Early versus delayed umbilical cord clamping in preterm infants (Review)

Rabe H, Reynolds G, Diaz-Rossello J

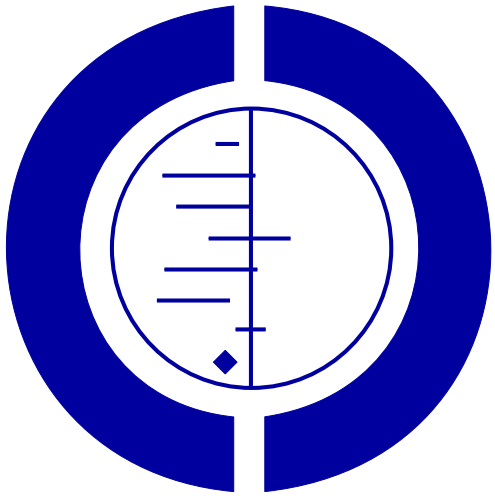

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TABLE OF CONTENTS

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ABSTRACT

Background
Optimal timing for clamping of the umbilical cord at birth is unclear. Early clamping allows for immediate resuscitation of the newborn. Delaying clamping may facilitate transfusion of blood between the placenta and the baby.

Objectives
To delineate the short- and long-term effects for infants born at less than 37 completed weeks' gestation, and their mothers, of early compared to delayed clamping of the umbilical cord at birth.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group trials register (2 February 2004), the Cochrane Neonatal Group trials register (2 February 2004), the Cochrane Central Register of Controlled Trials (*The Cochrane Library,* Issue 1, 2004), PubMed (1966 to 2 February 2004) and EMBASE (1974 to 2 February 2004).

Selection criteria
Randomized controlled trials comparing early with delayed (30 seconds or more) clamping of the umbilical cord for infants born before 37 completed weeks' gestation.

Data collection and analysis
Three reviewers assessed eligibility and trial quality.

Main results
Seven studies (297 infants) were eligible for inclusion. The maximum delay in cord clamping was 120 seconds. Delayed cord clamping was associated with fewer transfusions for anaemia (three trials, 111 infants; relative risk (RR) 2.01, 95% CI 1.24 to 3.27) or low blood pressure (two trials, 58 infants; RR 2.58, 95% CI 1.17 to 5.67) and less intraventricular haemorrhage (five trials, 225 infants; RR 1.74, 95% CI 1.08 to 2.81) than early clamping.

Authors' conclusions
Delaying cord clamping by 30 to 120 seconds, rather than early clamping, seems to be associated with less need for transfusion and less intraventricular haemorrhage. There are no clear differences in other outcomes.

PLAIN LANGUAGE SUMMARY

Delayed cord clamping for babies born early improves their health

In the womb, blood flows to and from the baby and the placenta bringing oxygen to the baby from the mother's blood. If the cord is left unclamped for a short time after the birth, some of the baby's blood from the placenta passes to the baby to help the flow of blood to the baby's lungs. In the review of studies on babies born prematurely, delaying cord clamping for just a very short time helped the babies to adjust to their new surroundings better. Further studies are needed on longer delays to see whether this brings even more benefits.

BACKGROUND

The comparative risks and benefits of early rather than late 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.

Cord clamping is part of the third stage of labour, which is the time between delivery of the infant and the placenta. 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, through the placenta. 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.

Suggested advantages of delaying clamping of the umbilical cord and subsequent increased placental transfusion include less respiratory distress (Linderkamp 1978), less need for blood transfusion later 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). 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 will be a separate Cochrane review of this topic for term infants (McDonald 2004).

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, midwifes, neonatologists as well as pregnant women. In the six trials reported in a previous systematic review (Elbourne 1995), there was considerable variation in transfusion strategies, intervention and outcomes and it was recommended that further, larger trials should be initiated before firm recommendations could be made. Since then, additional trials have been reported and a reappraisal of the available data is warranted.

OBJECTIVES

To delineate the short- and long-term effects in infants less than 37 completed weeks' gestation of placental transfusion at birth by delayed umbilical cord clamping and/or positioning below the introitus and/or milking of the umbilical cord.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials. Quasi-randomized trials were not included.

Types of participants

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

Types of intervention

Delayed (30 seconds or more) versus immediate umbilical cord clamping. This could be with or without oxytocin, with or without the baby held below the level of the placenta, and with or without milking of the cord towards the infant.

Subgroup analyses

(1) By position relative to the level of the placenta: infant below the level of the placenta before clamping or infant at or above the level of the placenta before clamping;
(2) by use of oxytocin: with or without oxytocin;
(3) by milking of the cord: with or without milking;
(4) by route for delivery: vaginal or abdominal route;

(5) by gestational age: less than 32 completed weeks' gestation or 32 or more completed weeks.

Sensitivity analyses
(1) By quality of studies.

Types of outcome measures

Overall (infant)
(1) Requirement for resuscitation;
(2) Apgar score at five and ten minutes;
(3) hypothermia during first hour of life on admission or in labour ward;
(4) death.

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 2, 3 or 4).

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 6 and 12 months of age.

Central nervous system
(1) Intraventricular haemorrhage (IVH) all grades;
(2) IVH grades three and four;
(3) periventricular leukomalacia.

Gastrointestinal
(1) Necrotizing enterocolitis.

Overall (mother's)
(1) Death;
(2) postpartum haemorrhage;
(3) complications with delivery of placenta;
(4) effects on rhesus-isoimmunization;
(5) psychological well-being;
(6) bonding to the infant;
(7) anxieties;
(8) mother's views.

Overall (father's)
(1) Psychological well-being;
(2) bonding to the infant;
(3) anxieties;
(4) father's views.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Pregnancy and Childbirth Group methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group trials register (2 February 2004).

The Cochrane Pregnancy and Childbirth Group's trials register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

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

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Cochrane Neonatal Group trials register (2 February 2004), the Cochrane Central Register of Controlled Trials (*The Cochrane Library,* Issue 1, 2004), PubMed (1966 to 2 February 2004) and EMBASE (1974 to 2 February 2004) using the following terms:
umbilical-cord AND clamp* AND (preterm OR premature OR infant, premature).

METHODS OF THE 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 three trials (McDonnell 1997; 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.

