trials, we will adjust their sample sizes using the methods described in the *Handbook* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there was 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. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Due to the nature of the studied interventions cross-over designs are not possible.

Other unit of analysis issues

Other unit of analysis issues could include, e.g. multiple pregnancies or more than two treatment groups, which need specialist statistical analysis. However, these type of trials have, so far, not been reported for cord clamping interventions.

Dealing with missing data

For included studies, we noted levels of attrition. We had planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis but levels of attrition in the included studies were generally low.

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, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Where there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually, and where there appeared to be asymmetry we planned to use formal tests for funnel plot asymmetry. For continuous outcomes we planned to use the test proposed by Egger 1997, and for dichotomous outcomes the test proposed by Harbord 2006. If asymmetry was detected in any of these tests or was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it. For most outcomes in this review too few studies contributed data to carry out this planned analyses.

For all meta-analyses we ordered studies according to weight so that we would be able to identify any obvious differences in effect associated with smaller studies.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. If we suspected clinical heterogeneity sufficient to expect that the underlying treatment effects would differ between trials, or if substantial statistical heterogeneity was detected, we planned to use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. In this version of the review we identified little statistical heterogeneity between studies.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. By position of the baby relative to the level of the placenta before cord clamping: below the level of the placenta; at the level of the placenta; above the level of the placenta; or position not known or unclear.
2. By whether the woman was given oxytocin as a uterotonic drug before cord clamping: with oxytocin; no oxytocin before clamping; unclear or not known whether oxytocin given.
3. By milking of the cord: with milking; without milking; unclear or not known whether milking.
4. By route for birth: vaginal, abdominal, or mixed or not known.
5. By gestational age at birth: less than 32 completed weeks' gestation, 32 or more completed weeks, gestation mixed or not known.

We planned to restrict subgroup analyses to the primary outcomes. In this version of the review there was insufficient information in the trial reports to allow us to carry out planned subgroup analysis other than for cord milking. We assessed differences between subgroups by inspection of the subgroups' confidence intervals with non-overlapping confidence intervals suggesting a statistically significant difference in treatment effect between the subgroups. Where sufficient data were available, we carried out more formal statistical tests to assess differences between subgroups by applying the interaction tests available in RevMan 2011.

Sensitivity analysis

We planned sensitivity analysis by study quality based on allocation concealment, excluding studies with high risk of bias or unclear risk of bias. We carried out this analysis for primary outcomes only.

RESULTS

Description of studies

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

Results of the search

From the May 2011 search, fifteen trials qualified for inclusion into this review. We excluded 10 studies (*see* Characteristics of excluded studies). We updated the search on 26 June 2012 and added the new reports to Studies awaiting classification.

Included studies

See Characteristics of included studies for more detail of participants and interventions, such as gestational age, mode of delivery, positioning of the infant and length of cord clamping time.

The trials enrolled preterm babies between 24 and 36 weeks' gestation. For some studies the unit of randomisation was the baby, but for most mother-infant pairs were randomised. There was some inconsistency in both the intervention and the control procedures between studies and wide variation in outcome measures.

The women recruited into the trials were all expecting to deliver their infants prematurely. The infants in the studies by Kinmond 1993 and Ultee 2008 were all delivered vaginally, while those in the trial carried out by Nelle 1998 were delivered by caesarean section only. All other trials included women undergoing both methods of delivery.

Interventions compared

At birth, blood flow in the umbilical arteries and veins usually continues for a few minutes. The additional blood volume transferred to the infant during this time is known as placental transfusion. The interventions in the review are aimed at modifying placental transfusion. For the analysis graphs where we have combined data across studies comparing a range of interventions, we have therefore used the terms 'more placental transfusion' and 'less placental transfusion'.

Interventions in the included studies were as follows.

Early cord clamping: the definition of early umbilical cord clamping was not clear in most studies except for McDonnell 1997 where the exact time to cord clamping in the immediate group was five seconds and in Ultee 2008 where the mean recorded time was 13.4 seconds. It seems likely that there is a time lag between delivery and cord clamping and that variation may be up to 10 seconds or more. In Rabe 2000, early cord clamping was defined as clamping at 20 seconds and there was no immediate clamped group for comparison. We have included this study in this review because we believe that there is close proximity to the immediate clamped groups, and that in clinical practice such delays may occur. Furthermore, it allows the review to focus on at least 20 seconds interval between early and late cord clamping.

Delayed cord clamping: the definition of delayed umbilical cord clamping varied between studies. McDonnell 1997 had a mean timed delay of 31 seconds, Rabe 2000 45 seconds, Hofmeyr 1988 and Hofmeyr 1993 60 and 120 seconds, Aladagandy 2006 and Baezinger 2007 60 to 90 seconds, Kugelman 2007, Mercer 2003 and Mercer 2006 30 to 45 seconds, and Strauss 2008 60 seconds. Ultee 2008 had the longest timing with 180 seconds, but in a study group of more mature preterm infants of 34 to 36 weeks' gestation. The exact time to clamping was not given in other studies, nor was there an adequate description of how the timing was done and by whom. The number of babies allocated to delayed cord clamping but in whom resuscitation was considered necessary before the allocated time is described in several studies. In Hofmeyr 1988 for example, eight of 24 babies in the delayed clamping group required earlier intervention.

Cord milking: this is a technique, sometimes called stripping the cord, in which the cord is pinched between the fingers and the hand then moved towards the baby before releasing the cord. The aim is to move blood towards the baby, so that blood transfers from the placental bed to the baby more quickly than occurs from just waiting before clamping the cord. Hosono 2008 describes the technique used in this study as: infants are placed at or below the level of the placenta. Approximately 20 cm of the umbilical cord is vigorously milked towards the umbilicus two or three times before clamping the cord. The speed of milking is approximately 20 cm per two seconds. This means that the baby might receive a bolus of blood in a short time period.

Position of the baby in relation to the placenta: the position in relation to the placenta or uterus varied between studies. It is accepted that positioning the baby below the placenta during caesarean section is difficult, and that for most studies the baby lies on the mother's thighs above the level of the uterus whilst waiting to clamp the umbilical cord. Most studies have positioned the baby at the level of the introitus for vaginal deliveries. Only in one study (Rabe 2000) was the baby kept at or more than 20 cm below the placenta. Subgroup analysis based on position of the baby in relation to the placenta has not therefore been possible. In one study (Ultee 2008), the baby was placed on the mother's abdomen in vaginally delivered infants.

Uterotonic drugs (Syntocinon or ergometrine): the use of pharmacologic stimulants to the uterus after delivery is not consistent between studies or is ill defined. However, Hofmeyr 1988 had shown that there is no significant difference in the two groups allocated to delayed umbilical cord clamping with or without ergometrine. We have therefore not attempted a subgroup analysis on this variable.

Outcome measures

No two studies had the same outcome objectives and there were wide and varied definitions in the type of outcome measured. Similarly, the manner of reporting the same outcome varied between studies. We requested raw data from all authors in order to clarify issues and to improve our reporting for those outcomes that, a priori, we considered important. The authors of several studies have stated that they performed a pilot or feasibility study and these were powered to answer short-term specific questions only. In gen-

eral, the studies that we included are not powered individually to answer the range of clinical questions that we feel are important in day-to-day neonatal practice.

Umbilical cord blood analysis

No study described how and when the cord blood was obtained (whether from placenta, cord, isolated segment, etc).

Subgroup analysis

Subgroup analysis by position or effects on mothers and fathers was not possible in this version of the review due to lack of data.

While two studies included only women undergoing vaginal deliveries (Kinmond 1993; Ultee 2008), we have not included results for subgroup analysis by mode of delivery as, either no data, or no estimable data were available for our primary outcomes. We carried out subgroup analysis by delayed cord clamping versus cord milking for out primary outcomes (*comparison 2*).

Risk of bias in included studies

Individual assessments of risk of bias for included studies are set out in the Characteristics of included studies tables. Overall summaries of assessments of bias in included studies are set out in Figure 1 and Figure 2, and are briefly described below.

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

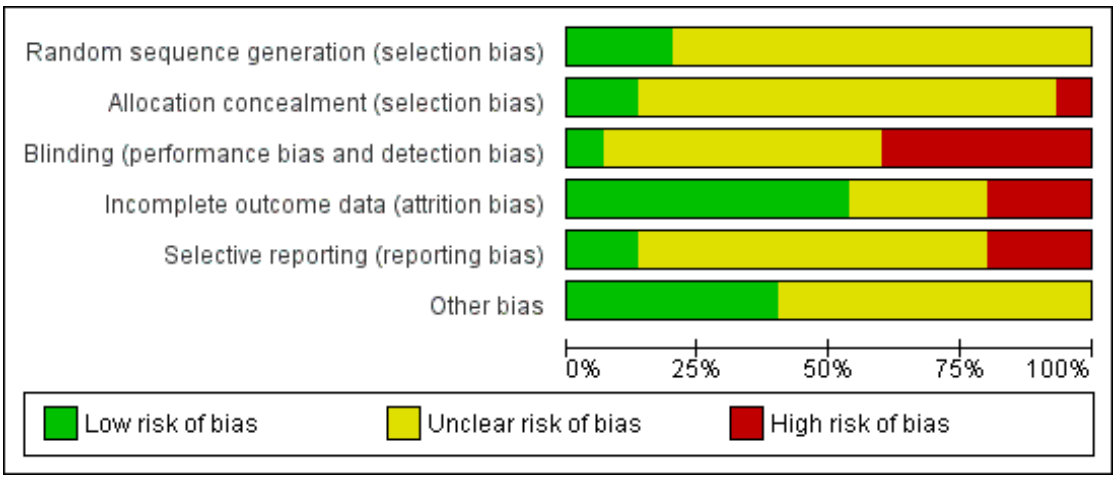
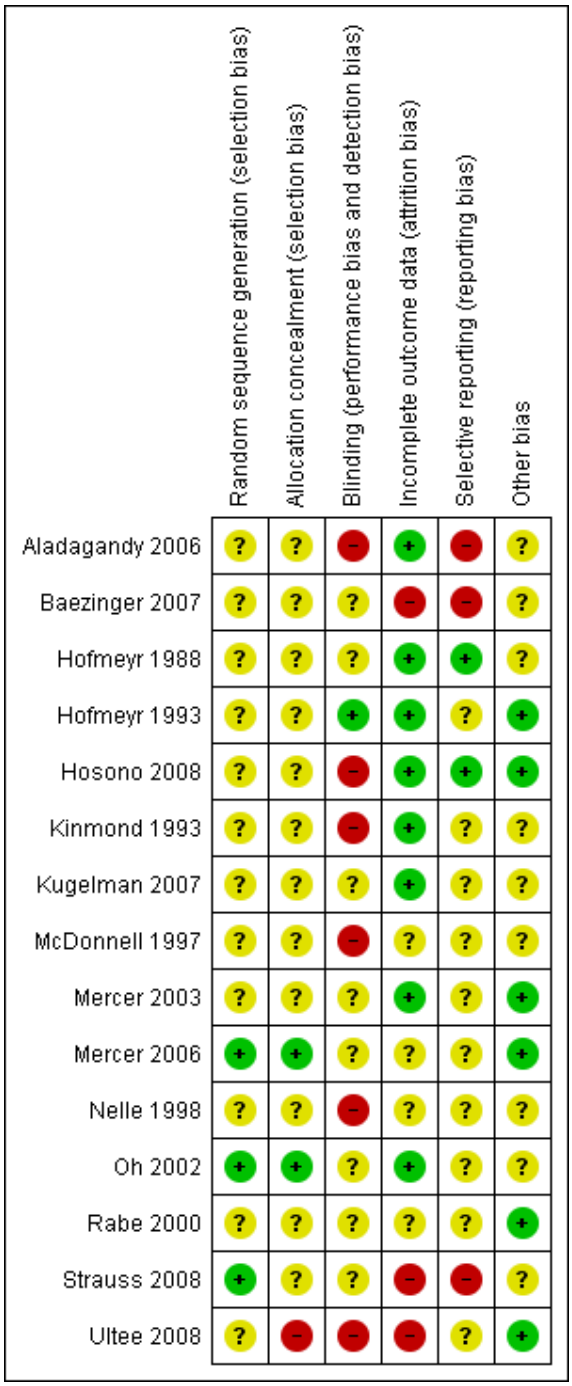


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The method used to generate the randomisation sequence in the included studies was generally not well described. Only three studies clearly described the method used to determine the sequence for group allocation: Mercer 2006 used a computer-generated method, Strauss 2008 a table of random numbers and Oh 2002 used an external randomisation service. In the remaining 12 studies the method used to generate the randomisation sequence was either not mentioned, or was not described in sufficient detail to allow us to judge risk of bias. In some studies the sample was stratified by factors such as gestational age or estimated birth weight (*see* Characteristics of included studies).

The methods used to conceal allocation at the point of randomisation were not that well described although only one study (Ultee 2008) described using methods that we judged were at high risk of bias. In this study, one of the staff providing care carried out randomisation and there were post randomisation exclusions if the baby had a low Apgar score at one or five minutes. In 12 of the studies there was insufficient information to allow us to judge whether or not methods were at low risk of bias.

Blinding

For this type of intervention blinding participants and the staff present at delivery to group allocation is not possible. For outcome assessment it may be possible to blind assessors collecting data. We assessed all included studies at either high risk of bias or unclear for this domain. For some outcomes lack of blinding may be an important source of bias while the impact of lack on blinding on outcomes such as laboratory tests is less clear. We have noted in the Characteristics of included studies tables where investigators have attempted blinding of outcome assessors. None of the studies reported on the success of blinding.

Incomplete outcome data

Most of outcome data in included studies were collected soon after the birth, and loss to follow-up was not generally a problem. In three studies post randomisation exclusions or loss to follow-up meant that results were difficult to interpret and we assessed these studies as high risk of bias (Baezinger 2007; Strauss 2008; Ultee 2008). In eight of the studies all of the women randomised were accounted for in the analysis or there was minimal loss which was explained. In four of the studies there was insufficient information (for example, denominators were not provided in tables) to allow us to make a clear judgement about whether loss to follow-up or exclusions were likely to introduce bias.

Selective reporting

For most of the included studies only published data were available to us, and we did not have access to trial registration reports or study protocols. Under these circumstances we were not able to assess whether authors had omitted to report findings for all of their pre-specified outcomes. We were not able to detect any clear instances of outcome reporting bias.

Other potential sources of bias

In most of the included studies there were no obvious other sources of bias, and in most cases there were descriptions of the characteristics of participants so that it was clear that there were no obvious baseline differences between groups. In Baezinger 2007 and Strauss 2008, the size of the intervention and control groups were uneven; in the study by Hofmeyr 1988 there were baseline differences in the condition of infants and this made results more difficult to interpret; the Kinmond 1993 study was terminated early and there was a chance excess of boys in the intervention group (13/17) compared with controls (7/19); McDonnell 1997 also reported that there was imbalance for infant sex. The study by Nelle 1998 was reported in a brief abstract with little information on study methods and this meant that the overall risk of bias was unclear.

Effects of interventions

We included 15 studies involving 738 infants (data from several studies were reported in more than one publication).

