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Umbilical Cord Management for Newborns <34 weeks' gestation: a meta-analysis

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Conflict of Interest: Anna Lene Seidler is the chair of the iCOMP collaboration, a meta-analysis on cord clamping management using individual participant data. Lelia Duley was Chief Investigator for the Cord Pilot Trial, collaborator for APTS, and a member of the Secretariat for iCOMP. She was awarded an NIHR grant for applied research for a program of work on care at very preterm birth, which included the Cord Pilot Trial. Gill Gyte was an investigator for the Cord Pilot Trial. Heike Rabe is main author for two included studies in this review. In the event that an author of this review was also an author on an included study, they did not assess eligibility, extract data, or assess risk of bias for the study on which they were an author. Roger Soll and Colleen Ovelman work in the editorial office for Cochrane Neonatal, which received a contract from the American Heart Association as a Knowledge
Synthesis Unit to undertake this systematic review for ILCOR. Roger Soll was a collaborator for The Australian Placental Transfusion Study (APTS). The other authors have indicated they have no potential conflicts of interest to disclose.

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**Abbreviations:**
GRADE: Grading of Recommendations Assessment, Development and Evaluation  
ECC: Early cord clamping  
DCC: Delayed cord clamping  
ICM: Intact-cord milking  
RR: Relative risk  
CI: Confidence interval  
ILCOR: International Liaison Committee on Resuscitation  
RCT: Randomized controlled trial  
CoSTR: Consensus on Science with Treatment Recommendations  
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
WHO: World Health Organization  
NNB: Number needed to benefit  
IVH: Intraventricular hemorrhage  
NEC: Necrotizing enterocolitis  
MD: Mean difference  
CCM: Cut-cord milking  
NMA: Network meta-analysis

**Table of Contents Summary:**
This systematic review and meta-analysis synthesizes the effects of umbilical cord management strategies (timing of clamping, cord milking) in preterm infants <34 weeks' gestational age.
Contributors’ Statement:

Ms. Seidler conceptualized the protocol, designed the data collection forms, selected studies for inclusion, extracted data, assessed risk of bias and certainty of evidence, carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript.
Ms. Gyte conceptualized the protocol, designed the data collection forms, selected studies for inclusion, extracted data, assessed risk of bias and certainty of evidence, carried out the analyses and reviewed the manuscript.
Ms. Ovelman assisted with protocol development and study selection, checked data extractions, risk of bias assessments, carried out subgroup analyses and reviewed and prepared the manuscript.
Dr. Soll conceptualized the protocol, supervised study selection, data extraction, risk of bias and certainty of evidence assessments, and data analyses, and drafted, reviewed and revised the manuscript.
Drs. Rabe, Díaz-Rossello, Duley, Aziz, Testoni, Davis, Schmölzer, and Askie conceptualized the protocol and critically reviewed the manuscript for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Abstract

Background

The International Liaison Committee on Resuscitation prioritized scientific review of umbilical cord management strategies at preterm birth.

Objectives

To determine the effects of umbilical cord management strategies (including timing of cord clamping and cord milking) in preterm infants <34 weeks' gestation.

Methods

Cochrane Central Register of Controlled Trials, MEDLINE, PubMed, Embase, CINAHL and trial registries were searched through July 2019 for randomized controlled trials (RCT) assessing timing of cord clamping and/or cord milking. Two authors independently assessed trial eligibility, extracted data, appraised risk of bias, and assessed evidence certainty (GRADE).

Results

We identified 42 randomized controlled trials (including 5772 infants) investigating four different comparisons of cord management interventions. Compared to early cord clamping (ECC), delayed cord clamping (DCC) and intact-cord milking (ICM) may slightly improve survival, however, both are compatible with no effect (DCC: RR (95% CI) 1.02 (1.00, 1.04), n=2988 infants, moderate certainty evidence; ICM: RR (95% CI) 1.02 (0.98, 1.06), n=945 infants, moderate certainty evidence). DCC and ICM both probably improve hematologic measures but may not affect major neonatal morbidities.