DESCRIPTION OF STUDIES

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

Seven trials qualified for inclusion into this review. We excluded nine studies (*see* 'Characteristics of excluded studies'). The trials enrolled preterm babies between 24 and 33 weeks' gestation. There was some inconsistency in both the intervention and the control procedures between studies and wide variation in outcome measures. This limited the utility of each of the studies.

The women recruited into the trials were all expecting to deliver their infants prematurely. The infants in the study of Kinmond 1993 were all delivered vaginally, while those in the trial of Nelle 1998 were delivered by caesarean section only. All other trials allowed both ways of delivery.

Early or immediate umbilical cord clamping
The definition of early umbilical cord clamping has not been made clear in any study except McDonnell (McDonnell 1997) where the exact time to cord clamping in the immediate group is five 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 umbilical cord clamping
The definition of delayed umbilical cord clamping varies between studies. McDonnell 1997 had a mean timed delay of 31 seconds, Rabe 2000 45 seconds, and Hofmeyr 1988 and Hofmeyr 1993 60 and 120 seconds. The exact time to clamping is not given in other studies, nor is 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 only two studies. In Hofmeyr 1988 for example, 8 of 24 babies in the delayed clamping group required earlier intervention. There are insufficient data to determine whether there is any additional benefit for delay in cord clamping beyond 30 to 60 seconds.

Position in relation to the placenta
The position in relation to the placenta or uterus varies 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.

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

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

Subgroup analysis
Subgroup analysis on position, milking of the cord, effects on mothers and fathers is not possible for lack of data. Stratification by gestational age has only been possible for a limited number of criteria.

Outcome measures

No two studies are similar in their outcome objectives and there is a wide and varied definition of the type of outcome measured. Similarly, the manner of reporting the same outcome varies between studies. We have requested raw data from all authors in order to clarify and normalize our evaluation more effectively, in line with the clinical outcomes that, a priori, we considered important. The authors of most recent studies have declared that they have performed a pilot or feasibility study and have been powered to answer short term specific questions only. In general the studies that we have included are not powered to answer the range of clinical questions that we feel are important in day-to-day neonatal practice.

METHODOLOGICAL QUALITY

Randomization

Randomization was largely appropriate and well described except for the study of Nelle 1998, which has only been published in abstract format. Most studies claim to pilot a certain cord clamping time and an intervention and have therefore not been powered to detect small differences. The study of Hofmeyr 1993 is the largest of the seven included studies with 86 infants. Randomization was largely by sealed envelope, after allocation by random number table in later studies (McDonnell 1997; Rabe 2000) or by card shuffling in earlier studies (Hofmeyr 1988; Hofmeyr 1993). These methods are appropriate to use.

Concealment of allocation was adhered to in all studies. Blinding towards the allocation of intervention after delivery of the baby was not possible, as the intervention has to be performed openly after birth.

RESULTS

Seven studies involving 297 infants were included.

(a) For the baby

Haematological outcome

There was no clear effect on haematocrit at birth or one hour (three trials, 112 infants; weighted mean difference (WMD) -3.24%, 95% confidence interval (CI) -5.66 to 0.83) and haematocrit at four hours (four trials, 134 infants; WMD -5.31%, 95% CI -7.19 to -3.42). Fewer infants allocated delayed clamping were transfused for anaemia of prematurity (three trials, 111 infants; 29/55 versus 14/55; relative risk (RR) 2.01, 95% CI 1.24 to 3.27). Peak bilirubin concentration is also higher for infants allocated delayed rather than early clamping (three trials, 111 infants, WMD 21.49 mmol/litre, 95% CI 38.04 to 4.94). Treatment for hyperbilirubinaemia is reported by only one study, which was too small for reliable conclusions (39 infants, RR 0.95, 95% CI 0.58 to 1.56). Data on exchange transfusion are not reported by any of the studies.

Cardiovascular effects

Infants allocated delayed clamping were also less likely to need transfusion for low blood pressure at birth (two trials, 58 infants, RR 2.58, 95% CI 1.17 to 5.67). There was insufficient evidence for any firm conclusions on the effect of timing of cord clamping on the need for inotropic support at birth, or treatment for patent ductus arteriosus.

Intraventricular haemorrhage

There was reduction in the relative risk of intraventricular haemorrhage associated with delayed, rather than early, cord clamping (five trials, 225 infants; RR 1.74, 95% CI 1.08 to 2.81). For severe intraventricular hemorrhage (Grade 3 and 4) the numbers of events (two versus three) were too small for any firm conclusions (three trials, 161 infants; RR 0.86, 95% CI 0.15 to 4.75). Only one study (31 infants) reported periventricular leucomalacia.

Respiratory effects

Even taken together, these trials were too small for any firm conclusion about possible respiratory effects of the alternative strategies for timing of umbilical cord clamping. Respiratory distress syndrome is reported only in two studies (75 infants, RR 0.83, 95% CI 0.59 to 1.15), and only one trial reports severe respiratory distress (39 infants, RR 1.27, 95% CI 0.33 to 4.93). Use of surfactant was reported in two trials (85 infants; RR 0.78, 95% CI 0.34 to 1.79) and ventilation for respiratory distress by three trials (121 infants, RR 0.91, CI 95% 0.65 to 1.28). There was insufficient evidence for any reliable conclusions about the effects on days on oxygen, oxygen dependency at day 28 of life (one trial 36 infants, RR 6.30, 95% CI 0.35 to 113.81), or chronic lung disease at 36 weeks' corrected age (two trials, 65 infants; RR 0.97, CI 95% 0.35 to 2.69).

Gastrointestinal effects

There were insufficient data for any reliable conclusion about possible differential effects on necrotizing enterocolitis (two trials, 72 infants, RR 2.08, 95% CI 0.52 to 8.37).

Other outcomes

There was insufficient evidence for any reliable conclusions about the effect on the risk of the baby dying (six trials, 278 infants; RR 1.05 95% CI 0.41 to 2.73).

Data on the analysis of cord pH did not show a significant difference between early and delayed umbilical cord clamping (three trials, 123 infants, WMD 0.01, 95% CI 0.03 to 0.05). Similarly, there was no difference in temperature on admission (one trial, 39 infants; WMD 0.20, 95% CI 0.43 to 0.03) or in Apgar scores at five minutes (three trials, 161 infants, RR 1.17, 95% CI 0.62 to 2.20).