(a) Delayed (more placental transfusion) versus immediate (less placental transfusion) cord clamping: 15 studies, 738 infants

Primary outcomes

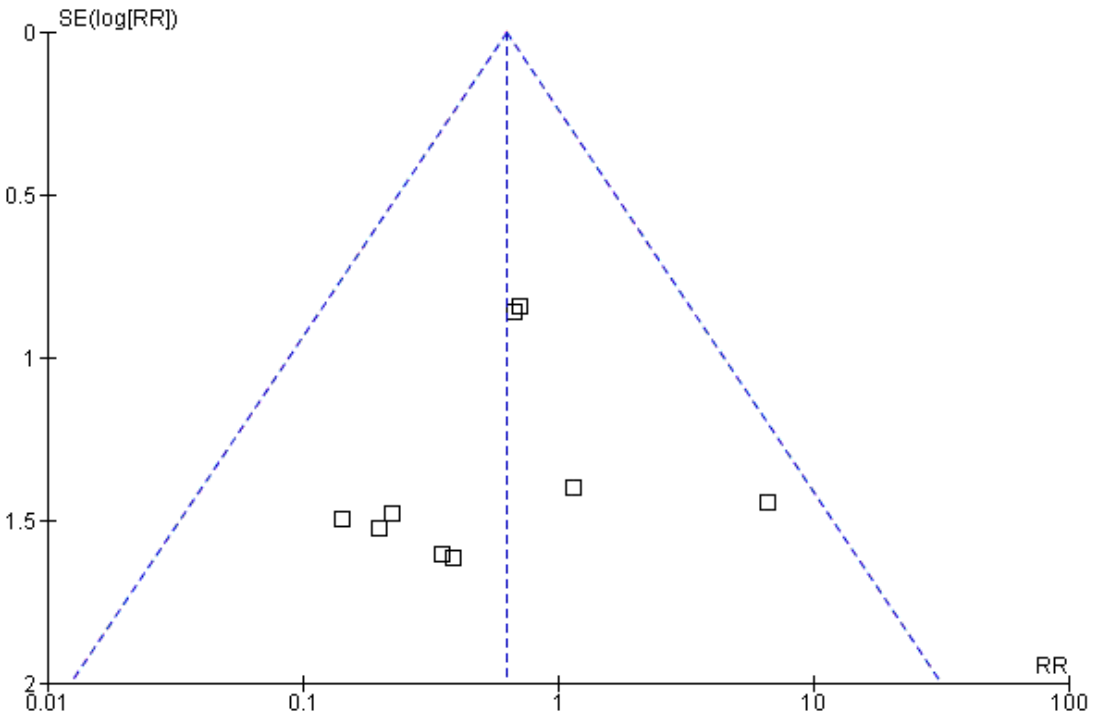
For the baby

Death of the baby

Thirteen of the included studies with a total of 668 infants reported infant death (largely death before discharge from hospital), and overall there were 27 deaths. In the group allocated more placental transfusion 3.1% (10/319) babies died before hospital discharge compared with 4.9% (17/349) of those allocated less placental transfusion (unweighted percentages), there was no clear difference

between groups in the risk of death (risk ratio (RR) 0.63, 95% confidence interval (CI) 0.31 to 1.28) (Analysis 1.1) We did not identify statistical heterogeneity or find evidence of funnel plot asymmetry for this outcome (Figure 3).

Figure 3. Funnel plot of comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), outcome: 1.1 Infant death (up to discharge/variable).



Death or neurosensory disability at age two to three years

No trials reported these outcomes at age two to three years. One trial (Mercer 2006) reported outcomes after discharge from hospital: neurodevelopmental outcome at a median age of seven months. Of the 72 children recruited, five died before seven months. Of the 67 survivors, nine were lost to follow-up. Fifty-eight children were assessed at age seven months (corrected for gestation at birth). There were no significant differences between the groups in the Bayley II mean scores for Mental Development Index and Psychomotor Developmental Index (data not shown).

Intraventricular haemorrhage (IVH)- ultrasound diagnosis grade three and four

Severe IVH (grade three and four) was reported in six trials (Analysis 1.2). There were 12 events in 305 babies (5/154 versus 7/151) with a RR of 0.68 (95% CI 0.23 to1.96) for babies allocated more placental transfusion rather than less placental transfusion.

Periventricular leukomalacia

Only two studies (71 infants) (Analysis 1.3) reported periventricular leukomalacia; overall, there were three events which is insufficient evidence for any reliable conclusions (RR 1.02, 95% CI 0.19 to 5.56).

For the mother

Postpartum haemorrhage (blood loss greater than 500 mL)

None of the included studies reported results for this outcome.

Secondary outcomes

For the baby

Apgar score at one, five and 10 minutes

Mean Apgar scores were reported at one minute (three trials, 184 infants, mean difference (MD) (random-effects) 0.30, 95% CI -0.52 to 1.12) (Analysis 1.4); five minutes (three trials, 184 infants MD 0.12, 95% CI -0.20 to 0.43) (Analysis 1.5); and 10 minutes (one trial, 39 infants, MD 0.00, 95% CI -1.05 to 1.05) (Analysis 1.6). There were no clear differences between groups at any of these time points. There was no statistically significant difference between the groups in Apgar scores less than eight at five minutes (three trials, 161 infants, RR 0.86, 95% CI 0.45 to 1.62) (Analysis 1.7).

Hypothermia during first hour of life, on admission to special care unit or in delivery room

None of the studies reported on hypothermia in the delivery room. Three studies (143 infants) (Analysis 1.8) reported mean infant temperature on admission to special care unit; there was no clear difference between the groups (MD 0.14, 95% CI -0.03, to 0.31).

Respiratory

Respiratory distress syndrome

Respiratory distress syndrome was reported by three small studies (total 115 babies). There was no clear difference between the two groups (RR 1.16, 95% CI 0.89 to 1.50) (Analysis 1.9). Only one trial (39 infants) reported results for severe respiratory distress and this study was too small for any reliable conclusions about the difference between the two groups (RR 0.79, 95% CI 0.20 to 3.07) (Analysis 1.10).

Other respiratory outcomes

Use of surfactant was reported in two trials with 85 infants (Analysis 1.11); there was no clear difference between the groups (RR 1.28, 95% CI 0.56 to 2.93). Despite difficulties with definitions, five trials involving 265 infants reported ventilation for some form of respiratory distress (RR 0.97, 95% CI 0.71 to 1.31) (Analysis 1.12).

Need for oxygen at 28 days after birth was reported by two trials (76 infants) (Analysis 1.13), and there was no clear difference between the groups (RR 0.48, 95% CI 0.15 to 1.59). Need for oxygen at 36 weeks' gestational age was reported by five trials (209 infants); there was also no clear difference between the groups (RR 0.69, 95% CI 0.42 to 1.13) (Analysis 1.14).

The number of infants with chronic lung disease (Northway Stage two, three or four) was not reported in any of the included studies.

Cardiovascular outcomes

Infants allocated to more placental transfusion were less likely to need transfusion for low blood pressure after birth although the difference between groups did not reach statistical significance. There was moderate heterogeneity for this outcome (I^2 = 33%) so we used a random-effects model and results represent the average treatment effect (four trials, 130 infants, RR 0.52, 95% CI 0.24 to 1.11) (Analysis 1.15). The mean arterial blood pressure was significantly higher in those allocated more placental transfusion, both at birth (two trials, 97 infants, MD 3.52, 95% CI 0.60 to 6.45) (Analysis 1.16) and at age four hours (two trials, 111 infants, MD 2.49, 95% CI 0.26 to 4.72) (Analysis 1.17), but at 24 hours of age the arterial blood pressure is reported by just one trial (38 infants) (Analysis 1.18).

Need for inotropic support

Overall, infants in the delayed clamping group had significantly less need for inotropic support (RR 0.42, 95% CI 0.23 to 0.77) (Analysis 1.19).

Treatment for patent ductus arteriosus

There was no clear difference between the groups in respect of treatment for patent ductus arteriosus (five trials, 223 infants, RR 1.04, 95% CI 0.60 to 1.81) (Analysis 1.20).

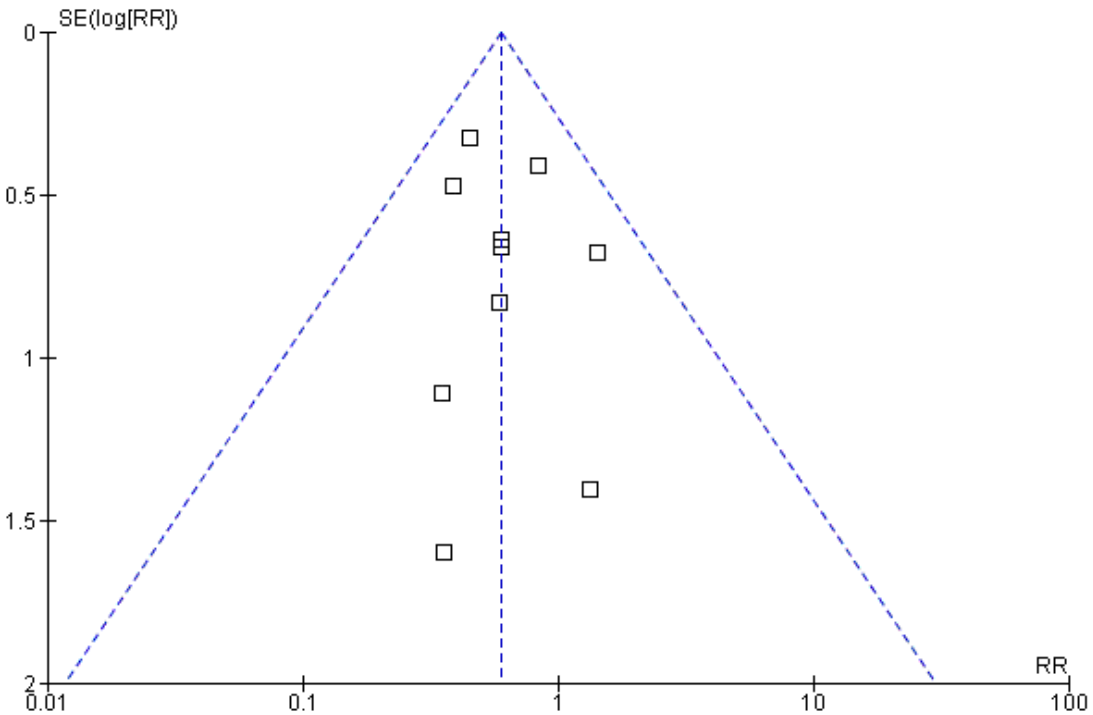
Central nervous system

IVH all grades

IVH is a risk factor for adverse developmental outcome. However, this risk is largely associated with severe IVH (grade 3 or 4) which is a primary outcome for this review. Ten trials (539 infants) reported IVH (all grades). Allocation to more placental transfusion

was associated with a lower risk ratio for IVH (all grades) (RR 0.59, 95% CI 0.41 to 0.85). There was no evidence of statistical heterogeneity or funnel plot asymmetry for this outcome (Analysis 1.21; Figure 4).

Figure 4. Funnel plot of comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), outcome: 1.21 Intraventricular haemorrhage (all grades).



Gastrointestinal

Necrotising enterocolitis

Necrotising enterocolitis was reported in five trials with a lower risk associated with more placental transfusion (241 infants, RR 0.62, 95% CI 0.43 to 0.90) (Analysis 1.22).

Haematological

Anaemia, number or volume of blood transfusions

Seven studies (392 infants) reported the number of infants requiring blood transfusion for anaemia. Overall 24% (44/186) of those allocated more placental transfusion had blood transfusion for anaemia compared with 36% (5/206) of those allocated less placental transfusion, giving a RR for this reduction of 0.61 (95% CI 0.46 to 0.81) (Analysis 1.23). There was also a reduction in the overall number of blood transfusions given in the delayed clamping group (five trials, 210 infants, MD -1.26, 95% CI -1.87 to -0.64; Analysis 1.24).

Hyperbilirubinaemia (jaundice)

The peak bilirubin concentration was higher for infants allocated more placental transfusion rather than less placental transfusion

(seven trials, 320 infants, MD 15.01 mmol/L, 95% CI 5.62 to 24.40) (Analysis 1.25). One small trial (35 infants) reported red cell mass after birth, which are insufficient data for reliable conclusions.

The bilirubin level above which treatment was started is likely to differ between centres, and the criteria for treating hyperbilirubinaemia in each study were not stated. However, treatment (phototherapy) was reported by three studies (180 infants, RR 1.21, 95% CI 0.94 to 1.55) (Analysis 1.26) with no significant difference between the groups, although there was a non-significant trend towards more phototherapy for infants allocated more placental transfusion. Data on exchange transfusion were not reported by any of the studies.

Other pre-specified secondary outcomes including blood counts at six and 12 months of age (haemoglobin and ferritin) were not reported.

Non-prespecified outcomes

One study (Baezinger 2007) reported mean regional tissue oxygenation of the brain at four hours (39 infants, MD 6.44, 95% CI 5.47 to 7.41) (Analysis 1.24) and 24 hours of age (39 infants, MD 4.29 95% CI 3.44 to 5.14) (Analysis 1.28) with statistically significantly higher values for the delayed cord clamping group.

There was an increase in haematocrit MD at birth or one hour (seven trials, 318 infants, MD 3.26%, 95% CI 1.79 to 4.74) (Analysis 1.29), haematocrit at four hours (five trials, 173 infants, MD 5.40%, 95% CI 3.62 to 7.17) (Analysis 1.30) and haematocrit at 24 hours (three trials, 199 infants, MD 3.28%. 95% CI 1.34 to 5.22) (Analysis 1.31). Two trials (81 infants) reported blood volume after birth (MD 8.41, 95% CI 2.14 to 14.67) (Analysis 1.32). The results in these two trials varied and we used a random-effects model for this outcome. A further post-hoc analysis to include sepsis as an outcome was generated by Mercer 2006. This outcome was reported by two trials (137 infants, average RR 0.34, 95% CI 0.05 to 2.11) (Analysis 1.34).

There was no evidence of a difference between groups for the number of babies with retinopathy of prematurity (reported in one study) (Analysis 1.35). Mean cord pH was examined in three studies and there was no significant difference between groups (Analysis 1.36). Mean length of stay in hospital was reported in only one of the included studies, and although it was reduced in the delayed cord clamping group the difference between groups was not statistically significant (Analysis 1.37).

For the mother

None of the included studies reported results for any of our secondary outcomes for mothers (death; manual removal of the placenta; psychological well-being, anxiety, maternal views, bonding with the infant or effects of rhesus-iso-immunisation).

For the father

None of the included studies reported results for any of our secondary outcomes for fathers (psychological well-being, anxiety, fathers' views or bonding with the infant).

Subgroup analysis: delayed cord clamping versus cord milking

Only one trial (with 40 infants) evaluated cord milking, all the remaining trials evaluated delayed cord clamping. We found no clear evidence of differences between these subgroups in the effects on the primary outcomes (Analysis 2.1; Analysis 2.2; Analysis 2.3).

Sensitivity analysis

For our primary outcomes we carried out sensitivity analysis separating studies where risk of bias associated with allocation concealment was low, or unclear/high. This did not alter the interpretation of results (Analysis 3.1; Analysis 3.2; Analysis 3.3).

DISCUSSION

Summary of main results

This updated review now includes data from 15 trials involving more than 700 mother and baby pairs. Most trials compared alternative timings for cord clamping. For the three primary outcomes of infant death, severe intraventricular haemorrhage, and periventricular leukomalacia the confidence intervals for the risk ratio are wide and so there is insufficient evidence for reliable conclusions about the differential effects of these alternative policies for care at birth. No study has yet reported the fourth primary outcome of neurodevelopment at age two to three years.

More placental transfusion, rather than less placental transfusion, is associated with fewer blood transfusions for anaemia and for low blood pressure. More placental transfusion also appears to protect against intraventricular haemorrhage (all grades), although the clinical significance of this is unclear as there are too few data for any reliable conclusions about the comparative effect on severe intraventricular haemorrhage (grades three or four) and no trials have assessed neurodevelopment of the children at age two to three years. Necrotising enterocolitis and sepsis also appear to be reduced, but these outcomes are only reported for a limited number of studies in the review. There is no clear difference in the effect on Apgar scores, or temperature on admission to special care unit; although again, these outcomes were not reported for all trials.

Overall, even when taking all trial results together, most outcomes had wide confidence intervals and so results should be interpreted with caution. Nevertheless, later umbilical cord clamping to allow

more placental transfusion at preterm birth appears to be associated with a reduction in the risk ratio of intraventricular haemorrhage (all grades) and the need for transfusion, either for anaemia or for low blood pressure and less risk for necrotising enterocolitis. These effects may be related to an improvement in the circulating neonatal blood volume, and better control of blood pressure, following greater placental transfusion.