Limitations

For many of the included comparisons and outcomes, certainty of evidence was low. Our subgroup analyses were limited by few studies reporting subgroup data.

Conclusions
Delayed cord clamping appears to be associated with some benefit for infants born <34 weeks. Cord milking needs further evidence to determine potential benefits or harms. The ideal cord management strategy for preterm infants is still unknown, but early clamping may be harmful.

**PROSPERO Protocol Registration:** CRD42019155475
Background

Immaturity of multiple organ systems puts preterm babies born at less than 34 weeks’ gestation at high risk for mortality and morbidities such as intraventricular hemorrhage, and they are more likely to need resuscitation and stabilization at birth compared to those born late preterm or at term. They therefore require different policies and management than infants born late preterm or term.

Umbilical cord management affects every one of the 15 million babies born preterm annually. There is growing evidence that umbilical cord management at birth may influence survival, and major neonatal morbidities associated with preterm birth. Currently, there are several alternative cord management strategies, including deferring clamping based on timing or consideration of the infants’ respiratory status (from here on referred to as delayed cord clamping), or milking the intact or cut cord.

Several mechanisms are proposed to explain how cord management might influence infant mortality and morbidity. At the time of birth approximately 30% of the fetal-placental circulation is outside the fetus. If the cord is not clamped immediately at birth, blood flow between the placenta and the infant may continue which may increase placental transfusion - the net transfer of blood from the placenta to the infant. Cord management at birth impacts not only the volume of placental transfusion to the infant, but also the cardiovascular transition around the onset of breathing and/or ventilation. Early cord clamping before establishment of respiration may be associated with major hemodynamic consequences especially in extremely preterm and non-vigorous babies who are at high risk of brain injuries.

In 2015, the International Liaison Committee on Resuscitation (ILCOR) statement gave a weak recommendation for delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth. The statement identified many knowledge gaps
regarding cord management for both infant and maternal outcomes. To derive stronger recommendations, more evidence is required on existing strategies (such as delayed cord clamping, and milking of the intact or cut cord) and innovative techniques (such as resuscitation with intact-cord) in a variety of neonatal populations. There have been many randomized controlled trials (RCTs) published since the latest ILCOR recommendations in 2015, including the largest to date addressing delayed cord clamping at preterm birth. This systematic review and meta-analysis includes this latest evidence. Simultaneously, the ILCOR Consensus on Science with Treatment Recommendations (CoSTR) was completed in collaboration with the Cochrane Neonatal group. This will be published separately.

Objective
To determine the effects of different umbilical cord management strategies (including timing of clamping and cord milking) at preterm birth <34 weeks' gestational age.

Methods
This review was conducted following the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adheres to the PRISMA reporting guidelines. The protocol was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019155475). Full methods are detailed in Appendix 1.

Eligibility criteria: We considered all randomized controlled trials and cluster randomized controlled trials comparing alternative umbilical cord management strategies at preterm birth <34 weeks' gestational age or with low birth weight <2500 g. Studies were included if they reported a mean gestational age of <34 weeks or if more than 80% of the births were <34 weeks’ gestation.

Studies comparing the following umbilical cord management interventions were included in this review:
1. **Early cord clamping**, defined as application of a clamp to the cord less than 30 seconds of birth, without cord milking;

2. **Later (delayed) cord clamping**, defined as application of a clamp to the cord greater than or equal to 30 seconds after birth or based on physiologic parameters (such as when cord pulsation has ceased or breathing has been initiated), without cord milking;

3. **Intact-cord milking (also referred to as “stripping”),** defined as repeated compression of the cord from the placental side toward the infant with the connection to the placenta intact at any time point within the first few minutes after birth;

4. **Cut-cord milking (also referred to as “stripping”),** defined as drainage of the cord by compression from the cut end toward the infant after clamping and cutting a long segment.