(b) For the mothers

No trials reported outcome for the women.

DISCUSSION

The trials included in this review varied in respect of positioning of the infant, how quickly the umbilical cord was clamped for the early group, how long it was delayed for the delayed group and in other aspects of management of the third stage of labour. Data are not available for a number of our prespecified outcomes, and similarly the planned subgroup analyses were not feasible. In particular, there were no data on the potential effects on psychological well-being of the mothers and fathers, and their bonding with the infants.

Overall, even when taking all trial results together, most outcomes had wide confidence intervals, so the results should be interpreted with caution. Nevertheless, later umbilical cord clamping for the preterm infant appears to be associated with a reduction in the relative risk of intraventricular haemorrhage (IVH) and the need for transfusion, either for anaemia or for low blood pressure. These effects may be related to an improvement in the circulating blood volume, and better control of blood pressure, secondary to greater placental transfusion if the umbilical cord is not clamped too quickly. Even though no direct studies on circulating blood volume in the control and intervention groups have been performed, the higher blood pressure and the less need for blood transfusions later suggest a higher circulating blood volume in infants when umbilical cord clamping is delayed by at least 30 seconds. Perhaps this issue could be addressed in future trials.

Surprisingly, as the rationale for early clamping is to provide respiratory support, there are few data on respiratory outcomes. As one clinical concern about delayed umbilical cord clamping is hypothermia, it is also surprising that this outcome is only addressed by one small trial.

The trials were too small for any reliable conclusions about the possible comparative effects on the risk of death. Nevertheless, there are problems with death as an outcome for this review. Variations in clinical practice over time have substantially influenced the risk of death for preterm infants. These background variations in clinical practice may alter the risk of death more than the intervention itself. 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 the comment in the report suggests that survival at this low birthweight was more the exception than the rule.

There is a strikingly high rate of intraventricular haemorrhage in both studies by Hofmeyr et al (Hofmeyr 1988; Hofmeyr 1993), which were conducted in South Africa. Other studies conducted in high-income countries have less IVH, and therefore less power to demonstrate any clinically important effects on the risk of IVH. Recent reports in the literature on even major grade 3 or 4 intraventricular haemorrhage suggest that these might not always be associated with major neurological impairment (Schmidt 2001).

On the questions about optimal positioning of the infant, milking of the cord and combination of these with a delay of umbilical cord clamping, this review cannot give any analysis because of lack of data. Further studies should include these issues.

AUTHORS' CONCLUSIONS

Implications for practice

Delaying umbilical cord clamping for between 30 and 120 seconds in the preterm infant less than 37 weeks' gestation appears to be better than clamping within 30 seconds, as it is associated with a reduction in the risk of intraventricular haemorrhage and less need for blood transfusion.

Implications for research

There remain a considerable number of topics to study about the short- and long-term effects of alternative policies for positioning the infant and timing of clamping of the umbilical cord for preterm infants less than 37 weeks' gestation. Further large trials are needed, to provide more precise estimates of these effects, to provide information about effects on more substantive outcomes, and to examine the possible impact of other manoeuvres during delivery. These trials should include assessment of long-term neurodevelopmental outcome of the children. The reviewers are aware of two further studies that are in progress (Holland 1998; Mercer 2004) and look forward to incorporating these new data as soon as possible.

NOTES

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

FEEDBACK

Morley, January 2005

Summary

A total of 297 preterm infants were recruited to the seven randomized trials included in your review. The conclusion was that delayed clamping seemed to reduce the risk of anemia (blood transfusion) and of intraventricular hemorrhage. All these trials should have complied with the Nuremberg code of 1948 and the World Medical Association's ethical restrictions for medical research on

human subjects (Helsinki 1964) Regarding informed consent, six of the seven trials appear to be in gross violation.

The seventh trial, by Kinmond et al (Kinmond 1993), involved 36 preterm infants, 17 in the delayed clamping group had gravity assisted placental transfusion for 30 seconds, and 19 had immediate cord clamping. No infants in the delayed clamping group needed blood transfusion, in the immediate clamping group they received 23 ml per kilogramme. The delayed group needed an average of 3 days of supplemental oxygen compared to 10 days for the immediate group. Three infants in the immediate clamping group developed chronic lung disease compared with none in the delayed clamping group. Two infants from each group had an intraventricular haemorrhage, although those in the immediately clamped group developed enlarged ventricles (loss of brain tissue); those in the delayed group did not. The conclusions of your review could have been reached based on the Kinmond study alone.

These results from Kimmond's trial should have guided subsequent researchers in an ethically correct direction. Prospective parents of preterm infants should have had them explained to them, in words that they could understand, in order to give informed consent for possible immediate clamping. Informed parental choice on the adverse effects of immediate clamping would have eliminated this option for the control group of a randomised trial.

Kinmond's rationale was to give the neonate a placental transfusion by holding the child 20 cms below the vulva for 30 seconds before clamping the cord. The unsurprising result was that placental transfusion obviated the need for blood transfusion, and that hypovolemic / ischemic complications (shock lung, anemia, germinal matrix hemorrhagic infarction) were ameliorated.
This review addresses only the time of clamping delay; however, a preterm infant held 20 cms above the level of the placenta for 60 seconds before clamping could be severely compromised by gravitational blood loss into the placenta. Delayed clamping per se thus becomes a very questionable benefit, contradicting the conclusions of your review. The critical factor that assures the health and welfare of the preterm baby is the amount of placental transfusion that occurs before the cord is clamped, regardless of the timing.

Thus an alternative study design, using as controls a cohort of babies whose cord vessels close physiologically - without any cord clamping - is required. If need be, these children could go to the nursery with cord and placenta intact. A preterm infant attached to a functioning placenta by a vigorously pulsating cord does not require "resuscitation;" it will reflexively switch from placental life support to its own life support systems physiologically, and it will clamp its own cord at precisely the correct, physiological time. Kinmond comments, "We did not time the onset of respiration in relation to cord clamping, but many infants in the regulated group were already crying." Oxygenated blood constricts and closes the umbilical arteries. [1]

There are no reported complications of delivering preterm infants in this manner, and researchers should have no difficulty in obtaining ethical informed consent for a very large control cohort with which to compare Kinmond's method. Gravity, uterine contraction, and a time delay of 20 minutes or more may be required to provide the preterm infant with a blood volume optimal for its survival.