Surprisingly, as one of the rationales for early clamping is to allow the infant to be transferred to a resuscitaire for respiratory support, there are few data on respiratory outcomes. No study reported on spontaneous onset of respiration. A clinical concern about delayed umbilical cord clamping is the potential for the baby to get cold and develop hypothermia. This did not occur in the three trials that report temperature and there is no clear evidence that Apgar scores are significantly different.

One small study has evaluated milking of the cord (Hosono 2008) which reports positive effects on haemoglobin after birth, better blood pressure and less need for donor blood transfusion. It is too early to say whether this method would be better compared with delaying cord clamping, even though some obstetricians and midwives might prefer it. Future large studies could compare the various methods of achieving placental transfusion such as delayed cord clamping and milking of the cord.

Overall completeness and applicability of evidence

There are several ways to potentially influence placental transfusion for preterm births. We have reflected this in our review by broadened the types of intervention to include any strategy that might influence placental transfusion.These strategies include early or delayed cord clamping, using gravity to assist placental transfusion by lowering the baby below the introitus or the level of the placenta, clamping the cord as close as possible to the placenta and then after cutting the cord allowing the residual blood in the cord to drain into the baby, and milking of the cord. Nevertheless, timing of cord clamping remains the most widely evaluated intervention, with all but one study comparing alternative timings for cord clamping. There were insufficient data for subgroup analysis - with no data on optimal positioning of the infant, oxytocics to the mother and combinations of these with a timing of cord clamping.

There are issues with interpreting death as an outcome in some of the trials. Variations in clinical practice over time have substantially influenced the risk of death following preterm birth. These background variations in clinical practice may influence the risk of death more than any change in placental transfusion. The five neonatal deaths in Hofmeyr's study (Hofmeyr 1988), for example, are quoted as being "< 1300 g birthweight". This study was performed in the late eighties in South Africa, where access to ventilatory support for very preterm infants would have been, and still is, limited. In more recent years, and in most intensive care units in high-income countries, ventilatory support for these babies would have been offered. In the Hofmeyr 1988 study it is not clear whether ventilation was possible for these babies, but a comment in the report suggests that survival at this low birthweight was more the exception than the rule. Similarly, there is a high incidence of intraventricular haemorrhage in Hofmeyr 1988 and Hofmeyr 1993), both studies conducted in South Africa. The other studies conducted in high-income countries have a lower incidence of intraventricular haemorrhage, and therefore less power to demonstrate any clinically important effects on this risk.

The ideal volume and duration of placental transfusion is not known. Most attention has focused on the volume of placental transfusion, but duration may also be important. This seems particularly important to assess for preterm births allowing longer for placental transfusion may facilitate the immature infant making the transition from fetal circulation to neonatal circulation.

Quality of the evidence

The trials included in this review were largely of unclear risk of bias. Only three studies were low risk for sequence generation, and two were low risk for concealment of allocation. No studies were low risk for all assessments of quality, and eight trials were at high risk of bias for at least one assessment.

No outcome in this review was reported by all included studies. The most complete reporting was for death of the baby (reported by 13 trials with 668 infants) and intraventricular haemorrhage (all grades) (reported by 10 trials with 559 infants). Of the remaining 35 outcomes, 23 were reported by a maximum of three trials. Although it was not possible to check the protocols for these trials, selective reporting is a concern.

Potential biases in the review process

We are aware of potential biases in the reviewing process; and we took some steps to minimise bias (such as data extraction which was carried out by two review authors independently).

Agreements and disagreements with other studies or reviews

We are not aware of other reviews.

AUTHORS' CONCLUSIONS

Implications for practice

More, rather than less, placental transfusion will increase the neonatal blood volume at birth. This review suggests the increased

circulating volume improves blood pressure, reduces the need for blood transfusion, risk of intraventricular haemorrhage and necrotising enterocolitis. The effects on the important primary outcomes for this review are unclear. Disability-free survival is a key concern for children born preterm, and long-term follow-up for children recruited to these trials is needed to provide a reliable basis for recommendations about clinical practice.

Based on the available data, the European consensus guidelines on resuscitation of the preterm infant have recommended a slight delay of 30 to 45 seconds before clamping the umbilical cord to facilitate placento-fetal transfusion (Sweet 2010).

Implications for research

The review suggests potential benefit for strategies to allow more placental transfusion, rather than less placental transfusion. However, studies to date are small, have some risk of bias, are often imprecise in defining outcomes, do not report data for all important outcomes, and lack long-term follow-up with neurodevelopmental assessments. To reliably compare strategies for influencing placental transfusion, we need large high-quality trials, with sufficient power to reliably assess clinically relevant differences in important outcomes.

Larger multicentre studies are essential and demand international collaboration to provide a scientific rationale for improving the delivery and resuscitation of the preterm infant. Future studies should include more data on respiratory outcomes, especially on onset of spontaneous breathing of the preterm baby and on long-term neurodevelopmental outcome at two years of age. They should also report treatment details and outcomes for the mother.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aladagandy 2006

Methods	Randomised controlled trial, stratified randomisation list for gestational age group (24-26, 27-29, 30-32) and type of delivery (vaginal/caesarean)
Participants	46 mother-infant pairs at 24 weeks to 32 weeks' gestation. Exclusions: known major malformation, haemolytic disease, intrauterine transfusion
Interventions	Control group: cord clamping immediately after birth. Intervention: cord clamping time 30-90 sec, with infant held as low as the cord allowed. If caesarean section, mother received 5 IU syntocinon intravenously at delivery of presenting part
Outcomes	Primary outcome: red cell volume measured at 4 h of age.
Notes	Same protocol for a multicentre trial as Baezinger 2007. There is no overlap in the data reported, as this paper reports results for a different centre. Scotland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was performed by a stratified randomisation list, just before delivery". It was not clear how this sequence was generated
Allocation concealment (selection bias)	Unclear risk	Randomisation occurred "just before delivery". It was not clear whether staff allocating women to groups would be aware of randomisation group before delivery and could therefore anticipate which group a women would be assigned to
Blinding (performance bias and detection bias) All outcomes	High risk	Although there was no blinding in this study it is not clear that lack of blinding had an impact on the outcomes assessed (mean fetal blood volume and haematocrit levels). It is not clear whether lack of blinding may have affected other aspects of care
Incomplete outcome data (attrition bias) All outcomes	Low risk	46 mother-infant pairs were randomised and all infants appeared to be accounted for in the analysis. Although 3/23 allocated to

Aladagandy 2006 (*Continued*)

		delayed clamping actually had early clamping (1 due to short cord, 2 asked for by neonatologist) there was an ITT analysis
Selective reporting (reporting bias)	High risk	No clinical outcomes were reported. It was stated that "clinical outcomes were not analyzed", implying they were collected. Baezinger 2007 which was a subset of the same multicentre study reported outcomes were "blood volume, need for red cell transfusion, and respiratory and neurological complications"
Other bias	Unclear risk	The study was stratified to reduce baseline imbalance.

Baezinger 2007

Methods	Randomised controlled trial, stratified randomisation list for gestational age group (24-26, 27-29, 30-32) and type of delivery (vaginal/caesarean)
Participants	39 mother-infant pairs at 24 weeks to 32 weeks' gestation. Exclusions: known major malformation, haemolytic disease, intrauterine transfusion
Interventions	Control group: cord clamping immediately after birth (< 20 sec). Intervention group: cord clamping time 60-90 s, with infant held as low as possible for vaginal births, and 15 cm below the placenta at caesarean section. All mothers received syntocinon intravenously
Outcomes	Outcomes: cerebral oxygenation evaluated by NIRS at 4, 24 and 72 h of age, mechanical ventilation, death before discharge from hospital
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Part of the same multicentre study as Aladagandy 2006. Described as 'selected randomly and assigned to an experimental group or a control group by a central study co-ordinator'. The uneven group size (15 vs 24) is discussed as being due to central randomisation - this suggests that randomisation was not stratified by centre

Baezinger 2007 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Part of the same multicentre study as Aladagandy 2006. Described as 'selected randomly and assigned to an experimental group or a control group by a central study co-ordinator'
Blinding (performance bias and detection bias) All outcomes	Unclear risk	It was stated that the neonatologist assessing the infants was not aware of group assignment. It is not clear whether lack of blinding of participants would affect the outcome measured in this study; it is possible that lack of blinding of staff may have influenced other aspects of care
Incomplete outcome data (attrition bias) All outcomes	High risk	This report states 39 infants were enrolled. However, group sizes were not balanced. There were missing data for some outcomes.
Selective reporting (reporting bias)	High risk	This study was part of a larger multicentre study. The outcome reported here was collected just for this subset. The outcomes in the main study were "blood volume, need for red cell transfusion, and respiratory and neurological complications", but these data are not reported
Other bias	Unclear risk	Uneven group size although the characteristics of the groups appeared similar

Hofmeyr 1988

Methods	Randomised controlled trial, randomisation cards, stratified by birthweight < 1500 g
Participants	38 mother-infant pairs, judged to be < 35 weeks' gestation and in advanced labour Exclusions: multiple pregnancies.
Interventions	Control: cord clamping immediately after birth. Intervention 1: cord camping delayed for 60 sec. Intervention 2: cord clamping delayed for 60 sec and ergometrine given at delivery
Outcomes	Outcomes: PVH/IVH assessed by cerebral ultrasound 6-72 h after birth, Apgar score at 5 min, birthweight, systolic blood pressure at 5 minutes, cord blood gas, death
Notes	As outcome for the 2 intervention groups was reported to be similar, they were combined in the reported analysis. Outcome data for these 2 intervention groups were not reported separately. South Africa

Hofmeyr 1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Allocation by "randomisation cards". No further information was provided on methods.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of the intervention was not possible. Knowledge of group allocation may have influenced other aspects of clinician behaviour, and assessment of some outcomes. Ultrasound examination was blind to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	38 mother-infant pairs were randomised. All women and babies appeared to be accounted for in the analyses
Selective reporting (reporting bias)	Low risk	Data for the outcomes listed in methods are reported. Assessment of risk of bias from published paper
Other bias	Unclear risk	There was some baseline imbalance between the groups, suggesting those allocated delayed clamping might have been at higher risk of IVH

Hofmeyr 1993

Methods	Randomised controlled trial, randomised sealed cards.
Participants	86 mother-infant pairs, with the woman expected to give birth to an infant weighing < 2000 g. Exclusion: cord around the neck.
Interventions	Control: cord clamped shortly after delivery, according to usual practice. Intervention: cord clamping time 60-120 sec, with the infant held at the level of the uterus for vaginal births and the infant held just above the level of the uterus for caesarean section (on the mothers' thighs)
Outcomes	Outcomes: death of the baby, PVH/IVH assessed by cerebral ultrasound 6-72 h after birth, Apgar score at 5 minutes, cord-pH, bilirubin

Hofmeyr 1993 (*Continued*)

Notes	8 infants allocated delayed clamping had the cord clamped early, either due to cord round the neck, or need for resuscitation. South Africa

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised sealed cards", no further information.
Allocation concealment (selection bias)	Unclear risk	"randomised sealed cards", no further information.
Blinding (performance bias and detection bias) All outcomes	Low risk	For the main outcomes there is low risk of bias. Blinding is not necessary for death, and the ultrasound to assess PVH/IVH was blind to study group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were accounted for in the analysis and analysis was according to randomisation
Selective reporting (reporting bias)	Unclear risk	Bilirubin was reported for only 30 infants.
Other bias	Low risk	Groups appeared similar at baseline. No other bias identified

Hosono 2008

Methods	Sealed numbered opaque envelopes.
Participants	40 mother-infant pairs as 24-28 weeks' gestation, and admitted at least 6 h before enrolment Exclusions: multiple pregnancies, major congenital anomalies or chromosomal anomalies, hydrops fetalis
Interventions	Control group: cord clamped immediately. Intervention group: infant placed below or at the level of the placenta and about 20 cm of the umbilical cord milked vigorously towards umbilicus 2-3 times (estimated speed 20 cm/sec)
Outcomes	Primary outcomes: not needing transfusion and total number of red blood cell transfusions. Secondary outcomes: haemoglobin and blood pressure on admission, polycythaemia, IVH, IVH grade 3 or 4, patent ductus, gut perforation, death

Hosono 2008 (*Continued*)

Notes	EPO from 3rd week onwards in both groups. Strict guidelines for indication of red cell transfusion depending on age and illness status. 63 women were assessed for eligibility A secondary analysis of blood pressure and urine output at 120 h of life has been reported, and it is unclear if this was prespecified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomly selected', no further information.
Allocation concealment (selection bias)	Unclear risk	Serially numbered opaque envelopes opened just before delivery. It was not stated if any envelopes were unaccounted for, or if they were opened in the correct order. Also as sequence generation is unknown it is possible the next allocation could be predicted
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of the intervention was not possible. Staff providing care may have modified their behaviour according to randomisation group. Some of the outcomes depended on clinical decisions that may have been affected by knowledge of group status, However, other outcomes are unlikely to have been affected by lack of blinding (e.g. infant death)
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 mother-infant pairs were randomised and there was no apparent loss to follow-up for the babies
Selective reporting (reporting bias)	Low risk	Risk of bias assessment from published study reports.
Other bias	Low risk	Groups appeared balanced at baseline. Other bias was not apparent

Kinmond 1993

Methods	Randomised controlled trial, 'sealed envelopes', no further information
Participants	36 mother-infant pairs, > 27 to < 33 weeks' gestation, vaginal delivery. Exclusions: haemolytic disease, major congenital malformations

Kinmond 1993 (*Continued*)

Interventions	Intervention group: positioning 20 cm below the introitus and cord clamped at 30 sec. Control group: management at the attendant's discretion. An observer recorded distance baby held relative to introitus time and time of cord clamping
Outcomes	Outcomes: initial packed red cell volume, peak serum bilirubin, transfusion requirement, respiratory impairment, arterial-alveolar oxygen ratio, duration of oxygen
Notes	For control group, mean time to cord clamping 10 sec, clamping within 20 sec for 18/19 and at 25 sec for 1. Scotland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Participants were "randomised immediately before delivery by means of sealed envelopes". Not clear if envelopes opaque or sequentially numbered or that all envelopes were accounted for.
Blinding (performance bias and detection bias) All outcomes	High risk	There was no mention of blinding in this study, although it is not clear how lack of blinding would have affected those outcomes measured
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 36 participants were accounted for in the analysis.
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report. We did not have access to the protocol
Other bias	Unclear risk	The study was 'terminated when exogenous surfactant was introduced because this influenced our respiratory outcomes'. There was a "chance excess of boys" in the delayed clamping group (13/17 vs 7/19 controls)

Kugelman 2007

Methods	Randomised, controlled trial, randomly prepared cards in sealed opaque envelopes, stratification by mode of delivery, and risk of pregnancy (pre-eclampsia, PIH)
Participants	65 mother-infant pairs, at > 24 weeks and < 35 weeks' gestation. Multiple pregnancies included
Interventions	Control group:cord clamped immediately < 10 sec. Intervention group: positioning of infant 20-30 cm below level of introitus (vaginal delivery) or below level of the incision at caesarean section
Outcomes	Outcomes : baby death, blood transfusion. peak bilirubin, serum complement, immunoglobulins between group, risk, of sepsis, sepsis events, antibiotic therapy
Notes	Data on sepsis and infection reported as a secondary analysis, and unclear if it was prespecified. Israel