**Outcomes:** Review outcomes were selected in consultation with representatives from the World Health Organization (WHO) and ILCOR. They comprised infant and maternal outcomes that were seen as clinically relevant and therefore likely to change clinical practice. All outcomes and their definitions have been summarized in Table 1. Pre-specified subgroup analyses, search strategy, study selection, data extraction, risk of bias evaluation, certainty of evidence assessment, and data synthesis are detailed in Appendix 1.

**Results**

**Literature search and study selection**

Forty-two studies (reported in 102 articles) including 5772 infants met the inclusion criteria for the review, of which 41 studies (including 5,676 infants) had data which could be included in the meta-analysis (see Figure 1: study flow diagram; Appendix 3: full list of included studies per comparison).

**Study and participant characteristics of included studies**

Study characteristics and participant characteristics for the included studies are outlined for each comparison in Supplementary Tables 1a-1d and Tables 2a-2d, respectively.
All of the included studies were individual randomized controlled trials (unit of randomization was either the mother or the infant). Studies were undertaken in a range of countries, but most were high-income, using the World Bank country classifications. Most studies excluded infants with complications such as major malformations or congenital anomalies.

**Risk of bias**

Risk of bias is summarized in Figure 2. The majority of studies were at low risk of selection bias (62% low for random sequence generation, 71% low for allocation concealment). All included studies were at high risk of performance bias, as it is difficult, if not impossible, to blind the clinicians managing the infant’s care. Blinding of outcome assessment was rated separately for delivery room outcomes and outcomes assessed at a later stage. While risk of bias was high across all studies for delivery room outcomes (due to the nature of the intervention), it was low for most studies (55%) for other outcomes. Most studies were at low risk of attrition bias. There were some concerns regarding selective outcome reporting bias.

Evidence Profile Tables were collated for primary and key secondary outcomes applying the GRADE framework. These include details on risk of bias (Supplementary Tables 2 to 5).

**Synthesis of results**

**Comparison 1. Later (delayed) cord clamping (DCC) compared to early cord clamping (ECC)**

We identified 23 studies including 3514 infants comparing delayed cord clamping DCC to early cord clamping ECC. Studies were undertaken in a range of countries, mostly high-income. Most studies included births before 32 to 34 weeks' gestation and were conducted at a single center (78%), but the largest RCTs were multi-center (22%). The studies covered a variety of timings of cord clamping and positioning of the infant. Timing of DCC ranged between 30 seconds and ≥120 seconds, with half the studies (52%) delayed by 30-45 seconds.
Timing of early or immediate cord clamping ranged from within 5 seconds to within 30 seconds across studies; most studies (69%) clamped within 10 seconds.

Results for all primary and key outcomes are summarized in Table 3a. Compared to ECC, DCC may improve neonatal survival (or reduce neonatal mortality) or may make no difference (survival: risk ratio (RR) 1.02, 95% confidence interval (CI) 1.00 to 1.04 (Figure 3); Number needed to benefit (NNB) 50, 95% CI 25 to no benefit; 16 studies, 2988 infants; I² = 0%, (certainty of evidence moderate). This translates into a RR 0.80 (95% CI 0.63 to 1.02) for the inverse outcome of mortality (post-hoc analysis, Supplementary Table 6).

There was no clear difference in the number of infants with severe intraventricular hemorrhage (IVH) (RR 0.98, 95% CI 0.67 to 1.42) and necrotizing enterocolitis (NEC) (RR 0.83, 95% CI 0.61 to 1.13). There was little to no difference for chronic lung disease (RR 1.03, 95% CI 0.94 to 1.13) and hyperbilirubinemia treated by phototherapy (RR 0.99, 95% CI 0.95 to 1.03).