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Author's reply

We disagree with the accusation that six of the seven trials in this review failed to comply with either the Nuremberg code or the Helsinki declaration. The basis for this accusation appears to be that the data from Kinmond 1993 provides definitive evidence of benefit for delayed clamping. This is patently untrue. Kinmond 1993 included just 36 children. There were no deaths in this study, and so no data are provided for the most substantive outcome in the review. For all outcomes reported, the number of events is small and the confidence intervals for the estimate of effect are large. Also, in all seven studies babies in the control group had early or immediate cord clamping. This reflects clinical practice in many parts of the world, where for many years the norm has been to clamp the cord as soon as possible after delivery. It is absolutely appropriate to use normal clinical practice as the control intervention.

As we discuss in our review, taken together the results of these seven trials present promising evidence that a delay in cord clamping may have benefits for babies born before term. However, further trials are needed to confirm that these are reflected in more substantive outcomes, such as baby death. We agree that other aspects of the management of the third stage also require evaluation. This evaluation should be in the context of randomised trials, however, as only then can we be sure that any comparison between the groups in unbiased.

Response from Heike Rabe, August 2005.

Contributors

Comment received from George Malcolm Morley, January 2005.

POTENTIAL CONFLICT OF INTEREST

Studies by the contact reviewer, which may be relevant for inclusion in this review, were not assessed by herself but by the two co-reviewers who, in agreement with the Cochrane Pregnancy and Childbirth group, have named other experts in the field for this purpose.

ACKNOWLEDGEMENTS

D Elbourne

W Oh, M McDonnell, M Nelle, S Kinmond and H Rabe who kindly provided additional information regarding their studies. The information about randomization for the trials by W Oh and M Nelle was directly obtained from the authors. The reviewers thank the authors for supplying the additional data and information.

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), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Hofmeyr 1988**
Methods	Randomized controlled trial, randomization cards, stratified by birthweight < 1500 g.
Participants	38 infants < 35 weeks. Exclusions: nil.
Interventions	Control: cord clamping immediately after birth. Intervention 1: cord camping delayed for 60 s Intervention 2: cord clamping delayed for 60 s and ergometrine given at delivery.
Outcomes	Primary outcome: cerebral Ultrasound 6-72 hours after birth. Secondary outcomes: Apgar scores, birthweight, systolic blood pressure at 5 minutes, cord blood gas, death.
Notes	
Allocation concealment	A

Study	**Hofmeyr 1993**
Methods	Randomized controlled trial, randomized sealed cards.
Participants	86 infants < 2000 g. Exclusion: cord around the neck.
Interventions	Control group: cord clamped immediately. Intervention: cord clamping time 60-120 s, infant held at the level of the uterus for vaginal deliveries, infant held above the level of the uterus for caesarean section (on the mothers' thighs).
Outcomes	Primary outcome: cerebral ultrasound at 24 h. Secondary outcome: Apgar score, cord-pH.
Notes	
Allocation concealment	A

Study	**Kinmond 1993**
Methods	Randomized controlled trial, sealed envelopes, stratification not given.
Participants	36 infants > 27 to < 33 weeks' gestation, vaginal delivery. Exclusions: haemolytic disease, major congenital malformations.
Interventions	Regulated group: positioning 20 cm below the introitus and cord clamped at 30 s. Non-regulated group: time to cord clamping recorded, management at the attendant's discretion.

Characteristics of included studies (*Continued*)

Outcomes	Primary outcome: initial packed red cell volume, peak serum bilirubin, transfusion requirement, respiratory impairment, arterial-alveolar oxygen ratio, duration of oxygen.
Notes	
Allocation concealment	A

Study	**McDonnell 1997**
Methods	Randomized controlled trial, randomization by sealed opaque envelope, stratified by vaginal or caesarean section, 26 to 29 weeks, 30 to 33 weeks.
Participants	46 infants 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	
Allocation concealment	A

Study	**Nelle 1998**
Methods	Randomized controlled trial. Randomization by sealed opaque envelopes.
Participants	19 infants < 1500 g. Born by caesarean section.
Interventions	Control: cord clamped immediately after birth. Intervention: cord clamping after 30 s and positioning of the infant 30 cm below placenta.
Outcomes	Primary 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	
Allocation concealment	B

Study	**Oh 2002**
Methods	Randomized controlled trial. Randomization method by sealed opaque envelopes.
Participants	Infants 24-28 weeks.
Interventions	Control group: immediate cord clamping < 5 s. Intervention: 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, intraventricular haemorrhage, necrotizing enterocolitis, retinopathy of prematurity, late onset sepsis, patent ductus arteriosus, blood transfusions.
Notes	
Allocation concealment	A

Study	**Rabe 2000**
Methods	Randomized controlled trial, opaque sealed envelopes.

Characteristics of included studies (*Continued*)

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 s. Intervention: 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, intraventricular haemorrhage, patent ductus arteriosus, phototherapy.
Notes	
Allocation concealment	A

h: hours
IUGR: intrauterine growth restriction
s: seconds

Characteristics of excluded studies

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	Randomized 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.
Saigal 1972	Sequential allocation procedure, which is not a randomized trial.
Saigal 1977	Sequential allocation procedure, which is not a randomized trial.
Spears 1966	Randomisation procedure was unclear. Gestational age of the low birth eight infants was not given.
Strauss 2003	Even though the title states "delayed versus immediate cord clamping", the intervention in delayed group less than 30 weeks' gestation consisted of harvesting and retransfusion of placental blood. No separate data are given for the group of 31 to 36 weeks' gestation.
Taylor 1963	Inadequate randomization. Largely term infants.