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random assignment "was performed with a system of randomly prepared cards in sealed nontransparent envelopes..."
Allocation concealment (selection bias)	Unclear risk	Random assignment "was performed with a system of randomly prepared cards in sealed nontransparent envelopes..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was described as masked. However, clinical staff at delivery would be aware of group assignment but staff were asked not to record group status in case notes in an attempt to reduce detection bias for some outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	65 participants were randomised and all appeared to be accounted for in the analyses
Selective reporting (reporting bias)	Unclear risk	Assessment from published study reports. Outcomes on infection and sepsis not mentioned in first report. Hence unclear whether all outcomes collected have been reported.
Other bias	Unclear risk	

McDonnell 1997

Methods	Randomised controlled trial, randomisation by sealed opaque envelope, stratified by vaginal or caesarean section, 26 to 29 weeks, 30 to 33 weeks
Participants	46 infants at 26 to 33 weeks, vaginal or caesarean section, single or multiple pregnancies Exclusions: severe fetal distress, IUGR with abnormal umbilical Doppler waveforms, fetal hydrops, fetal malformations, Rhesus incompatibility
Interventions	Control group: cord clamped immediately. Intervention group: cord clamped at 30 s, infant positioned between legs of the mother, Syntocinon at birth of the infant
Outcomes	Primary outcome: haematocrit at 4 h. Secondary outcomes: Apgar score, temperature on admission, requirement for ventilation, oxygen, surfactant, peak serum bilirubin, inotropic support, cerebral ultrasound, blood transfusion, death
Notes	Unit of randomisation was the infant - so for twin pregnancies each infant randomised separately. Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence not stated. There was stratification by gestational age and type of delivery
Allocation concealment (selection bias)	Unclear risk	"sealed opaque envelopes". Not clear if envelopes numbered and used sequentially
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not mentioned. It is possible that lack of blinding could influence other aspects of care and the recording of outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	46 infants were randomised. It was not clear how many infants were in each randomised group. It appeared that all were accounted for in the analysis, although it was not clear whether there were any missing data. Analysis was according to randomisation group.
Selective reporting (reporting bias)	Unclear risk	Assessment of risk of bias from published trial report. Several outcomes were not reported in the brief trial report although the authors offer other data on request

Other bias	Unclear risk	Groups appeared similar at baseline although there were more boys in the immediate clamping group (15 vs 9, denominators not clear)

Mercer 2003

Methods	Randomised controlled trial, randomisation by sealed opaque envelopes
Participants	32 mother-infant pairs < 32 weeks, vaginal or caesarean section delivery. Exclusion: obstetrician's refusal to participate, major congenital anomalies, multiple gestations, intend to withhold care, severe maternal illnesses, placenta abruption or previa
Interventions	Control group: cord clamped between 5-10 sec after delivery. Intervention group: at birth infant held 10 to 15 inches below the level of the placenta in vaginal deliveries or below the incision at caesarean section. Cord clamped at 30-45 sec
Outcomes	Primary outcome: mean arterial blood pressure on arrival in the neonatal unit. Secondary outcomes: Apgar scores, initial blood sugars, initial haematocrit, mean blood pressure over 4 h of life, 12 h, number of volume expanders in 12 h of life, SNAPPE II scores, serum bilirubin levels, days on ventilation or oxygen, IVH, suspected necrotising enterocolitis, days on ventilation or oxygen, oxygen use at 36 weeks and at discharge, volume of blood transfusions
Notes	USA.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"system of randomly prepared cards in sealed nontransparent envelopes."
Allocation concealment (selection bias)	Unclear risk	"system of randomly prepared cards in sealed nontransparent envelopes."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	It is not clear whether lack of blinding would have had an effect on the outcomes measured. There was an attempt to achieve blinding for some of the outcomes assessed as staff were requested not to record group assignment on case notes
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 participants were randomised and all appeared to be accounted for in the analysis. 2 babies in the delayed clamping group were not treated according to protocol but they

		were analysed according to randomisation
Selective reporting (reporting bias)	Unclear risk	Assessment from published study report.
Other bias	Low risk	Groups appeared similar at baseline. Other bias not apparent

Mercer 2006

Methods	Randomised controlled trial, randomisation by sealed opaque envelope, computer-generated number system random number system, stratification by gestation: 24-27 and 28-32 weeks
Participants	72 mother-infant pairs < 33 weeks, vaginal or caesarean section delivery. Exclusions: obstetrician's refusal to participate, major congenital anomalies, multiple gestations, intend to withhold care, severe maternal illnesses, placenta abruption or previa
Interventions	Control group: cord clamped between 5-10 sec after delivery. Intervention group: at birth infant held 10 to 15 inches below the level of the placenta in vaginal deliveries or below the incision at caesarean section. Cord clamped at 30-45 sec
Outcomes	Primary outcome: broncho-pulmonary dysplasia (defined as oxygen therapy at 36 weeks) . Secondary outcomes: death, Apgar scores, temperature on arrival at neonatal unit, highest serum bilirubin level, initial and hourly blood pressure for 4 h, initial haematocrit, suspected necrotising enterocolitis, IVH, late onset sepsis, retinopathy of prematurity, neurodevelopment at age 7 months
Notes	58/67 (87%) alive at discharge from hospital assessed at age 7 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A statistician who was not involved in the trial developed a computer-generated random number system. Block-stratified randomisation was used..." to take account of gestational age
Allocation concealment (selection bias)	Low risk	"Two sets of cards labelled for randomisation were enclosed in sequenced, opaque envelopes containing group assignment..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was not blinded although the groups status was not recorded on case notes in an attempt to reduce detection bias

Mercer 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	72 were randomised (36 in each group) Although there were some protocol violations but analysis was according to randomisation group. There were 3 early deaths in the immediate cord clamping group and this group was then excluded from subsequent analysis as they were no longer eligible to experience outcomes; this may have introduced bias due to competing outcomes. By 7 months there had been 5 deaths and of the 67 remaining 58 were followed up for longer-term outcomes
Selective reporting (reporting bias)	Unclear risk	Risk of bias assessment from published study report.
Other bias	Low risk	No baseline imbalance between groups apparent. Other bias not identified

Nelle 1998

Methods	Randomised controlled trial. Randomisation by sealed opaque envelopes
Participants	19 infants < 1500 g. Born by caesarean section.
Interventions	Control group: cord clamped immediately after birth. Intervention: cord clamping after 30 sec and positioning of the infant 30 cm below placenta
Outcomes	Outcomes: mean arterial blood pressure, left ventricular output, mean cerebral blood flow velocity, haemoglobin, haematocrit, systemic and cerebral haemoglobin transport, volume expansion during the first 24 h
Notes	Reported as abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Sealed, opaque envelopes (information provided by the author)

Nelle 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding. Not clear whether outcomes would be affected by lack of blinding. Other aspects of care may have been affected by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear whether full data were available for all participants
Selective reporting (reporting bias)	Unclear risk	Reported in brief abstract.
Other bias	Unclear risk	Very little information on study methods.

Oh 2002

Methods	Randomised controlled trial.
Participants	33 infants 24-28 weeks.
Interventions	Control group: immediate cord clamping < 5 s. Intervention group: delayed cord clamping 30-45 s.
Outcomes	Primary outcome: haematocrit at 4 h. Secondary outcomes: resuscitation, Apgar score, blood pressure during the first 12 h, IVH, necrotising enterocolitis, retinopathy of prematurity, late onset sepsis, patent ductus arteriosus, blood transfusions
Notes	Published as abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by phone call to external randomisation service
Allocation concealment (selection bias)	Low risk	Randomisation by external telephone randomisation service.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The study was not blinded although it was stated that efforts were made to "avoid revelation of grouping of infants to the attending physicians"
Incomplete outcome data (attrition bias) All outcomes	Low risk	33 were randomised and all appeared to be accounted for in the analysis
Selective reporting (reporting bias)	Unclear risk	Assessment from published reports. The main study paper was published in 2011; the first report (in abstract

		form) in 2002. It is not clear why so long elapsed before the publication of study findings.
Other bias	Unclear risk	No baseline imbalance between groups was apparent. Many eligible women were not randomised for logistic reasons. Other bias not identified

Rabe 2000

Methods	Randomised controlled trial, opaque sealed envelopes.
Participants	40 infants < 33 weeks. Exclusions: multiple pregnancies, Rhesus incompatibility, fetal hydrops, congenital malformation, Apgar < 3 at 0 minutes
Interventions	Control group: cord clamping at 20 sec. Intervention group: cord clamping at 45 s and positioning of the infant below the level of placenta, if possible, oxytocin at delivery of the first shoulder
Outcomes	Primary outcome: number of blood transfusions during first 6 weeks of life. Secondary outcomes: Apgar score, temperature on admission, blood pressure at 1, 4 and 24 h, volume resuscitation during first 24 h, inotropic support, degree of respiratory distress, IVH, patent ductus arteriosus, phototherapy
Notes	England.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	"by opening a sealed dark envelope". Not clear if envelopes were opened in a sequential order.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was an attempt to blind outcome assessors (group status was not recorded in notes). It was not clear whether lack of blinding affected clinical care or decisions that may have influenced outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	40 participants were randomised and 39 were included in the analysis. 1 baby in the late clamping group had cord clamping at 30 sec due to clinical concern, and was excluded from the analysis

Rabe 2000 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Assessment of bias from published study report.
Other bias	Low risk	Other bias not apparent. Study groups appeared similar at baseline

Strauss 2008

Methods	Randomised controlled trial. Stratified by gestation (< 30 weeks, > 30 weeks). The main outcomes for this study were neonatal haematological measures. As these were not possible to measure in babies < 30 weeks, 53 infants recruited before 30 weeks' gestation are excluded
Participants	158 infants < 36 weeks' gestation. Of whom 105 30-36 weeks. Exclusion: congenital abnormality.
Interventions	Control group: cord clamping immediately within 2-5 sec (not exceeding 15 sec). Intervention group: vaginal delivery: infant positioned 10 to 12 inch below introitus of the mother, cord clamped 3-5 cm from infant's abdomen at 60 s. Caesarean section: infant positioned beside the supine mother's thigh and cord clamped as above
Outcomes	Primary outcome: neonatal red cell volume/mass. Secondary outcome: reduction in red cell blood transfusion by 50%, Apgar, death, IVH
Notes	Infants < 30 weeks randomised to delayed cord clamping had immediate cord clamping and placental blood harvesting for re-transfusion within 24 h after birth. This group of infants is not further recorded in the publication. The study data on 30-36 weeks' gestation babies is reported. USA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers. Stratified by gestation (< 30 weeks, > 30 weeks)
Allocation concealment (selection bias)	Unclear risk	"written instructions in sealed envelopes opened immediately before delivery." Not clear whether envelopes numbered and opaque.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Because the focus of this trial was on haematological outcomes it is unlikely that lack of blinding of women had an impact on outcomes. It is possible staff who were aware of group assignment may had altered other aspects of care. It was stated that labo-

		ratory staff were blind to group assignment Lack of blinding may have influenced other aspects of clinician behaviour and the recording of outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition and missing data were not clearly described. For babies less than 30 weeks' gestation there was major loss to follow-up (but data for these infants have not been included in the review as they did not undergo true early clamping). Of 105 deliveries after 30 weeks all seemed to be accounted for in the analysis although the authors reported some missing data for some variables
Selective reporting (reporting bias)	High risk	In this study the protocol was different for babies of different gestational ages and in the main study paper results were reported for infants greater than 30 weeks only. Assessment of risk of bias from published study report.
Other bias	Unclear risk	The study groups were not balanced in terms of size (60 in the immediate clamping group and 45 delayed). The reason for uneven group size for births < 30 weeks' gestation was not explained

Ultee 2008

Methods	Randomised controlled trial, blinded box with loose papers. 4 (10%) post randomisation exclusions. Data for 37/41 (90%) reported, with 34/41 (83%) for follow-up at 10 weeks
Participants	41 mother-infant pairs 34-36 weeks' gestation, vaginal delivery only. Exclusion: congenital abnormality, maternal diabetes, expected serious perinatal pathology, and twins. Reasons for exclusion included post randomisation criteria: Apgar scores < 5 at 1 min, <7 at 5 min
Interventions	Control group: infant placed on mother's abdomen and cord clamped within 30 s (mean 13.4 s -(SD 5.6s)) Intervention group: Infant placed on mother's abdomen and cord clamped after 180 s)
Outcomes	Outcomes: blood glucose levels at 1, 2 and 3 h of age, haemoglobin and haematocrit at 1 h and 10 weeks. Ferritin at 10 weeks.

Notes	Control group < 30 s, but actual time < 20 sec. The Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No pre-specified sequence.
Allocation concealment (selection bias)	High risk	"... subjects were randomly assigned ... by pulling the category out of a blinded box with loose papers". The same person carried out randomisation, delivered clinical care and collected some outcome data
Blinding (performance bias and detection bias) All outcomes	High risk	It was stated that some clinical staff were unaware of groups assignment. However, the same person delivered care and assessed Apgar score and low score was a reason for post-randomisation exclusion (although this would not have been assessed until AFTER the designated intervention period)
Incomplete outcome data (attrition bias) All outcomes	High risk	41 were randomised and outcome data were available for 37. There were 4 post-randomisation exclusions, 2 because of protocol violations and a further 2 because of a low Apgar score at 1 and 5 minutes. Exclusion because of an outcome (low Apgar) raises serious concern about potential for bias No ITT analysis.
Selective reporting (reporting bias)	Unclear risk	Assessment of bias from published study report.
Other bias	Low risk	Groups appeared similar at baseline and other bias was not apparent

EPO: erythropoietin
h: hours
ITT: intention to treat
IUGR: intrauterine growth restriction
IVH: intraventricular haemorrhage
min: minutes

NIRS: near-infrared spectroscopy
PIH: pregnancy-induced hypertension
PVH: periventricular haemorrhage
SD: standard deviation
sec: seconds
vs: versus

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

Study	Reason for exclusion
Aitchison	Trial plan only. No data recorded with this citation.
Frank 1967	This was a non-randomised study in which delayed cord clamping was defined as that performed after the second breath
Ibrahim 2000	Randomised trial with adequate concealment. The intervention consisted of a delay in cord clamping of 20 seconds. Control infants had their cord clamped immediately. The study was excluded for the reason that the intervention group at a cord clamping time of less than 30 seconds. Delay of cord clamping was defined in the protocol for this review to be of at least 30 seconds duration
Narendra 1998	Abstract only, further details on patients and study not available from the authors
Rabe 2011	Randomised study of 58 preterm infants between 24 and 32 +6/7 weeks' gestation comparing 2 interventions: group with 30 seconds of delayed cord clamping, and group with 4 times milking the cord. This type of comparison does not match the current comparison groups in this review
Saigal 1972	Sequential allocation procedure, which is not a randomised trial
Saigal 1977	Sequential allocation procedure, which is not a randomised trial
Spears 1966	Randomisation procedure was unclear. Gestational age of the low birthweight infants was not given
Taylor 1963	Inadequate randomisation. Largely term infants.
Zisovska 2008	Inadequate randomisation. Hardly any data on the study group in published abstract

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

Backes 2011

Methods	
Participants	
Interventions	

Backes 2011 (*Continued*)

Outcomes	
Notes	

Chu 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Gokmen 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

March 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Oh 2011

Methods	
Participants	
Interventions	

Oh 2011 (*Continued*)

Outcomes	
Notes	

Pongmee 2010

Methods	Randomised controlled trial.
Participants	43 infants < 35 weeks' gestation. Exclusions: placenta praevia, placental abruption, gestational diabetes, intrauterine growth restriction, twin-twin transfusion syndrome, major congenital abnormalities
Interventions	Control group: immediate cord clamping. Intervention group: 2 x milking of cord along 30 cm after cord cutting
Outcomes	Primary outcomes: initial haematocrit, need for blood transfusion, morbidity Secondary outcome: haematocrit at 2 weeks of age and at term postmenstrual age
Notes	Study published as abstract only, awaiting full publication.