DCC probably improves hematologic measures. Peak hemoglobin and hematocrit (%) were probably higher for DCC compared to ECC within 24 hours after birth (peak hemoglobin: mean difference (MD) 1.24 g/dL, 95% CI 0.01 to 2.47; peak hematocrit: MD 2.63%, 95% CI 1.85 to 3.42) and peak hematocrit was higher within seven days after birth (MD 2.70%, 95% CI 1.88 to 3.52).

The evidence was unclear for survival without moderate or severe neurodevelopmental impairment in early childhood (RR 0.96, 95% CI 0.78 to 1.17). None of the included studies assessed other early childhood outcomes. Compared with ECC, DCC may make little or no difference to maternal complications including any postpartum hemorrhage≥500 mL (RR 0.93, 95% CI 0.54 to 1.62), severe postpartum hemorrhage≥1000 mL, use of therapeutic uterotonic agents, blood transfusion, manual removal of the placenta, or postpartum infection.
No studies reported on maternal deaths, severe morbidity or additional treatment for postpartum hemorrhage. One study reported on mothers’ views and experiences.\textsuperscript{23,24}

Other outcomes are detailed in Supplementary Table 7a. Few differences were found except for hematological outcomes: Compared to ECC, infants in the DCC group had less inotropic support for hypotension during the first 24 hours of life (RR 0.36, 95% CI 0.17 to 0.75), a higher measurement of lowest mean arterial blood pressure in the first 12 hours of life (MD 1.79 mmHg, 95% CI 0.53 to 3.05), lower incidence of any blood transfusion (RR 0.83, 95% CI 0.77 to 0.90), and a lower total number of blood transfusions per infant (MD -0.63, 95% CI -1.08 to -0.17) during hospital course.

**Comparison 2. Intact-cord milking compared to early cord clamping**

We identified 13 studies comparing intact-cord milking (ICM) with early cord clamping (ECC) (Table 2b). Studies in Comparison 2 included 1170 infants, all were single center. Two studies (18%) included only preterm births <30 weeks. Timing of ECC ranged between clamping immediately and within 20 seconds of birth, and most studies (69%) clamped immediately. For ICM, the cord was milked between 2 and 4 times, with most studies (54%) milking 3 times.

Compared with ECC, ICM may make no difference, slightly decrease or slightly improve survival to discharge (RR 1.02, 95% CI 0.98 to 1.06; I\(^2\) =24%), 10 studies, 945 infants, (certainty of evidence moderate) (Figure 4). This translates into an RR 0.77 (95% CI 0.49, 1.23) for the inverse outcome of mortality (post-hoc analysis, Supplementary Table 6). We found no clear difference for severe IVH (RR 0.72, 95% CI 0.44 to 1.19), chronic lung disease (RR 1.02, 95% CI 0.63 to 1.65), and NEC (RR 0.80, 95% CI 0.55 to 1.18) and there was little or no difference for hyperbilirubinemia treated by phototherapy (RR 1.04, 95% CI 0.94 to 1.16).
ICM probably improves hematologic measures within 24 hours after birth. Peak hemoglobin and hematocrit (%) were higher for ICM compared to ECC within 24 hours after birth (peak hemoglobin: MD 1.18 g/dL, 95% CI 0.65 to 1.71; peak hematocrit: MD 3.04%, 95% CI 1.28 to 4.80). Evidence was uncertain for peak hematocrit and hemoglobin within 7 days after birth.

Limited data are available regarding outcomes in later infancy. Certainty of evidence was very low for moderate to severe neurodevelopmental impairment in early childhood (RR 0.75, 95% CI 0.21 to 2.71) and cerebral palsy in early childhood (RR 2.65, 95% CI 0.88 to 7.97). There were no studies assessing sensory outcomes in later infancy.

The evidence is uncertain about maternal complications including severe postpartum hemorrhage ≥ 1000 mL or blood transfusion, and there were no studies assessing other maternal complications such as postpartum hemorrhage ≥ 500 mL (Table 3b).