Characteristics of ongoing studies

Study	**Holland 1998**
Trial name or title	Placento-fetal (autologous) Transfusion at birth in infants born preterm: a randomized, controlled trial.
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

Characteristics of ongoing studies (*Continued*)

	c. Transfusion requirements.
Starting date	1998
Contact information	BM Holland Queen Mother's Hospital Glasgow G3 8SH
Notes	Trial completed in 2001

Study	**Mercer 2004**
Trial name or title	Randomized controlled trial of delayed cord clamping in infants born between 24 and 31 +6/7 weeks' gestation.
Participants	Infants between 24 and 31 +6/7 weeks' gestation stratified into 2 groups: 24 to 27 +6/7 and 28 to 31 +6/7 weeks' gestation.
Interventions	Positioning of infant 10-15 inches below mother's introitus at vaginal delivery or 10-15 inches below the level of the placenta at caesarean section, cord clamping time at 30 to 45 seconds.
Outcomes	Primary outcome: Chronic lung disease, NEC, medical morbidity at 7 months corrected age and neurodevelopmental outcome at 18 months corrected age.
Starting date	2003
Contact information	J Mercer Women and Children's Hospital Providence, Rhode Island USA
Notes	Trial ongoing

CRIB: Critical Risk Index for Babies
NEC: necrotising enterocolitis
RCV: red cell volume

ANALYSES

Comparison 01. Early versus delayed cord clamping

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death of the baby	6	278	Relative Risk (Fixed) 95% CI	1.05 [0.41, 2.73]
02 Transfused for anaemia	3	111	Relative Risk (Fixed) 95% CI	2.01 [1.24, 3.27]
03 Transfused for low blood pressure	2	58	Relative Risk (Fixed) 95% CI	2.58 [1.17, 5.67]
04 Number of transfusions	3	98	Weighted Mean Difference (Fixed) 95% CI	1.28 [0.58, 1.98]
05 Haematocrit at birth or 1 hour (%)	3	112	Weighted Mean Difference (Fixed) 95% CI	-3.21 [-5.62, -0.80]
06 Haematocrit at 4 hours of life (%)	4	134	Weighted Mean Difference (Fixed) 95% CI	-5.40 [-7.28, -3.52]
08 Serum bilirubin peak (mmol/litre)	3	111	Weighted Mean Difference (Fixed) 95% CI	-21.49 [-38.04, -4.94]
09 Hyperbilirubinemia (treated)	1	39	Relative Risk (Fixed) 95% CI	0.95 [0.58, 1.56]
11 Inotropics for low blood pressure	3	118	Relative Risk (Fixed) 95% CI	2.17 [0.51, 9.12]
12 Patent ductus arteriosus	3	118	Relative Risk (Fixed) 95% CI	0.79 [0.36, 1.72]
13 Intraventricular haemorrhage	5	225	Relative Risk (Fixed) 95% CI	1.74 [1.08, 2.81]
14 Severe intraventricular haemorrhage	3	161	Relative Risk (Fixed) 95% CI	0.86 [0.15, 4.75]

15 Periventricular leucomalacia	1	31	Relative Risk (Fixed) 95% CI	0.31 [0.01, 7.15]
16 Respiratory distress syndrome	2	75	Relative Risk (Fixed) 95% CI	0.83 [0.59, 1.15]
17 Severe respiratory distress syndrome	1	39	Relative Risk (Fixed) 95% CI	1.27 [0.33, 4.93]
18 Ventilated for respiratory distress syndrome	3	121	Relative Risk (Fixed) 95% CI	0.91 [0.65, 1.28]
19 Surfactant treatment	2	85	Relative Risk (Fixed) 95% CI	0.78 [0.34, 1.79]
21 Oxygen supplementation at 28 days	1	36	Relative Risk (Fixed) 95% CI	6.30 [0.35, 113.81]
22 Oxygen supplementation at 36 weeks	2	65	Relative Risk (Fixed) 95% CI	0.97 [0.35, 2.69]
23 Necrotizing enterocolitis	2	72	Relative Risk (Fixed) 95% CI	2.08 [0.52, 8.37]
24 Cord pH	3	123	Weighted Mean Difference (Fixed) 95% CI	0.01 [-0.03, 0.05]
25 Apgar score at 5th minute < 8	3	161	Relative Risk (Fixed) 95% CI	1.17 [0.62, 2.20]
26 Temperature on admission (degrees Celsius)	1	39	Weighted Mean Difference (Fixed) 95% CI	-0.20 [-0.43, 0.03]

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Transfusion [utilization]; Cerebral Hemorrhage [prevention & control]; Constriction; Hematocrit; Infant, Newborn; *Infant, Premature [blood]; Randomized Controlled Trials; Respiration Disorders; Time Factors; *Umbilical Cord

MeSH check words

Humans

COVER SHEET

Title	Early versus delayed umbilical cord clamping in preterm infants
Authors	Rabe H, Reynolds G, Diaz-Rossello J
Contribution of author(s)	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 reviewers 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 completed the corrections to the statistics. All three reviewers commented on the review and agreed on the conclusion.
Issue protocol first published	2001/3
Review first published	2004/4
Date of most recent amendment	21 August 2005
Date of most recent SUBSTANTIVE amendment	01 July 2004
What's New	8 December 2004 Corrected error in data in tables 01.05 and 01.06. This did not affect the results.
Date new studies sought but none found	Information not supplied by author

Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	02 February 2004
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Heike Rabe Consultant Neonatologist Trevor Mann Baby Unit Brighton and Sussex University Hospitals, Royal Sussex Country Hospital Eastern Road Brighton BN2 5BE UK E-mail: heike.rabe@bsuh.nhs.uk Tel: +44 1273 696955 Fax: +44 1273 664614
DOI	10.1002/14651858.CD003248.pub2
Cochrane Library number	CD003248
Editorial group	Cochrane Pregnancy and Childbirth Group
Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Early versus delayed cord clamping, Outcome 01 Death of the baby

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 01 Death of the baby

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Hofmeyr 1988	0/14	5/24		50.8	0.15 [0.01, 2.55]
Hofmeyr 1993	1/40	1/46		11.4	1.15 [0.07, 17.80]
× Kinmond 1993	0/19	0/17		0.0	Not estimable
McDonnell 1997	2/23	0/23		6.2	5.00 [0.25, 98.75]
Oh 2002	3/17	2/16		25.4	1.41 [0.27, 7.38]
Rabe 2000	1/20	0/19		6.3	2.86 [0.12, 66.11]
Total (95% CI)	133	145		100.0	1.05 [0.41, 2.73]