Sekhavat 2008

Methods	Randomised controlled trial, allocation method not mentioned in abstract
Participants	52 infants of 26 to 34 weeks' gestation.
Interventions	Control group: immediate cord clamping at 10 to 15 seconds. Intervention group: delayed cord clamping at 30 to 60 seconds
Outcomes	Primary outcomes: blood pressure, haematocrit and blood glucose Secondary outcomes: typical complications from prematurity.
Notes	Study published as abstract only, awaiting full trial publication

Sommers 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Sommers 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Strauss 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	

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

Holland 1998

Trial name or title	Placento-fetal (autologous) Transfusion at birth in infants born preterm: a randomised, controlled trial
Methods	
Participants	Infants < 33 weeks' gestation.
Interventions	Positioning of the infant below the placenta as far as possible. Vaginal delivery: delay of cord clamping 40 to 90 seconds. Caesarean section: cord clamping 40 to 90 seconds after syntocinon
Outcomes	Primary outcome: median arterial/alveolar PO2 ratio over the first 24 hours of life. Secondary outcome: a. CRIB score b. RCV c. Transfusion requirements.
Starting date	1998
Contact information	BM Holland Queen Mother's Hospital Glasgow G3 8SH

Holland 1998 (*Continued*)

Notes	Trial completed in 2001. Results not available. 2 centres have published part of their centre's results (Aladagandy 2006; Baezinger 2007).

Hosono 2010

Trial name or title	A multicentre randomised control study of the effect of umbilical cord milking in avoiding red cell transfusions in extremely immature infants
Methods	Randomised controlled multicentre trial.
Participants	Preterm infants with recruitment beginning in 2008.
Interventions	Details not available.
Outcomes	Avoidance of red cell transfusion.
Starting date	Currently recruiting.
Contact information	Dr S Hosono.
Notes	Ongoing trial, details published in trial registration report

Ping 2010

Trial name or title	Immediate versus delayed cord clamping on newborns.
Methods	Randomised controlled trial several arms.
Participants	Preterm and term infants. Exclusion: stillbirths.
Interventions	Normal births: control group1: clamping the cord within 10 seconds of delivery; intervention 1. delayed cord clamping after 90 seconds; intervention 2: delay cord clamping until pulsations cease. Asphyxiated infants: control group 2: clamping the cord within 10 seconds of delivery; intervention 3: delay cord clamping until pulsations cease and resuscitate infant during this time
Outcomes	Not specified in trials register.
Starting date	September 2009.
Contact information	Dr Zhang Hong Yu, Hainan Medical Centre.
Notes	Ongoing trial.

RCV: red cell volume

DATA AND ANALYSES

Comparison 1. More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infant death (up to discharge/variable)	13	668	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.31, 1.28]
2 Severe intraventricular haemorrhage	6	305	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.23, 1.96]
3 Periventricular leukomalacia	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.19, 5.56]
4 Apgar score at 1 minute	3	184	Mean Difference (IV, Random, 95% CI)	0.30 [-0.52, 1.12]
5 Apgar score at 5 minutes	3	184	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.20, 0.43]
6 Apgar score at 10 minutes	1	39	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.05, 1.05]
7 Apgar score at 5th minute < 8	3	161	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.45, 1.62]
8 Temperature on admission (degrees Celsius)	3	143	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.03, 0.31]
9 Respiratory distress syndrome	3	115	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.89, 1.50]
10 Severe respiratory distress syndrome	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.20, 3.07]
11 Surfactant treatment	2	85	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.56, 2.93]
12 Ventilated for respiratory distress syndrome	5	265	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.31]
13 Oxygen supplementation at 28 days	2	76	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.15, 1.59]
14 Oxygen supplementation at 36 weeks	5	209	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.13]
15 Transfused for low blood pressure	4	130	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.24, 1.11]
16 Mean arterial blood pressure after birth	2	97	Mean Difference (IV, Fixed, 95% CI)	3.52 [0.60, 6.45]
17 Mean arterial blood pressure at 4 h of age	2	111	Mean Difference (IV, Fixed, 95% CI)	2.49 [0.26, 4.72]
18 Mean arterial blood pressure at 24 h of age	1	38	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-6.44, 5.84]
19 Inotropics for low blood pressure	4	158	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.23, 0.77]
20 Patent ductus arteriosus	5	223	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.60, 1.81]
21 Intraventricular haemorrhage (all grades)	10	539	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.41, 0.85]
22 Necrotising enterocolitis	5	241	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.43, 0.90]
23 Transfused for anaemia	7	392	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.46, 0.81]
24 Number of transfusions	5	210	Mean Difference (IV, Fixed, 95% CI)	-1.26 [-1.87, -0.64]
25 Serum bilirubin peak (mmol/litre)	7	320	Mean Difference (IV, Fixed, 95% CI)	15.01 [5.62, 24.40]
26 Hyperbilirubinemia (treated)	3	180	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.94, 1.55]

27 Mean regional tissue oxygenation of the brain at 4 h of age	1	39	Mean Difference (IV, Fixed, 95% CI)	6.44 [5.47, 7.41]
28 Mean regional tissue oxygenation of the brain at 24 h of age	1	38	Mean Difference (IV, Fixed, 95% CI)	4.29 [3.44, 5.14]
29 Haematocrit at birth or 1 hour (%)	7	318	Mean Difference (IV, Random, 95% CI)	3.26 [1.79, 4.74]
30 Haematocrit at 4 hours of life (%)	5	173	Mean Difference (IV, Fixed, 95% CI)	5.40 [3.62, 7.17]
31 Haematocrit at 24 hours after birth (%)	3	199	Mean Difference (IV, Fixed, 95% CI)	3.28 [1.34, 5.22]
32 Blood volume after birth	2	81	Mean Difference (IV, Random, 95% CI)	8.41 [2.14, 14.67]
33 Red cell mass after birth	1	35	Mean Difference (IV, Fixed, 95% CI)	5.30 [0.05, 10.55]
34 Sepsis	2	137	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.05, 2.11]
35 Retinopathy of prematurity	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.39, 1.52]
36 Cord pH	3	123	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.03]
37 Length of stay	1	32	Mean Difference (IV, Fixed, 95% CI)	-16.4 [-38.06, 5.26]

Comparison 2. More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infant death (up to discharge/variable)	13	668	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.31, 1.28]
1.1 Delayed clamping	12	628	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.28, 1.36]
1.2 Cord milking	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.57]
2 Severe intraventricular haemorrhage	6	305	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.23, 1.96]
2.1 Delayed clamping	5	265	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.20, 3.66]
2.2 Cord milking	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.43]
3 Periventricular leukomalacia	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.19, 5.56]
3.1 Delayed clamping	1	31	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [0.14, 72.69]
3.2 Cord milking	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.08]

Comparison 3. More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infant death (up to discharge/variable)	13	668	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.31, 1.28]
1.1 Low risk of bias	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.10, 1.59]

1.2 Risk of bias unclear or high	11	563	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.32, 1.73]
2 Severe intraventricular haemorrhage	6	305	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.23, 1.96]
2.1 Low risk of bias	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.92]
2.2 Risk of bias unclear or high	5	233	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.24, 2.36]
3 Periventricular leukomalacia	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.19, 5.56]
3.1 Low risk of bias	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Risk of bias unclear	2	71	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.19, 5.56]

Analysis 1.1. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 1 Infant death (up to discharge/variable).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 1 Infant death (up to discharge/variable)

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mercer 2003	0/16	0/16		0.0 [0.0, 0.0]
Kinmond 1993	0/17	0/19		0.0 [0.0, 0.0]
Strauss 2008	0/45	0/60		0.0 [0.0, 0.0]
Ultee 2008	0/18	0/19		0.0 [0.0, 0.0]
Hofmeyr 1988	5/24	0/14		6.60 [0.39, 111.10]
Hofmeyr 1993	1/40	1/46		1.15 [0.07, 17.80]
Kugelman 2007	0/30	1/35		0.39 [0.02, 9.16]
Rabe 2000	0/19	1/20		0.35 [0.02, 8.10]
McDonnell 1997	0/23	2/23		0.20 [0.01, 3.95]
Baezinger 2007	0/15	3/24		0.22 [0.01, 4.04]
Oh 2002	2/16	3/17		0.71 [0.14, 3.70]
Hosono 2008	2/20	3/20		0.67 [0.12, 3.57]
Mercer 2006	0/36	3/36		0.14 [0.01, 2.67]
Total (95% CI)	**319**	**349**		**0.63 [0.31, 1.28]**

Total events: 10 (More placental trans), 17 (Less placental trans)

Heterogeneity: Chi^2 = 5.14, df = 8 (P = 0.74); I^2 =0.0%

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 2 Severe intraventricular haemorrhage.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 2 Severe intraventricular haemorrhage

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mercer 2003	0/16	0/16		0.0 [0.0, 0.0]
Rabe 2000	0/19	0/20		0.0 [0.0, 0.0]
Hofmeyr 1988	2/23	0/13		2.92 [0.15, 56.51]
Mercer 2006	0/36	1/36		0.33 [0.01, 7.92]
Hofmeyr 1993	1/40	2/46		0.58 [0.05, 6.11]
Hosono 2008	2/20	4/20		0.50 [0.10, 2.43]
Total (95% CI)	**154**	**151**		**0.68 [0.23, 1.96]**

Total events: 5 (More placental trans), 7 (Less placental trans)

Heterogeneity: Chi^2 = 1.28, df = 3 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 3 Periventricular leukomalacia.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 3 Periventricular leukomalacia

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McDonnell 1997	1/15	0/16		19.5 %	3.19 [0.14, 72.69]
Hosono 2008	1/20	2/20		80.5 %	0.50 [0.05, 5.08]
Total (95% CI)	**35**	**36**		**100.0 %**	**1.02 [0.19, 5.56]**

Total events: 2 (More placental trans), 2 (Less placental trans)

Heterogeneity: Chi^2 = 0.87, df = 1 (P = 0.35); I^2 =0.0%

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 4 Apgar score at 1 minute.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

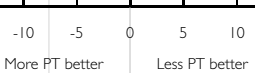
Outcome: 4 Apgar score at 1 minute

Study or subgroup	More placental trans N	Mean(SD)	Less placental trans N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Baezinger 2007	15	5 (2)	24	5 (2.67)		21.7 %	0.0 [-1.47, 1.47]
Hosono 2008	20	5.4 (2)	20	4.2 (1.8)		28.9 %	1.20 [0.02, 2.38]
Strauss 2008	45	7 (1.6)	60	7.1 (1.8)		49.4 %	-0.10 [-0.75, 0.55]
Total (95% CI)	**80**		**104**			**100.0 %**	**0.30 [-0.52, 1.12]**

Heterogeneity: Tau^2 = 0.24; Chi^2 = 3.64, df = 2 (P = 0.16); I^2 =45%

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

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 5 Apgar score at 5 minutes.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

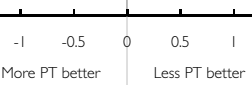
Outcome: 5 Apgar score at 5 minutes

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Baezinger 2007	15	8 (1.67)	24	8 (1.77)		8.1 %	0.0 [-1.10, 1.10]
Hosono 2008	20	7.3 (1.7)	20	6.9 (1.7)		8.9 %	0.40 [-0.65, 1.45]
Strauss 2008	45	8.4 (0.7)	60	8.3 (1.1)		82.9 %	0.10 [-0.25, 0.45]
Total (95% CI)	**80**		**104**			**100.0 %**	**0.12 [-0.20, 0.43]**

Heterogeneity: Chi^2 = 0.33, df = 2 (P = 0.85); I^2 =0.0%

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable

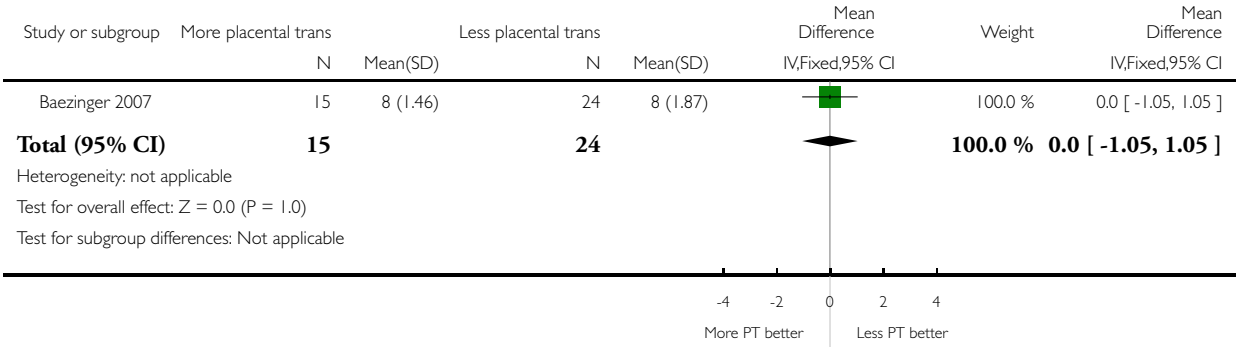


Analysis 1.6. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 6 Apgar score at 10 minutes.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 6 Apgar score at 10 minutes

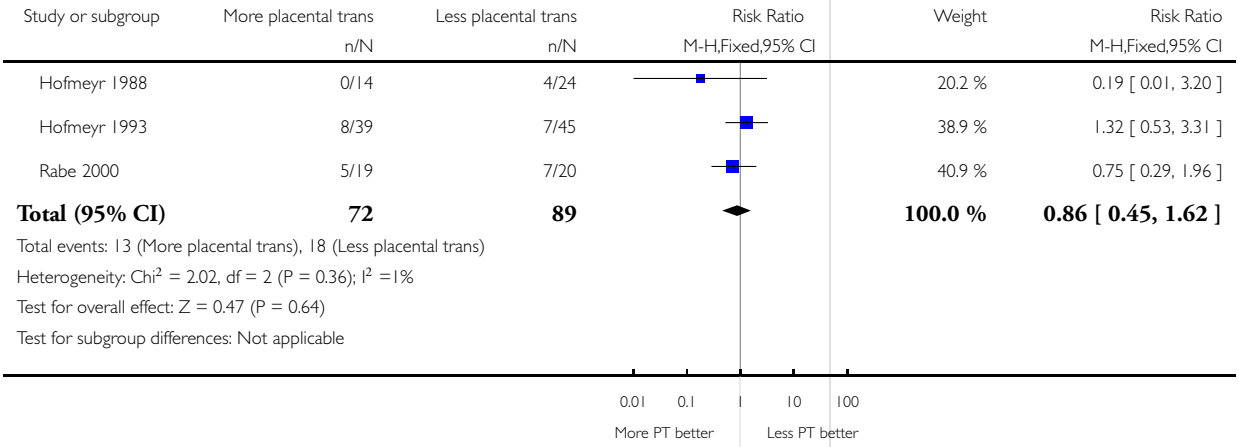


Analysis 1.7. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 7 Apgar score at 5th minute < 8.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 7 Apgar score at 5th minute < 8



Analysis 1.8. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 8 Temperature on admission (degrees Celsius).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

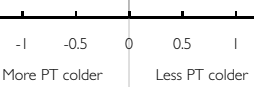
Outcome: 8 Temperature on admission (degrees Celsius)

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Mercer 2003	16	36.28 (0.55)	16	36.33 (0.55)		20.1 %	-0.05 [-0.43, 0.33]
Mercer 2006	36	36.17 (0.66)	36	36 (0.83)		24.3 %	0.17 [-0.18, 0.52]
Rabe 2000	19	37.1 (0.15)	20	36.9 (0.5)		55.6 %	0.20 [-0.03, 0.43]
Total (95% CI)	**71**		**72**			**100.0 %**	**0.14 [-0.03, 0.31]**

Heterogeneity: Chi^2 = 1.25, df = 2 (P = 0.54); I^2 =0.0%

Test for overall effect: Z = 1.63 (P = 0.10)