Other outcomes are detailed in Supplementary Table 7b. In infants, few differences were found with the exception of less inotropic support for hypotension during the first 24 hours of life (RR 0.61, 0.44 to 0.84) and fewer infants receiving at least one blood transfusion (RR 0.73, 95% CI 0.56 to 0.94) in the ICM group.

**Comparison 3. Cut-cord milking compared to early cord clamping**

We identified one single center study of 60 infants evaluating cut-cord milking (CCM) compared to early cord clamping (ECC). The evidence was uncertain for the incidence of survival or its inverse mortality to hospital discharge, with no deaths in either group.

Evidence was also uncertain for severe IVH (RR 0.33, 95% CI 0.01 to 7.87), chronic lung disease (RR 1.00, 95% CI 0.07 to 15.26) and NEC (RR 0.50, 95% CI 0.05 to 5.22). CCM may increase peak hematocrit concentrations within 24 hours after birth (MD 3.34%, 95% CI 0.60 to 6.08). The study did not report other hematological measures and did not assess any
of the included early childhood or maternal outcomes. Other outcomes are detailed in Supplementary Table 7c.

Comparison 4. Later (delayed) cord clamping compared to intact-cord milking

We identified seven studies including 1073 infants comparing later (delayed) cord clamping (DCC) to intact-cord milking (ICM). The studies were published between 2011 and 2019, and most were single-center (71%). Timing of DCC ranged between 30 and 180 seconds, and most studies (71%) delayed 30-60 seconds. For ICM, the cord was milked between 3 and 4 times, with most studies (71%) milking 4 times.

Compared with ICM, DCC may make no difference, slightly decrease or slightly improve survival to discharge (RR 0.99, 95% CI 0.95 to 1.02; I² = 14%; 5 studies, 1000 infants, certainty of evidence moderate) (Figure 5). This translates into an RR 1.21 (95% CI 0.76, 1.94) for the inverse outcome of mortality (post-hoc analysis, Supplementary Table 6).

There were no clear differences for key neonatal morbidities of severe IVH (RR 0.60, 95% CI 0.32 to 1.12), chronic lung disease (RR 0.91, 95% CI 0.67 to 1.25), NEC (RR 1.57, 95% CI 0.83 to 2.97) and hyperbilirubinemia treated phototherapy (RR 1.05, 95% CI 0.90 to 1.24).

There were also no clear differences between DCC and ICM for hematologic measures within 24 hours (peak hemoglobin concentrations (g/dL): MD -0.02, 95% CI -0.56 to 0.53, peak hematocrit concentrations (%) MD -0.18, 95% CI -1.90 to 1.54). No studies reported data on peak hemoglobin or peak hematocrit concentration within 7 days after birth.

Limited data are available regarding outcomes in later infancy. Certainty of evidence was low for moderate to severe neurodevelopmental impairment (RR 0.22, 95% CI 0.01 to 4.40), cerebral palsy in early childhood (RR 0.36, 95% CI 0.01 to 8.65) and significant developmental delay in early childhood (RR 14.06, 95% CI 0.83 to 237.84). One study assessed legal blindness and reported no events, and no studies assessed hearing deficits.
No studies reported the included maternal outcomes. Other outcomes are detailed in Supplementary Table 7d. Few differences were found between ICM and DCC.

**Comparisons 5-8:** No studies were identified for any of these comparisons (DCC versus CCM, ICM versus CCM, DCC<60 sec versus DCC≥60 sec, time-based DCC versus physiological DCC).

**Subgroup analyses**

No patterns were identified in the subgroup analyses (Supplementary Table 8). The number of pre-specified subgroup analyses was large and p-values were not adjusted for multiple comparisons. Only two studies reported data by subgroup, limiting the ability to perform subgroup analyses.