Total events: 7 (Early), 8 (Delayed)

Test for heterogeneity chi-square=3.37 df=4 p=0.50 I^2 =0.0%

Test for overall effect z=0.11 p=0.9

Analysis 01.02. Comparison 01 Early versus delayed cord clamping, Outcome 02 Transfused for anaemia

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 02 Transfused for anaemia

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kinmond 1993	7/13	1/13		7.0	7.00 [1.00, 49.16]
McDonnell 1997	6/23	4/23		28.1	1.50 [0.49, 4.62]
Rabe 2000	16/20	9/19		64.9	1.69 [1.00, 2.85]
Total (95% CI)	56	55		100.0	2.01 [1.24, 3.27]

Total events: 29 (Early), 14 (Delayed)

Test for heterogeneity chi-square=2.26 df=2 p=0.32 I^2 =11.5%

Test for overall effect z=2.81 p=0.005

Analysis 01.03. Comparison 01 Early versus delayed cord clamping, Outcome 03 Transfused for low blood pressure

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

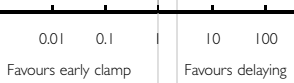
Outcome: 03 Transfused for low blood pressure

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nelle 1998	7/8	2/11		29.1	4.81 [1.34, 17.32]
Rabe 2000	7/20	4/19		70.9	1.66 [0.58, 4.78]
Total (95% CI)	28	30		100.0	2.58 [1.17, 5.67]

Total events: 14 (Early), 6 (Delayed)

Test for heterogeneity chi-square=1.58 df=1 p=0.21 I^2 =36.5%

Test for overall effect z=2.36 p=0.02



Analysis 01.04. Comparison 01 Early versus delayed cord clamping, Outcome 04 Number of transfusions

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 04 Number of transfusions

Study	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Kinmond 1993	13	1.91 (1.62)	13	0.46 (0.66)		54.0	1.45 [0.50, 2.40]
Oh 2002	17	4.00 (4.00)	16	3.60 (3.80)		6.9	0.40 [-2.26, 3.06]
Rabe 2000	20	2.40 (1.95)	19	1.20 (1.60)		39.1	1.20 [0.08, 2.32]
Total (95% CI)	50		48			100.0	1.28 [0.58, 1.98]

Test for heterogeneity chi-square=0.56 df=2 p=0.75 I^2 =0.0%

Test for overall effect z=3.59 p=0.0003

Analysis 01.05. Comparison 01 Early versus delayed cord clamping, Outcome 05 Haematocrit at birth or 1 hour (%)

Review: Early versus delayed umbilical cord clamping in preterm infants

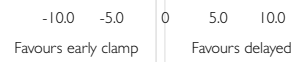
Comparison: 01 Early versus delayed cord clamping

Outcome: 05 Haematocrit at birth or 1 hour (%)

Study	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
McDonnell 1997	23	52.90 (7.10)	23	55.00 (7.70)		31.8	-2.10 [-6.38, 2.18]
Oh 2002	14	39.00 (5.60)	13	44.00 (7.10)		24.8	-5.00 [-9.85, -0.15]
Rabe 2000	20	48.10 (6.35)	19	51.10 (5.30)		43.4	-3.00 [-6.66, 0.66]
Total (95% CI)	57		55			100.0	-3.21 [-5.62, -0.80]

Test for heterogeneity chi-square=0.79 df=2 p=0.67 I^2 =0.0%

Test for overall effect z=2.61 p=0.009



Analysis 01.06. Comparison 01 Early versus delayed cord clamping, Outcome 06 Haematocrit at 4 hours of life (%)

Review: Early versus delayed umbilical cord clamping in preterm infants

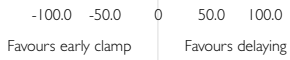
Comparison: 01 Early versus delayed cord clamping

Outcome: 06 Haematocrit at 4 hours of life (%)

Study	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Kinmond 1993	19	50.90 (4.50)	17	56.40 (4.80)		38.0	-5.50 [-8.55, -2.45]
McDonnell 1997	23	52.50 (7.00)	23	55.00 (7.00)		21.6	-2.50 [-6.55, 1.55]
Nelle 1998	8	46.00 (4.00)	11	55.00 (5.00)		21.6	-9.00 [-13.05, -4.95]
Oh 2002	17	40.00 (5.60)	16	44.40 (7.00)		18.8	-4.40 [-8.74, -0.06]
Total (95% CI)	67		67			100.0	-5.40 [-7.28, -3.52]

Test for heterogeneity chi-square=5.21 df=3 p=0.16 I^2 =42.5%

Test for overall effect z=5.63 p<0.00001



Analysis 01.08. Comparison 01 Early versus delayed cord clamping, Outcome 08 Serum bilirubin peak (mmol/litre)

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 08 Serum bilirubin peak (mmol/litre)

Study	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
McDonnell 1997	23	211.00 (42.00)	23	222.00 (42.00)		46.5	-11.00 [-35.27, 13.27]
Oh 2002	13	133.38 (53.00)	13	162.44 (64.90)		13.2	-29.06 [-74.61, 16.49]
Rabe 2000	20	118.50 (41.70)	19	149.60 (41.30)		40.3	-31.10 [-57.15, -5.05]
Total (95% CI)	56		55			100.0	-21.49 [-38.04, -4.94]