Test for subgroup differences: Not applicable

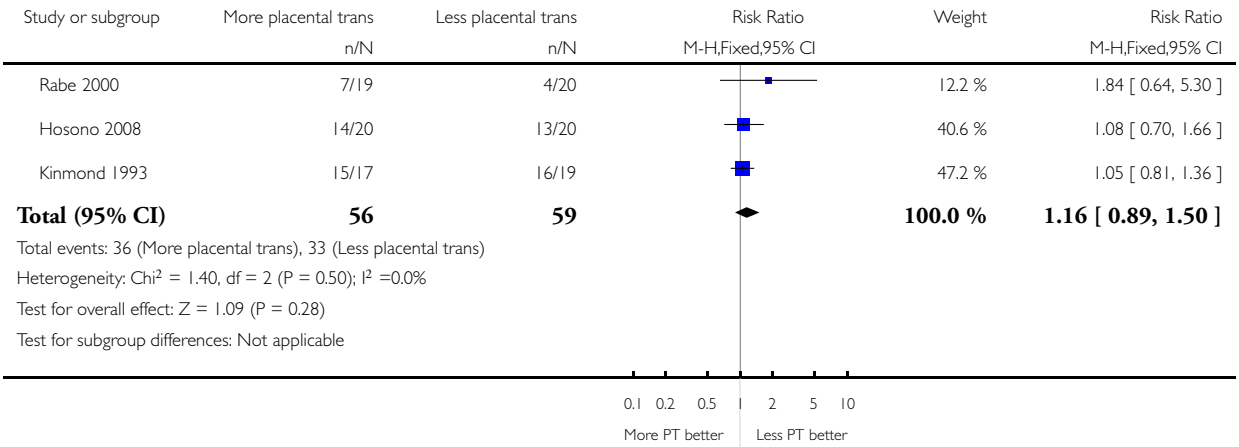


Analysis 1.9. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 9 Respiratory distress syndrome.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 9 Respiratory distress syndrome

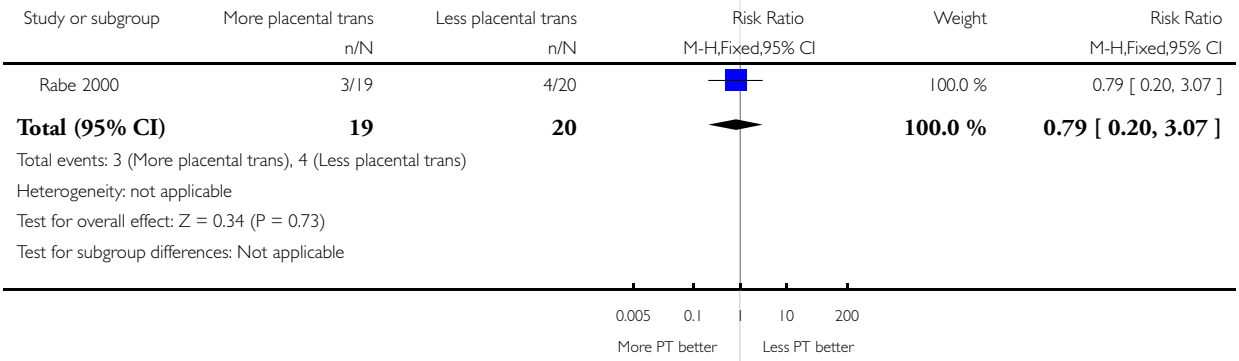


Analysis 1.10. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 10 Severe respiratory distress syndrome.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 10 Severe respiratory distress syndrome



Analysis 1.11. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 11 Surfactant treatment.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 11 Surfactant treatment

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rabe 2000	4/19	4/20		49.4 %	1.05 [0.31, 3.62]
McDonnell 1997	6/23	4/23		50.6 %	1.50 [0.49, 4.62]
Total (95% CI)	**42**	**43**		**100.0 %**	**1.28 [0.56, 2.93]**

Total events: 10 (More placental trans), 8 (Less placental trans)

Heterogeneity: $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0.0\%$

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 12 Ventilated for respiratory distress syndrome.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 12 Ventilated for respiratory distress syndrome

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Strauss 2008	3/45	7/60		13.5 %	0.57 [0.16, 2.09]
Rabe 2000	9/19	8/20		17.6 %	1.18 [0.58, 2.42]
McDonnell 1997	9/23	9/23		20.3 %	1.00 [0.49, 2.06]
Baezinger 2007	6/15	12/24		20.8 %	0.80 [0.38, 1.67]
Kinmond 1993	13/17	13/19		27.7 %	1.12 [0.75, 1.67]
Total (95% CI)	**119**	**146**		**100.0 %**	**0.97 [0.71, 1.31]**

Total events: 40 (More placental trans), 49 (Less placental trans)

Heterogeneity: Chi^2 = 1.71, df = 4 (P = 0.79); I^2 =0.0%

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 13 Oxygen supplementation at 28 days.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 13 Oxygen supplementation at 28 days

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinmond 1993	0/17	3/19		45.3 %	0.16 [0.01, 2.87]
Hosono 2008	3/20	4/20		54.7 %	0.75 [0.19, 2.93]
Total (95% CI)	**37**	**39**		**100.0 %**	**0.48 [0.15, 1.59]**
Total events: 3 (More placental trans), 7 (Less placental trans)					
Heterogeneity: Chi^2 = 0.97, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
Test for subgroup differences: Not applicable					

Analysis 1.14. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 14 Oxygen supplementation at 36 weeks.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 14 Oxygen supplementation at 36 weeks

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rabe 2000	3/19	3/20		10.3 %	1.05 [0.24, 4.59]
Oh 2002	3/13	3/13		10.6 %	1.00 [0.25, 4.07]
Hosono 2008	0/20	4/20		15.8 %	0.11 [0.01, 1.94]
Mercer 2003	5/16	9/16		31.7 %	0.56 [0.24, 1.29]
Mercer 2006	8/36	9/36		31.7 %	0.89 [0.39, 2.04]
Total (95% CI)	**104**	**105**		**100.0 %**	**0.69 [0.42, 1.13]**

Total events: 19 (More placental trans), 28 (Less placental trans)

Heterogeneity: Chi^2 = 2.76, df = 4 (P = 0.60); I^2 =0.0%

Test for overall effect: Z = 1.47 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 15 Transfused for low blood pressure.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 15 Transfused for low blood pressure

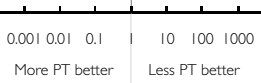
Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Hosono 2008	0/20	0/20		0.0 [0.0, 0.0]
Nelle 1998	2/11	7/8		0.21 [0.06, 0.75]
Rabe 2000	4/19	7/20		0.60 [0.21, 1.73]
Mercer 2003	5/16	6/16		0.83 [0.32, 2.18]
Total (95% CI)	**66**	**64**		**0.52 [0.24, 1.11]**

Total events: 11 (More placental trans), 20 (Less placental trans)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 2.97$, df = 2 (P = 0.23); $I^2 = 33\%$

Test for overall effect: Z = 1.70 (P = 0.090)

Test for subgroup differences: Not applicable

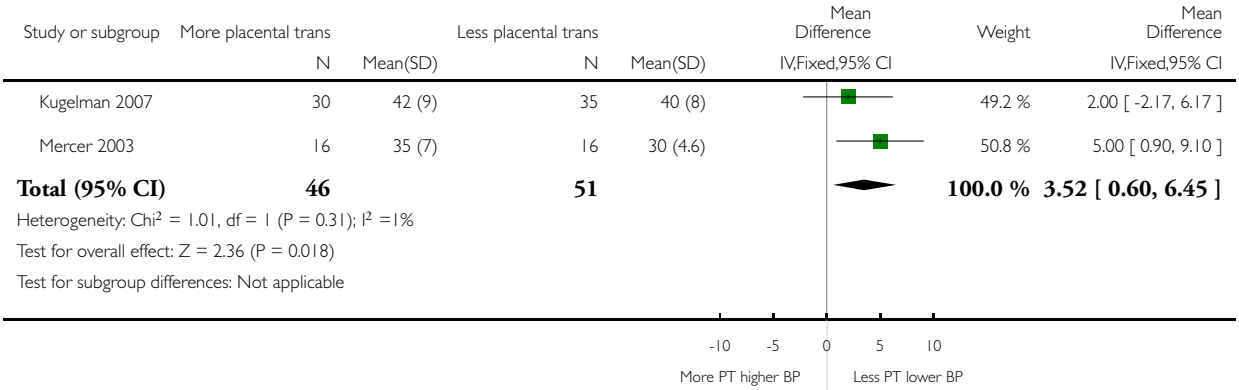


Analysis 1.16. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 16 Mean arterial blood pressure after birth.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 16 Mean arterial blood pressure after birth

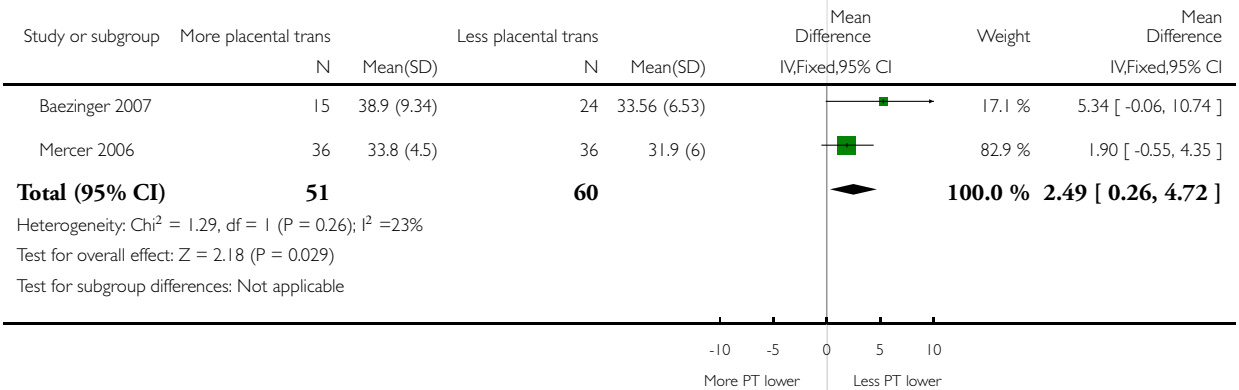


Analysis 1.17. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 17 Mean arterial blood pressure at 4 h of age.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 17 Mean arterial blood pressure at 4 h of age

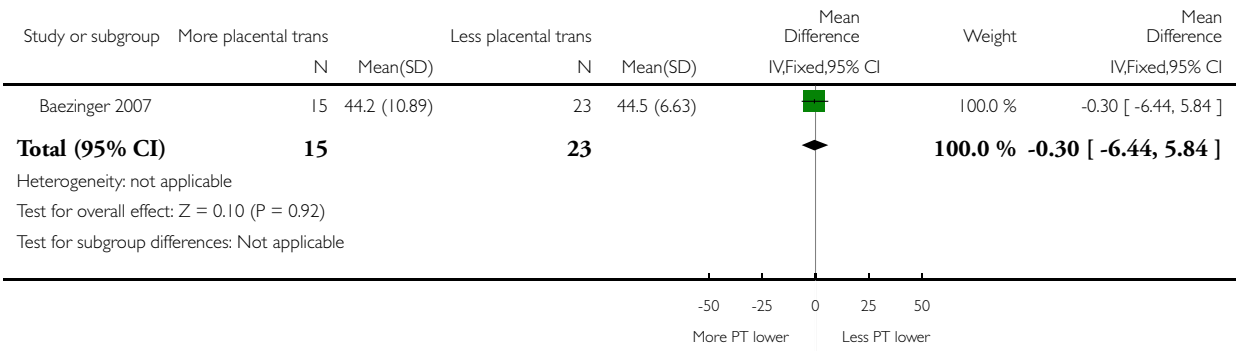


Analysis 1.18. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 18 Mean arterial blood pressure at 24 h of age.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 18 Mean arterial blood pressure at 24 h of age



Analysis 1.19. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 19 Inotropics for low blood pressure.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 19 Inotropics for low blood pressure

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Oh 2002	0/16	0/17		0.0 [0.0, 0.0]
Rabe 2000	0/19	2/20		0.21 [0.01, 4.11]
McDonnell 1997	2/23	3/23		0.67 [0.12, 3.62]
Hosono 2008	7/20	17/20		0.41 [0.22, 0.77]
Total (95% CI)	**78**	**80**		**0.42 [0.23, 0.77]**

Total events: 9 (More placental trans), 22 (Less placental trans)

Heterogeneity: $Chi^2 = 0.50$, df = 2 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 2.84 (P = 0.0045)

Test for subgroup differences: Not applicable

Analysis 1.20. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 20 Patent ductus arteriosus.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 20 Patent ductus arteriosus

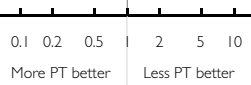
Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kugelman 2007	2/30	2/35		9.9 %	1.17 [0.17, 7.79]
Rabe 2000	2/19	2/20		10.5 %	1.05 [0.16, 6.74]
McDonnell 1997	3/23	3/23		16.1 %	1.00 [0.22, 4.45]
Oh 2002	7/16	5/17		26.0 %	1.49 [0.59, 3.74]
Hosono 2008	5/20	7/20		37.5 %	0.71 [0.27, 1.88]
Total (95% CI)	**108**	**115**		**100.0 %**	**1.04 [0.60, 1.81]**

Total events: 19 (More placental trans), 19 (Less placental trans)

Heterogeneity: Chi^2 = 1.18, df = 4 (P = 0.88); I^2 =0.0%

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 21 Intraventricular haemorrhage (all grades).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 21 Intraventricular haemorrhage (all grades)

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Strauss 2008	1/45	1/60		1.5 %	1.33 [0.09, 20.75]
McDonnell 1997	0/15	1/16		2.5 %	0.35 [0.02, 8.08]
Oh 2002	4/16	3/17		5.0 %	1.42 [0.37, 5.37]
Rabe 2000	1/19	3/20		5.1 %	0.35 [0.04, 3.09]
Kugelman 2007	2/30	4/35		6.4 %	0.58 [0.11, 2.96]
Mercer 2003	3/16	5/16		8.6 %	0.60 [0.17, 2.10]
Hosono 2008	3/20	5/20		8.6 %	0.60 [0.17, 2.18]
Hofmeyr 1993	8/40	11/46		17.7 %	0.84 [0.37, 1.87]
Hofmeyr 1988	8/23	10/13		22.1 %	0.45 [0.24, 0.85]
Mercer 2006	5/36	13/36		22.5 %	0.38 [0.15, 0.97]
Total (95% CI)	**260**	**279**		**100.0 %**	**0.59 [0.41, 0.85]**

Total events: 35 (More placental trans), 56 (Less placental trans)

Heterogeneity: Chi^2 = 4.55, df = 9 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 2.82 (P = 0.0048)

Test for subgroup differences: Not applicable

Analysis 1.22. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 22 Necrotising enterocolitis.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 22 Necrotising enterocolitis

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kugelman 2007	0/30	0/35		0.0 [0.0, 0.0]
Rabe 2000	0/19	1/20		0.35 [0.02, 8.10]
Oh 2002	2/16	4/17		0.53 [0.11, 2.51]
Mercer 2003	8/16	14/16		0.57 [0.34, 0.96]
Mercer 2006	14/36	20/36		0.70 [0.42, 1.16]
Total (95% CI)	**117**	**124**		**0.62 [0.43, 0.90]**

Total events: 24 (More placental trans), 39 (Less placental trans)

Heterogeneity: $Chi^2 = 0.48$, df = 3 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 2.53 (P = 0.011)

Test for subgroup differences: Not applicable

Analysis 1.23. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 23 Transfused for anaemia.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 23 Transfused for anaemia