**Discussion**

**Summary of main findings**

In this systematic review and meta-analysis, we identified 42 eligible studies with 5722 infants comparing cord management interventions. Compared to early clamping, delayed clamping may slightly improve infant survival but may make no difference (moderate quality evidence). We found moderate to high quality evidence that delayed clamping does not reduce or increase major neonatal morbidities, but it probably improves hematologic measures and may reduce the use for inotropes and blood transfusions in infants.

Compared to early clamping, intact milking may result in increased survival, slightly reduced survival, or no difference. We found low to moderate quality evidence indicating no clear difference in major neonatal morbidities such as chronic lung disease, IVH and NEC. Intact milking probably improves hematologic measures.

For the one study comparing early cord clamping with cut-cord milking, the evidence was very uncertain for infant survival and major morbidities. Cut-cord milking may increase peak hematocrit within 24 hours after birth.
Compared to intact-cord milking, delayed clamping probably results in little to no difference in survival, major neonatal morbidities, and hematologic measures. Across all comparisons, many of the infants could not be classified into the correct subgroup categories, and thus, meaningful subgroup differences are not possible to detect with the current data.

**Agreement and disagreement with previous research**

The latest comprehensive review in this area was a Cochrane review with searches conducted in November 2017. That review found a reduction in infant death for delayed compared to early clamping, a slight reduction in any IVH, but no reduction in severe IVH. There was insufficient evidence to derive conclusions for cord milking. Our review adds new information, since we identified and included eleven additional recently published trials.

While previous reviews included preterm infants up to 36 weeks’ gestational age, our review is limited to infants up to 34 weeks’. Although late preterm infants have increased risk for admission to neonatal intensive care and poor developmental outcome compared to term infants, they do not have the same serious morbidities experienced by less mature preterm infants. Therefore, 18 studies included in the Cochrane review were excluded from the current review, leading to a slightly smaller total number of infants (188 less), despite the eleven additional trials.

Previous reviews included infant mortality as a primary outcome, while this review assesses the inverse of mortality, survival, since this is the standard ILCOR approach. This changes the relative effect measures, as shown in our post-hoc sensitivity analysis comparing risk ratios for survival and mortality using the same data (Supplementary Table 6). The reason for this is that relative risk depends on the incidence of an event, which is higher for survival than mortality. Thus, the same absolute number of deaths can translate into different relative
risk estimates for survival or mortality. For instance, in comparison 1, in the delayed clamping group, 1383 (93%) infants survived and 107 (7%) died. In the early clamping group, 1364 (91%) infants survived and 134 (9%) died. This equals a 2% absolute difference for both survival (93%-91%=2%) and mortality (9%-7%=2%). However, since survival was more common than mortality, the relative risk indicates a small 2% increase in survival (RR = 0.93/0.91 = 1.02), but a much larger 20% relative risk reduction for mortality (RR = 0.07/0.09 = 0.80).

For comparison 1 (early versus delayed clamping), the relative risk for mortality (indicating a 20% reduction) is similar to that reported in previous reviews (e.g. 27% relative risk reduction in the Cochrane review). While for previous reviews this finding was statistically significant, in the current review the confidence interval touches the line of no effect. This may be due to different eligibility criteria for gestational age (as outlined above), or to the more recent studies included in the current review. We did not find a difference in survival between intact-cord milking and delayed clamping (comparison 4). Point estimates for survival with intact milking compared to early clamping (comparison 2) are similar to point estimates for delayed compared to early clamping (comparison 1), but confidence intervals are wider in comparison 2 due to fewer included studies. This suggests that intact milking may be comparable to delayed clamping for the outcome of survival, but more evidence is needed to confirm this.