Test for heterogeneity chi-square=1.35 df=2 p=0.51 I^2 =0.0%

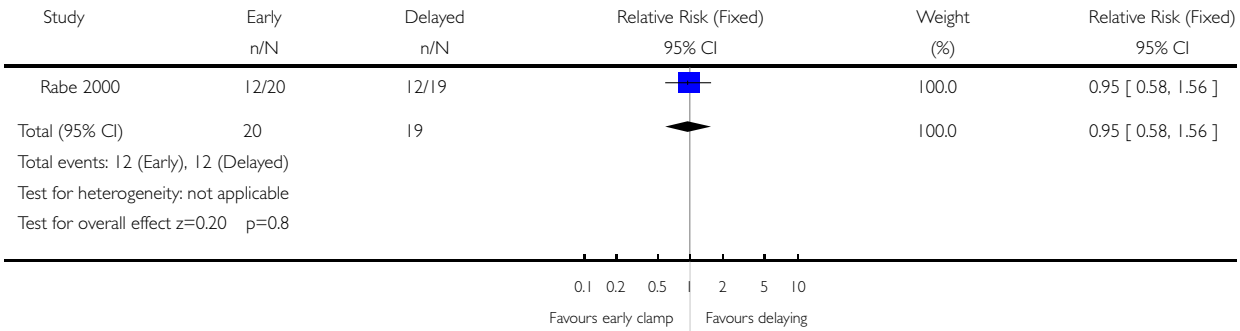
Test for overall effect z=2.55 p=0.01

Analysis 01.09. Comparison 01 Early versus delayed cord clamping, Outcome 09 Hyperbilirubinemia (treated)

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 09 Hyperbilirubinemia (treated)

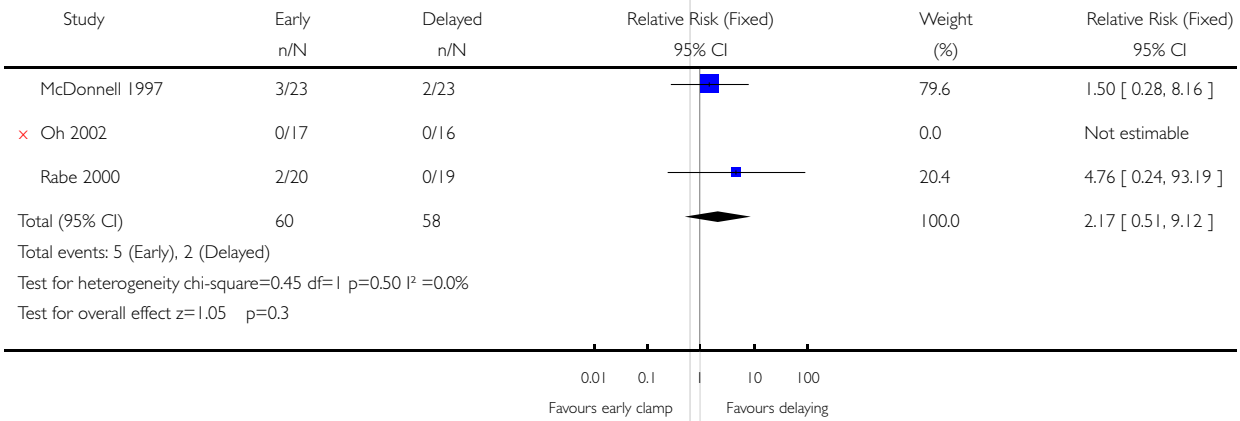


Analysis 01.11. Comparison 01 Early versus delayed cord clamping, Outcome 11 Inotropics for low blood pressure

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 11 Inotropics for low blood pressure



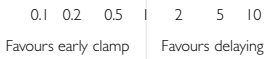
Analysis 01.12. Comparison 01 Early versus delayed cord clamping, Outcome 12 Patent ductus arteriosus

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 12 Patent ductus arteriosus

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
McDonnell 1997	3/23	3/23		26.7	1.00 [0.22, 4.45]
Oh 2002	4/17	6/16		55.0	0.63 [0.22, 1.82]
Rabe 2000	2/20	2/19		18.3	0.95 [0.15, 6.08]
Total (95% CI)	60	58		100.0	0.79 [0.36, 1.72]
Total events: 9 (Early), 11 (Delayed)					
Test for heterogeneity chi-square=0.31 df=2 p=0.86 I^2 =0.0%					
Test for overall effect z=0.60 p=0.5					



Analysis 01.13. Comparison 01 Early versus delayed cord clamping, Outcome 13 Intraventricular haemorrhage

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 13 Intraventricular haemorrhage

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Hofmeyr 1988	10/13	8/23		32.2	2.21 [1.17, 4.17]
Hofmeyr 1993	11/46	8/40		47.7	1.20 [0.53, 2.68]
McDonnell 1997	1/16	0/15		2.9	2.82 [0.12, 64.39]
Oh 2002	4/17	2/16		11.5	1.88 [0.40, 8.90]
Rabe 2000	3/20	1/19		5.7	2.85 [0.32, 25.07]
Total (95% CI)	112	113		100.0	1.74 [1.08, 2.81]
Total events: 29 (Early), 19 (Delayed)					
Test for heterogeneity chi-square=1.68 df=4 p=0.79 I^2 =0.0%					
Test for overall effect z=2.29 p=0.02					

Analysis 01.14. Comparison 01 Early versus delayed cord clamping, Outcome 14 Severe intraventricular haemorrhage

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 14 Severe intraventricular haemorrhage

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Hofmeyr 1988	0/13	2/23		63.3	0.34 [0.02, 6.64]
Hofmeyr 1993	2/46	1/40		36.7	1.74 [0.16, 18.47]
× Rabe 2000	0/20	0/19		0.0	Not estimable
Total (95% CI)	79	82		100.0	0.86 [0.15, 4.75]
Total events: 2 (Early), 3 (Delayed)					
Test for heterogeneity chi-square=0.71 df=1 p=0.40 I^2 =0.0%					
Test for overall effect z=0.18 p=0.9					

Analysis 01.15. Comparison 01 Early versus delayed cord clamping, Outcome 15 Periventricular leucomalacia

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 15 Periventricular leucomalacia

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
McDonnell 1997	0/16	1/15		100.0	0.31 [0.01, 7.15]
Total (95% CI)	16	15		100.0	0.31 [0.01, 7.15]
Total events: 0 (Early), 1 (Delayed)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.73 p=0.5					

Analysis 01.16. Comparison 01 Early versus delayed cord clamping, Outcome 16 Respiratory distress syndrome

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 16 Respiratory distress syndrome

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kinmond 1993	16/19	15/17		68.8	0.95 [0.74, 1.24]
Rabe 2000	4/20	7/19		31.2	0.54 [0.19, 1.56]
Total (95% CI)	39	36		100.0	0.83 [0.59, 1.15]

Total events: 20 (Early), 22 (Delayed)