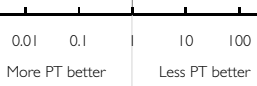
Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Strauss 2008	2/45	5/59		5.9 %	0.52 [0.11, 2.58]
Kugelman 2007	3/30	5/35		6.3 %	0.70 [0.18, 2.69]
McDonnell 1997	4/23	6/23		8.2 %	0.67 [0.22, 2.05]
Kinmond 1993	1/13	7/13		9.5 %	0.14 [0.02, 1.00]
Hosono 2008	7/20	14/20		19.0 %	0.50 [0.26, 0.97]
Rabe 2000	9/19	16/20		21.2 %	0.59 [0.35, 1.00]
Mercer 2006	18/36	22/36		29.9 %	0.82 [0.54, 1.24]
Total (95% CI)	**186**	**206**		**100.0 %**	**0.61 [0.46, 0.81]**

Total events: 44 (More placental trans), 75 (Less placental trans)

Heterogeneity: $Chi^2 = 4.50$, df = 6 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 3.46 (P = 0.00053)

Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 24 Number of transfusions.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 24 Number of transfusions

Study or subgroup	More placental trans N	Mean(SD)	Less placental trans N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Oh 2002	16	3.6 (3.8)	17	4.3 (4)		5.3 %	-0.70 [-3.36, 1.96]
Hosono 2008	20	1.7 (3)	20	4 (4.2)		7.4 %	-2.30 [-4.56, -0.04]
Mercer 2006	36	1.94 (3.1)	36	2.47 (3.7)		15.2 %	-0.53 [-2.11, 1.05]
Rabe 2000	19	1.2 (1.6)	20	2.4 (1.95)		30.3 %	-1.20 [-2.32, -0.08]
Kinmond 1993	13	0.46 (0.66)	13	1.91 (1.62)		41.8 %	-1.45 [-2.40, -0.50]
Total (95% CI)	**104**		**106**			**100.0 %**	**-1.26 [-1.87, -0.64]**

Heterogeneity: $Chi^2 = 1.97$, df = 4 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 4.01 (P = 0.000061)

Test for subgroup differences: Not applicable

Analysis 1.25. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 25 Serum bilirubin peak (mmol/litre).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 25 Serum bilirubin peak (mmol/litre)

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Oh 2002	13	162.44 (64.9)	13	133.38 (53)		4.2 %	29.06 [-16.49, 74.61]
Mercer 2003	16	140.2 (51.3)	16	138.51 (39.33)		8.8 %	1.69 [-29.98, 33.36]
Hosono 2008	20	139.4 (44.2)	20	132.6 (42.5)		12.2 %	6.80 [-20.07, 33.67]
Rabe 2000	19	149.6 (41.3)	20	118.5 (41.7)		13.0 %	31.10 [5.05, 57.15]
McDonnell 1997	23	222 (42)	23	211 (42)		15.0 %	11.00 [-13.27, 35.27]
Kugelman 2007	30	176.3 (47.9)	35	153.9 (39.33)		19.0 %	22.40 [0.87, 43.93]
Mercer 2006	36	172.71 (41.04)	36	162.45 (35.91)		27.8 %	10.26 [-7.55, 28.07]
Total (95% CI)	**157**		**163**			**100.0 %**	**15.01 [5.62, 24.40]**

Heterogeneity: Chi^2 = 3.70, df = 6 (P = 0.72); I^2 =0.0%

Test for overall effect: Z = 3.13 (P = 0.0017)

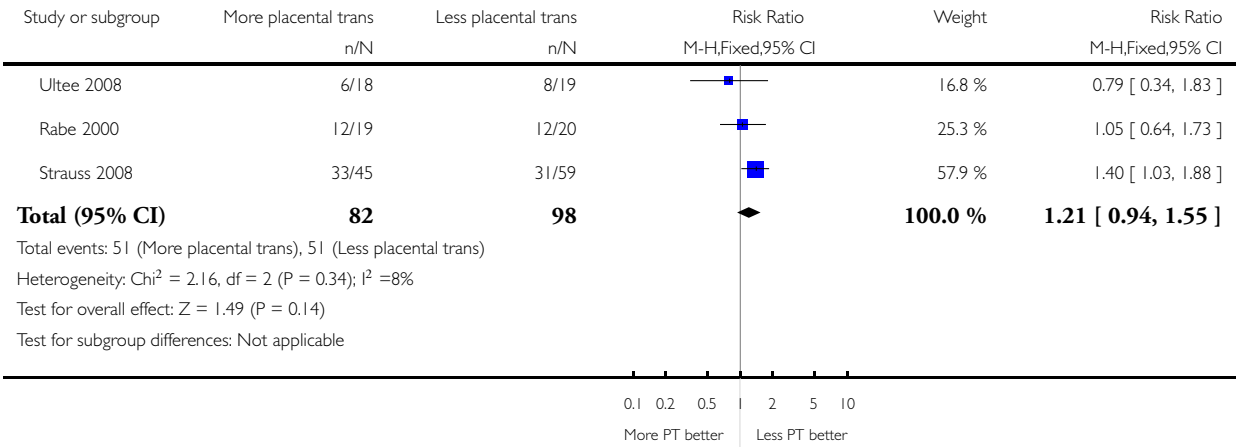
Test for subgroup differences: Not applicable

Analysis 1.26. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 26 Hyperbilirubinemia (treated).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 26 Hyperbilirubinemia (treated)

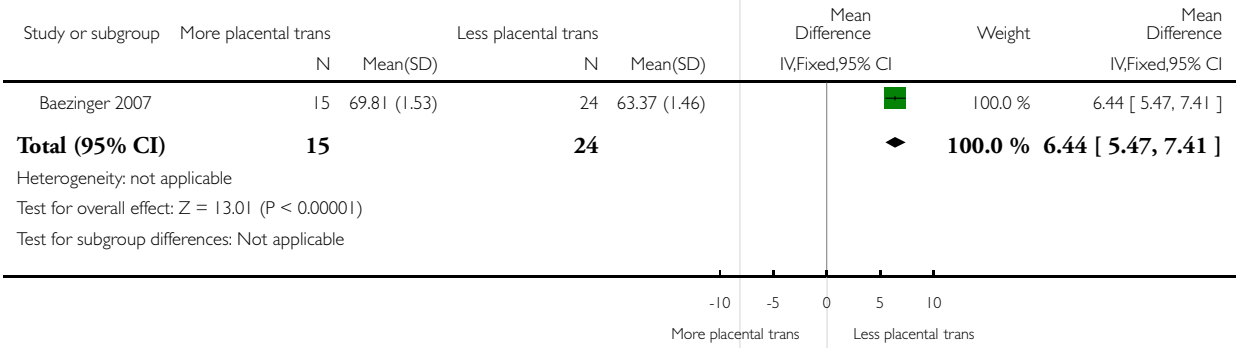


Analysis 1.27. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 27 Mean regional tissue oxygenation of the brain at 4 h of age.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 27 Mean regional tissue oxygenation of the brain at 4 h of age



Analysis 1.28. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 28 Mean regional tissue oxygenation of the brain at 24 h of age.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 28 Mean regional tissue oxygenation of the brain at 24 h of age

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Baezinger 2007	15	71.36 (1.34)	23	67.07 (1.26)		100.0 %	4.29 [3.44, 5.14]
Total (95% CI)	**15**		**23**			**100.0 %**	**4.29 [3.44, 5.14]**

Heterogeneity: not applicable

Test for overall effect: Z = 9.87 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.29. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 29 Haematocrit at birth or 1 hour (%).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 29 Haematocrit at birth or 1 hour (%)

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Mercer 2003	16	44 (10.8)	16	42 (9.8)		4.3 %	2.00 [-5.15, 9.15]
Ultee 2008	18	59 (12)	19	50 (9)		4.6 %	9.00 [2.14, 15.86]
Oh 2002	13	44 (7.1)	14	39 (5.6)		9.3 %	5.00 [0.15, 9.85]
McDonnell 1997	23	55 (7.7)	23	52.9 (7.1)		11.9 %	2.10 [-2.18, 6.38]
Rabe 2000	19	51.1 (5.3)	20	48.1 (6.35)		16.2 %	3.00 [-0.66, 6.66]
Kugelman 2007	30	53.5 (5.1)	35	50.7 (6.9)		25.4 %	2.80 [-0.13, 5.73]
Mercer 2006	36	49 (6)	36	46 (6)		28.3 %	3.00 [0.23, 5.77]
Total (95% CI)	**155**		**163**			**100.0 %**	**3.26 [1.79, 4.74]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.73$, df = 6 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 4.33 (P = 0.000015)

Test for subgroup differences: Not applicable

Analysis 1.30. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 30 Haematocrit at 4 hours of life (%).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

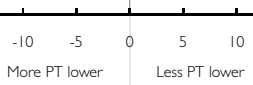
Outcome: 30 Haematocrit at 4 hours of life (%)

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Baezinger 2007	15	55.56 (8.42)	24	50.2 (7.73)		11.3 %	5.36 [0.09, 10.63]
Oh 2002	16	44.4 (7)	17	40 (5.6)		16.6 %	4.40 [0.06, 8.74]
Nelle 1998	11	55 (5)	8	46 (4)		19.1 %	9.00 [4.95, 13.05]
McDonnell 1997	23	55 (7)	23	52.5 (7)		19.2 %	2.50 [-1.55, 6.55]
Kinmond 1993	17	56.4 (4.8)	19	50.9 (4.5)		33.7 %	5.50 [2.45, 8.55]
Total (95% CI)	**82**		**91**			**100.0 %**	**5.40 [3.62, 7.17]**

Heterogeneity: $Chi^2 = 5.22$, df = 4 (P = 0.27); $I^2 = 23\%$

Test for overall effect: Z = 5.97 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.31. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 31 Haematocrit at 24 hours after birth (%).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 31 Haematocrit at 24 hours after birth (%)

Study or subgroup	More placental trans N	Mean(SD)	Less placental trans N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Baezinger 2007	15	55.93 (7.19)	23	49.74 (8.34)		15.2 %	6.19 [1.20, 11.18]
Strauss 2008	41	56 (8.32)	55	53 (8.16)		33.9 %	3.00 [-0.34, 6.34]
Kugelman 2007	30	52.8 (5.2)	35	50.2 (6)		50.9 %	2.60 [-0.12, 5.32]
Total (95% CI)	**86**		**113**			**100.0 %**	**3.28 [1.34, 5.22]**

Heterogeneity: Chi^2 = 1.58, df = 2 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 3.31 (P = 0.00093)

Test for subgroup differences: Not applicable

Analysis 1.32. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 32 Blood volume after birth.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

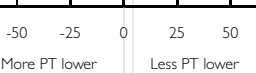
Outcome: 32 Blood volume after birth

Study or subgroup	More placental trans N	Mean(SD)	Less placental trans N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Aladagandy 2006	23	74.4 (11.5)	23	62.7 (7.8)		48.5 %	11.70 [6.02, 17.38]
Strauss 2008	11	42.1 (7.8)	24	36.8 (6.3)		51.5 %	5.30 [0.05, 10.55]
Total (95% CI)	**34**		**47**			**100.0 %**	**8.41 [2.14, 14.67]**

Heterogeneity: Tau^2 = 12.69; Chi^2 = 2.63, df = 1 (P = 0.10); I^2 =62%

Test for overall effect: Z = 2.63 (P = 0.0086)

Test for subgroup differences: Not applicable



Analysis 1.33. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 33 Red cell mass after birth.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 33 Red cell mass after birth

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Strauss 2008	11	42.1 (7.8)	24	36.8 (6.3)		100.0 %	5.30 [0.05, 10.55]
Total (95% CI)	**11**		**24**			**100.0 %**	**5.30 [0.05, 10.55]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							
Test for subgroup differences: Not applicable							

Analysis 1.34. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 34 Sepsis.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 34 Sepsis

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mercer 2006	1/36	8/36		45.8 %	0.13 [0.02, 0.95]
Kugelman 2007	2/30	3/35		54.2 %	0.78 [0.14, 4.35]
Total (95% CI)	**66**	**71**		**100.0 %**	**0.34 [0.05, 2.11]**

Total events: 3 (More placental trans), 11 (Less placental trans)

Heterogeneity: $Tau^2 = 0.84$; $Chi^2 = 1.91$, df = 1 (P = 0.17); $I^2 = 48\%$

Test for overall effect: Z = 1.16 (P = 0.24)

Test for subgroup differences: Not applicable

Analysis 1.35. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 35 Retinopathy of prematurity.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 35 Retinopathy of prematurity

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mercer 2006	10/36	13/36		100.0 %	0.77 [0.39, 1.52]
Total (95% CI)	**36**	**36**		**100.0 %**	**0.77 [0.39, 1.52]**

Total events: 10 (More placental trans), 13 (Less placental trans)

Heterogeneity: not applicable

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

Test for subgroup differences: Not applicable

Analysis 1.36. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 36 Cord pH.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

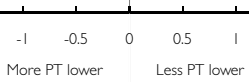
Outcome: 36 Cord pH

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Hofmeyr 1993	24	7.23 (0.2)	14	7.18 (0.11)		18.4 %	0.05 [-0.05, 0.15]
McDonnell 1997	23	7.2 (0.12)	23	7.23 (0.11)		40.5 %	-0.03 [-0.10, 0.04]
Rabe 2000	19	7.27 (0.13)	20	7.29 (0.07)		41.1 %	-0.02 [-0.09, 0.05]
Total (95% CI)	**66**		**57**			**100.0 %**	**-0.01 [-0.05, 0.03]**

Heterogeneity: Chi^2 = 1.85, df = 2 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 0.52 (P = 0.61)

Test for subgroup differences: Not applicable



Analysis 1.37. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 37 Length of stay.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

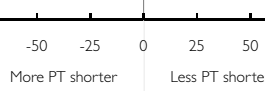
Outcome: 37 Length of stay

Study or subgroup	More placental trans		Less placental trans		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Mercer 2003	16	56.6 (35)	16	73 (27)		100.0 %	-16.40 [-38.06, 5.26]
Total (95% CI)	**16**		**16**			**100.0 %**	**-16.40 [-38.06, 5.26]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion, Outcome 1 Infant death (up to discharge/variable).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion

Outcome: 1 Infant death (up to discharge/variable)

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Delayed clamping				
Strauss 2008	0/45	0/60		0.0 [0.0, 0.0]
Ultee 2008	0/18	0/19		0.0 [0.0, 0.0]
Mercer 2003	0/16	0/16		0.0 [0.0, 0.0]
Kinmond 1993	0/17	0/19		0.0 [0.0, 0.0]
Hofmeyr 1988	5/24	0/14		6.60 [0.39, 111.10]
Hofmeyr 1993	1/40	1/46		1.15 [0.07, 17.80]
Kugelman 2007	0/30	1/35		0.39 [0.02, 9.16]
Rabe 2000	0/19	1/20		0.35 [0.02, 8.10]
McDonnell 1997	0/23	2/23		0.20 [0.01, 3.95]
Baezinger 2007	0/15	3/24		0.22 [0.01, 4.04]
Oh 2002	2/16	3/17		0.71 [0.14, 3.70]
Mercer 2006	0/36	3/36		0.14 [0.01, 2.67]
Subtotal (95% CI)	**299**	**329**		**0.62 [0.28, 1.36]**
Total events: 8 (More placental trans), 14 (Less placental trans)				
Heterogeneity: Chi^2 = 5.12, df = 7 (P = 0.65); I^2 =0.0%				
Test for overall effect: Z = 1.19 (P = 0.23)				
2 Cord milking				
Hosono 2008	2/20	3/20		0.67 [0.12, 3.57]
Subtotal (95% CI)	**20**	**20**		**0.67 [0.12, 3.57]**
Total events: 2 (More placental trans), 3 (Less placental trans)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.47 (P = 0.64)				
Total (95% CI)	**319**	**349**		**0.63 [0.31, 1.28]**
Total events: 10 (More placental trans), 17 (Less placental trans)				
Heterogeneity: Chi^2 = 5.14, df = 8 (P = 0.74); I^2 =0.0%				
Test for overall effect: Z = 1.28 (P = 0.20)				
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.94), I^2 =0.0%				