This review finds improved hematological measures and reduced use of inotropes for delayed clamping, and intact and cut milking compared to early clamping, in accordance with previous reviews. This supports the proposed mechanism of placental transfusion (i.e. increased net transfer of blood from the placenta to the infant) through delayed clamping or milking. Our findings do not suggest a difference between delayed clamping and milking with respect to hematological measures.
While previous reviews report differences in IVH rates for different cord management strategies, we did not find evidence for this in the current review. Animal models have demonstrated that during umbilical cord milking there was an increase in carotid blood flow and pressure. In addition, a recent trial comparing delayed clamping with milking was stopped early in the subgroup of very preterm infants (<28 weeks’ gestation), due to a higher incidence of severe IVH in the milking group. Thus, there may be different IVH risks related to cord management strategies depending on gestational age. Further evidence is required to resolve this question. In addition, not all studies in the current review were blinded for IVH, which is problematic since ultrasound diagnosis of IVH can be rater-dependent. Consequently, we downgraded certainty of evidence for this outcome.

Few studies reported developmental outcomes in early childhood, and the evidence was uncertain for all comparisons. One study published outcomes in early childhood for early clamping compared to delayed clamping (comparison 1) shortly after our search date, and was therefore not included in the analysis. This study found that delayed clamping may reduce the risk of death or adverse neurodevelopmental outcome at 2 years of age for children born <32 weeks, but confirmation in larger studies is needed.

**Implications for practice and research**

Cord management at preterm birth is an active research field, evidenced by the number of additional studies included in this review compared to previous reviews. The searches for the latest Cochrane update were conducted in November 2017. In less than two years (search to July 2019), we identified eleven new studies. Still, more evidence is being generated - a search in February 2019 identified an additional 62 ongoing trials evaluating cord management strategies in preterm infants.

Ultimately, we want to answer the question: ‘which cord management strategy is the best and for whom?’ The current study takes a step toward answering this question, by looking at
different comparisons analysed in pairwise meta-analyses. Yet, there is insufficient evidence, using aggregate data, to derive a definite answer, particularly when assessing differences for key infant subgroups. Once ongoing trials are completed, a network meta-analysis (NMA) will be possible, which allows comparing and ranking of multiple interventions simultaneously.\textsuperscript{42} For assessing differential treatment effects across subgroups, the use of individual participant data can increase statistical power and reduce the risk of ecological bias.\textsuperscript{43} The iCOMP Collaboration is collating individual participant data from ongoing and completed trials, to perform NMA and subgroup analyses to resolve remaining questions.\textsuperscript{41} Investigators planning future trials in this area should follow a prospective meta-analysis framework in collaboration with iCOMP, to target evidence gaps and avoid research waste.\textsuperscript{44}

**Strengths and limitations**

Strengths of this review include its rigorous methods, including a prospectively registered protocol, comprehensive search strategy, two reviewers independently completing each step of the review process, and the use of GRADE to determine certainty of evidence.\textsuperscript{45} The author team constitutes a collaboration of world experts in systematic reviews, neonatology, and obstetrics, including the ILCOR taskforce, the Cochrane Neonatal and Pregnancy & Childbirth groups, and independent experts in cord management.

Yet, there are several limitations. For many reported comparisons and outcomes, certainty of evidence was low or very low, or no studies were available. This was mainly due to imprecision, and in some cases due to inconsistency and risk of bias. For four of the pre-specified comparisons, no studies were identified. In this review, only pairwise comparisons are presented - we did not conduct analyses comparing all available comparisons simultaneously (network meta-analysis). Our subgroup analyses were limited by most studies not reporting outcomes separately by subgroup, highlighting the need for individual participant data to resolve these questions. Definitions for early and delayed clamping and
milking varied across studies. Delayed clamping ranged from 30 seconds to over 2 minutes, and early clamping ranged from within 5 seconds to within 30 seconds. Thus, in some instances early and delayed clamping groups may have received similar interventions.

**Conclusion**

Delayed cord clamping at preterm birth may be beneficial compared to early clamping, and these benefits appear to be hemodynamic, but additional evidence is required to confirm this. There is some evidence that intact-cord milking may be similarly beneficial, but this needs further study. Additional evidence from ongoing trials and individual participant data network meta-analysis is required to determine which cord management strategies are the most advantageous and for whom.

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