Test for heterogeneity chi-square=1.79 df=1 p=0.18 I^2 =44.0%

Test for overall effect z=1.14 p=0.3

Analysis 01.17. Comparison 01 Early versus delayed cord clamping, Outcome 17 Severe respiratory distress syndrome

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

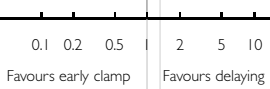
Outcome: 17 Severe respiratory distress syndrome

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Rabe 2000	4/20	3/19		100.0	1.27 [0.33, 4.93]
Total (95% CI)	20	19		100.0	1.27 [0.33, 4.93]

Total events: 4 (Early), 3 (Delayed)

Test for heterogeneity: not applicable

Test for overall effect z=0.34 p=0.7



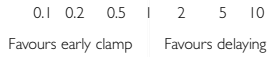
Analysis 01.18. Comparison 01 Early versus delayed cord clamping, Outcome 18 Ventilated for respiratory distress syndrome

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 18 Ventilated for respiratory distress syndrome

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kinmond 1993	13/19	13/17		42.9	0.89 [0.60, 1.34]
McDonnell 1997	9/23	9/23		28.2	1.00 [0.49, 2.06]
Rabe 2000	8/20	9/19		28.9	0.84 [0.41, 1.73]
Total (95% CI)	62	59		100.0	0.91 [0.65, 1.28]
Total events: 30 (Early), 31 (Delayed)					
Test for heterogeneity chi-square=0.11 df=2 p=0.94 I^2 =0.0%					
Test for overall effect z=0.55 p=0.6					



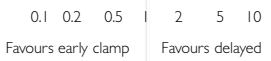
Analysis 01.19. Comparison 01 Early versus delayed cord clamping, Outcome 19 Surfactant treatment

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 19 Surfactant treatment

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
McDonnell 1997	4/23	6/23		59.4	0.67 [0.22, 2.05]
Rabe 2000	4/20	4/19		40.6	0.95 [0.28, 3.27]
Total (95% CI)	43	42		100.0	0.78 [0.34, 1.79]
Total events: 8 (Early), 10 (Delayed)					
Test for heterogeneity chi-square=0.17 df=1 p=0.68 I^2 =0.0%					
Test for overall effect z=0.58 p=0.6					



Analysis 01.21. Comparison 01 Early versus delayed cord clamping, Outcome 21 Oxygen supplementation at 28 days

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 21 Oxygen supplementation at 28 days

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kinmond 1993	3/19	0/17		100.0	6.30 [0.35, 113.81]
Total (95% CI)	19	17		100.0	6.30 [0.35, 113.81]
Total events: 3 (Early), 0 (Delayed)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.25 p=0.2					

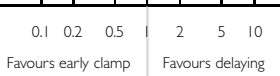
Analysis 01.22. Comparison 01 Early versus delayed cord clamping, Outcome 22 Oxygen supplementation at 36 weeks

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 22 Oxygen supplementation at 36 weeks

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Oh 2002	3/13	3/13		49.4	1.00 [0.25, 4.07]
Rabe 2000	3/20	3/19		50.6	0.95 [0.22, 4.14]
Total (95% CI)	33	32		100.0	0.97 [0.35, 2.69]
Total events: 6 (Early), 6 (Delayed)					
Test for heterogeneity chi-square=0.00 df=1 p=0.96 I^2 =0.0%					
Test for overall effect z=0.05 p=1					



Analysis 01.23. Comparison 01 Early versus delayed cord clamping, Outcome 23 Necrotizing enterocolitis

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 23 Necrotizing enterocolitis

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Oh 2002	4/17	2/16		80.1	1.88 [0.40, 8.90]
Rabe 2000	1/20	0/19		19.9	2.86 [0.12, 66.11]
Total (95% CI)	37	35		100.0	2.08 [0.52, 8.37]

Total events: 5 (Early), 2 (Delayed)

Test for heterogeneity chi-square=0.05 df=1 p=0.81 I^2 =0.0%

Test for overall effect z=1.03 p=0.3

Analysis 01.24. Comparison 01 Early versus delayed cord clamping, Outcome 24 Cord pH

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 24 Cord pH

Study	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Hofmeyr 1993	14	7.18 (0.11)	24	7.23 (0.20)		18.4	-0.05 [-0.15, 0.05]
McDonnell 1997	23	7.23 (0.11)	23	7.20 (0.12)		40.5	0.03 [-0.04, 0.10]
Rabe 2000	20	7.29 (0.07)	19	7.27 (0.13)		41.1	0.02 [-0.05, 0.09]
Total (95% CI)	57		66			100.0	0.01 [-0.03, 0.05]

Test for heterogeneity chi-square=1.85 df=2 p=0.40 I^2 =0.0%

Test for overall effect z=0.52 p=0.6

Analysis 01.25. Comparison 01 Early versus delayed cord clamping, Outcome 25 Apgar score at 5th minute < 8

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 25 Apgar score at 5th minute < 8

Study	Early n/N	Delayed n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Hofmeyr 1988	4/24	0/14		4.4	5.40 [0.31, 93.42]
Hofmeyr 1993	7/45	8/39		59.8	0.76 [0.30, 1.90]
Rabe 2000	7/20	5/19		35.8	1.33 [0.51, 3.48]
Total (95% CI)	89	72		100.0	1.17 [0.62, 2.20]

Total events: 18 (Early), 13 (Delayed)

Test for heterogeneity chi-square=2.02 df=2 p=0.36 I^2 =1.2%

Test for overall effect z=0.47 p=0.6

Analysis 01.26. Comparison 01 Early versus delayed cord clamping, Outcome 26 Temperature on admission (degrees Celsius)

Review: Early versus delayed umbilical cord clamping in preterm infants

Comparison: 01 Early versus delayed cord clamping

Outcome: 26 Temperature on admission (degrees Celsius)

Study	Early N	Early Mean(SD)	Delayed N	Delayed Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Rabe 2000	20	36.90 (0.50)	19	37.10 (0.15)		100.0	-0.20 [-0.43, 0.03]
Total (95% CI)	20		19			100.0	-0.20 [-0.43, 0.03]

Test for heterogeneity: not applicable

Test for overall effect z=1.71 p=0.09