Analysis 2.2. Comparison 2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion, Outcome 2 Severe intraventricular haemorrhage.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion

Outcome: 2 Severe intraventricular haemorrhage

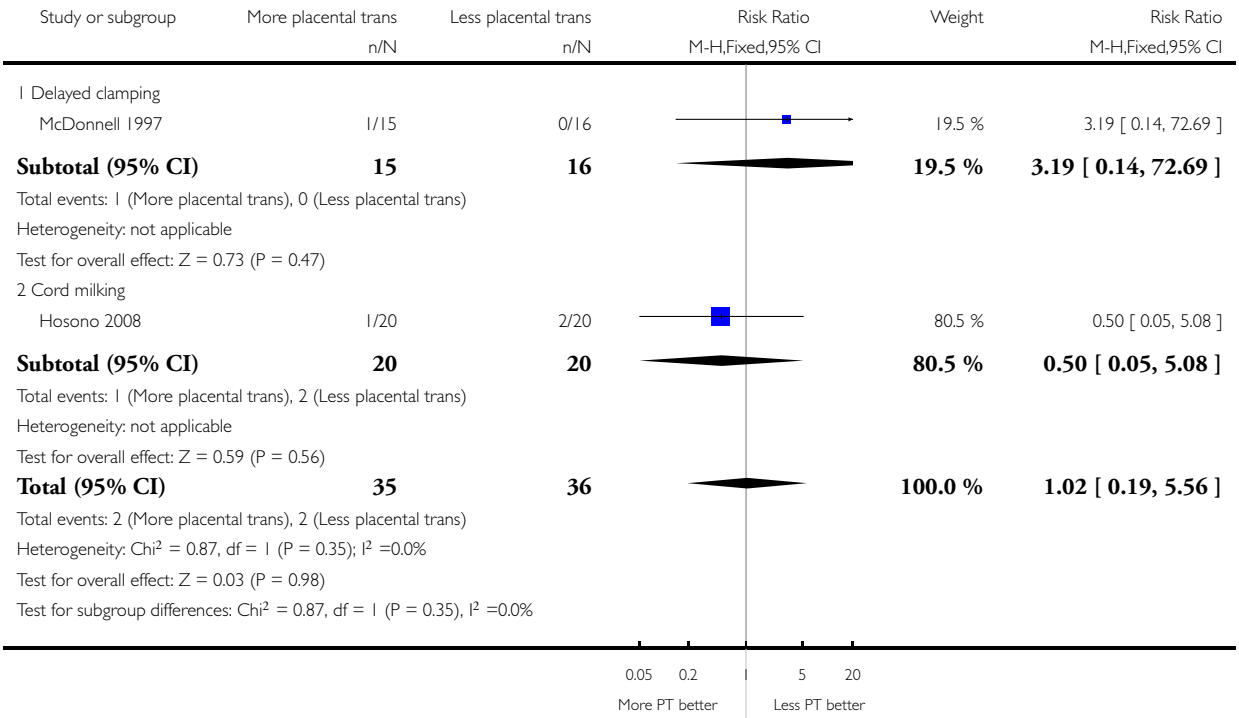
Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Delayed clamping				
Rabe 2000	0/19	0/20		0.0 [0.0, 0.0]
Mercer 2003	0/16	0/16		0.0 [0.0, 0.0]
Hofmeyr 1988	2/23	0/13		2.92 [0.15, 56.51]
Mercer 2006	0/36	1/36		0.33 [0.01, 7.92]
Hofmeyr 1993	1/40	2/46		0.58 [0.05, 6.11]
Subtotal (95% CI)	**134**	**131**		**0.85 [0.20, 3.66]**
Total events: 3 (More placental trans), 3 (Less placental trans)				
Heterogeneity: Chi^2 = 1.11, df = 2 (P = 0.58); I^2 =0.0%				
Test for overall effect: Z = 0.21 (P = 0.83)				
2 Cord milking				
Hosono 2008	2/20	4/20		0.50 [0.10, 2.43]
Subtotal (95% CI)	**20**	**20**		**0.50 [0.10, 2.43]**
Total events: 2 (More placental trans), 4 (Less placental trans)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.86 (P = 0.39)				
Total (95% CI)	**154**	**151**		**0.68 [0.23, 1.96]**
Total events: 5 (More placental trans), 7 (Less placental trans)				
Heterogeneity: Chi^2 = 1.28, df = 3 (P = 0.73); I^2 =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
Test for subgroup differences: Chi^2 = 0.24, df = 1 (P = 0.62), I^2 =0.0%				

Analysis 2.3. Comparison 2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion, Outcome 3 Periventricular leukomalacia.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 2 More placental transfusion versus less placental transfusion: subgroup analysis by strategy for more placental transfusion

Outcome: 3 Periventricular leukomalacia

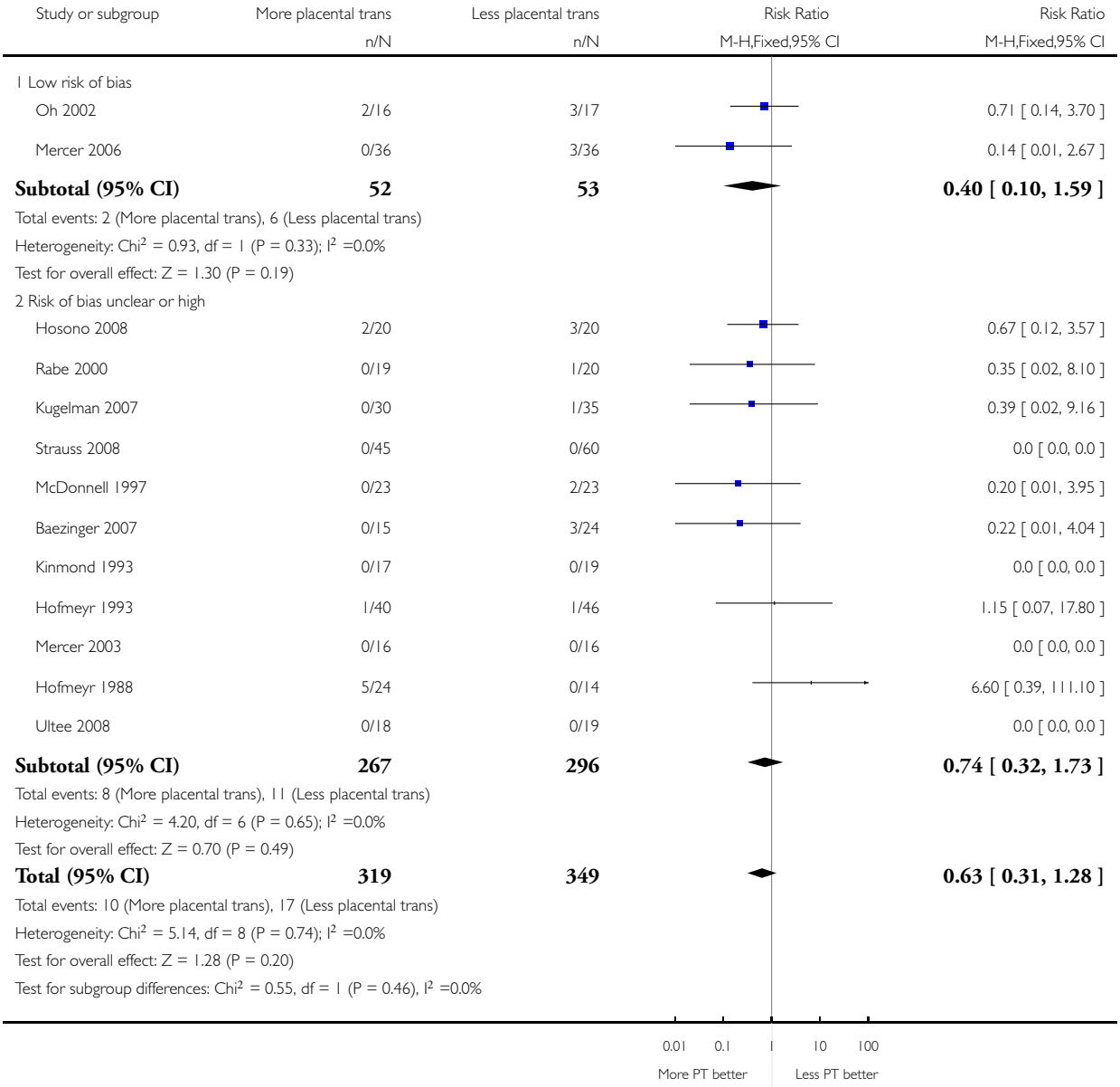


Analysis 3.1. Comparison 3 More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation, Outcome 1 Infant death (up to discharge/variable).

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 3 More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation

Outcome: 1 Infant death (up to discharge/variable)



Analysis 3.2. Comparison 3 More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation, Outcome 2 Severe intraventricular haemorrhage.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 3 More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation

Outcome: 2 Severe intraventricular haemorrhage

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias				
Mercer 2006	0/36	1/36		0.33 [0.01, 7.92]
Subtotal (95% CI)	**36**	**36**		**0.33 [0.01, 7.92]**
Total events: 0 (More placental trans), 1 (Less placental trans)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.68 (P = 0.50)				
2 Risk of bias unclear or high				
Rabe 2000	0/19	0/20		0.0 [0.0, 0.0]
Hofmeyr 1988	2/23	0/13		2.92 [0.15, 56.51]
Mercer 2003	0/16	0/16		0.0 [0.0, 0.0]
Hosono 2008	2/20	4/20		0.50 [0.10, 2.43]
Hofmeyr 1993	1/40	2/46		0.58 [0.05, 6.11]
Subtotal (95% CI)	**118**	**115**		**0.76 [0.24, 2.36]**
Total events: 5 (More placental trans), 6 (Less placental trans)				
Heterogeneity: Chi^2 = 1.11, df = 2 (P = 0.57); I^2 =0.0%				
Test for overall effect: Z = 0.48 (P = 0.63)				
Total (95% CI)	**154**	**151**		**0.68 [0.23, 1.96]**
Total events: 5 (More placental trans), 7 (Less placental trans)				
Heterogeneity: Chi^2 = 1.28, df = 3 (P = 0.73); I^2 =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%				

Analysis 3.3. Comparison 3 More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation, Outcome 3 Periventricular leukomalacia.

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 3 More placental transfusion versus less placental transfusion: sensitivity analysis by risk of bias for concealment of allocation

Outcome: 3 Periventricular leukomalacia

Study or subgroup	More placental trans n/N	Less placental trans n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low risk of bias					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (More placental trans), 0 (Less placental trans)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Risk of bias unclear					
Hosono 2008	1/20	2/20		80.5 %	0.50 [0.05, 5.08]
McDonnell 1997	1/15	0/16		19.5 %	3.19 [0.14, 72.69]
Subtotal (95% CI)	**35**	**36**		**100.0 %**	**1.02 [0.19, 5.56]**
Total events: 2 (More placental trans), 2 (Less placental trans)					
Heterogeneity: Chi^2 = 0.87, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)	**35**	**36**		**100.0 %**	**1.02 [0.19, 5.56]**
Total events: 2 (More placental trans), 2 (Less placental trans)					
Heterogeneity: Chi^2 = 0.87, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.03 (P = 0.98)					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Additional searching carried out in previous versions of the review

Authors searched the Cochrane Neonatal Group Trials Register (16 January 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 4), PubMed (1966 to 16 January 2008) and EMBASE (1974 to 16 January 2008) using the following terms:
umbilical-cord AND clamp* AND (preterm OR premature OR infant, premature).

Appendix 2. Methods used to assess trials included in previous versions of this review

We used the methods described in the Cochrane Reviewers' Handbook (Clarke 1999). In addition, we assessed the methodological quality of each study in terms of selection, performance, attrition and detection as described by the Neonatal Review Group. See Review Group's details for more information. This includes the independent evaluation of each trial by all reviewers.
Three reviewers extracted data independently using previously prepared data extraction forms. We resolved any discrepancies by discussion. Whenever the disagreement could not be resolved by consensus, the trial was referenced as one that is awaiting assessment until additional information is obtained. We extracted data presented in graphs and figures whenever possible, but were only included if three reviewers independently had the same results. We double-checked all data for discrepancies. We requested additional data from the authors of each trial. Authors provided additional data for seven trials (Aladagandy 2006; McDonnell 1997; Mercer 2003; Mercer 2006; Nelle 1998; Oh 2002; Rabe 2000). We entered data into the Review Manager software developed by The Cochrane Collaboration (RevMan 2003).
The statistical methods used were as follows:
(1) Analysis: We described adverse outcomes as adverse event rates (AER) and relative risk (RR), the ratio of adverse events in the treated and control groups. For measures of treatment effect we gave RR, relative risk reduction (1-RR), risk difference and number needed to treat (1/RD). For continuous data, we used mean and standard deviations with reference to the original data if necessary. We calculated weighted mean difference (WMD) where appropriate. For the WMD, the weight given to each study (i.e. how much influence each study has on the overall results of the meta-analysis) as determined by the precision of its estimate of effect which in the Review Manager statistical software is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.
(2) Heterogeneity: We tested clinically and statistically important heterogeneity at the $P < 0.05$ level and used subgroup analysis to explain heterogeneous data if possible.
(3) We specified subgroup analysis before review.

WHAT'S NEW

Last assessed as up-to-date: 1 November 2011.

Date	Event	Description
16 January 2012	New citation required and conclusions have changed	This updated review is based on an search carried out in May 2011. We have now included 15 studies and the weight of the evidence is greater. New authors have helped to update the review. We updated the search in June 2012 and added results to Studies awaiting classification for consideration in the next update
31 December 2011	New search has been performed	Search updated in May 2011, eight new studies added with 437 mother and infant pairs. Subgroup analyses added for cord milking. Methods updated in line with

(*Continued*)

		the new Cochrane Handbook

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 4, 2004

Date	Event	Description
30 November 2009	Amended	Search updated. Thirteen reports added to Studies awaiting classification
28 February 2009	Amended	Converted to new review format.
1 May 2008	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Graham Reynolds (GR) prepared the first draft of the protocol and commented on the second draft. Heike Rabe (HR) commented on the first draft of the protocol and wrote the second draft.

All review authors assessed studies independently. HR did not assess her own study. HR and GR entered study data. GR wrote the 'Methodological quality of included studies' section. HR completed all other sections of the review. JL Diaz-Rossello (JDR) completed the corrections to the statistics. All three review authors commented on the review and agreed on the conclusion.

For the update of this review the process of assessing the eligible studies and extracting the data were followed in the same way as described as above. HR updated the data tables and updated the text of the review. JDR and Therese Dowswell (TD) corrected the statistics. TD and Lelia Duley introduced the risk of bias tables, and revised the text of the review. All review authors agreed on the updated version of the review.

DECLARATIONS OF INTEREST

Studies by the contact author, which may be relevant for inclusion in this review, were not assessed by herself but by the co-authors who, in agreement with the Cochrane Pregnancy and Childbirth group, have named other experts in the field for this purpose. Lelia Duley was previously editor for this review, and currently holds a research grant which includes conducting a pilot randomised trial comparing deferred cord clamping with immediate cord clamping for births before 32 weeks' gestation. Graham Reynolds holds a research grant for a large multicentre trial to study ways to promote placental transfusion in preterm infants.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Some intended subgroup analysis could not be performed due to lack of suitable data.

NOTES

The title of the previously published protocol was 'Early versus delayed cord clamping in preterm infants'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Premature Birth; *Umbilical Cord; Blood Transfusion [utilization]; Cerebral Hemorrhage [prevention & control]; Hematocrit; Infant, Newborn; Infant, Premature [blood]; Ligation [standards]; Placental Circulation [*physiology]; Randomized Controlled Trials as Topic; Respiration Disorders; Time Factors

MeSH check words

Female; Humans; Pregnancy