Abstract

Introduction: Timing of umbilical cord clamping and other cord management strategies may improve outcomes at preterm birth. Trials comparing such strategies often recruit at different gestations and compare alternative policies, including immediate cord clamping, short (30 seconds), medium (45 seconds) or long deferrals (up to 5 minutes) and 'milking' the cord. Individual participant data (IPD) enables exploration of subgroups to give differential cord management recommendations for different groups of participants. Network meta-analysis (NMA) methods enable to compare and rank all available interventions using a combination of direct and indirect comparisons of multiple treatment options by integrating all the available data.

Objectives: 1) To evaluate the effectiveness of cord management strategies on neonatal mortality and morbidity overall and for different patient characteristics using IPD meta-analysis; and 2) to evaluate and rank the effect of different cord management strategies for preterm births on mortality using NMA.

Methods and analysis: Systematic search for all planned, ongoing and completed randomised controlled trials that compare alternative cord management policies (such as different timing of cord clamping and/or cord milking) at preterm birth (before 37 weeks' gestation). The trials will be identified by searching Medline, Embase, clinical trial registries, and other sources. IPD will be sought for all trials. First, deferred clamping and cord milking will be compared with immediate clamping in IPD meta-analyses. The primary outcome will be death (at any time). Secondary outcomes will include morbidities and harms. Effect differences will be explored for pre-specified subgroups of participants. Second, all identified cord management strategies will be compared and ranked in an IPD NMA for the primary outcome death, and differential treatments depending on participant characteristics will be identified using meta-regression and subgroup analyses. Inconsistency and heterogeneity will be explored.

Ethics and dissemination: Approved by the University of Sydney Human Research Ethics Committee (2018/886). Results will be relevant to clinicians, guideline-developers, policy-makers and the global research community, they will be disseminated to these groups through publications, conference presentations and media releases.

Registration

Keywords: Preterm birth, umbilical cord clamping, umbilical cord milking, placental transfusion, individual participant data meta-analysis, prospective meta-analysis, network meta-analysis

Introduction

Preterm birth is an important determinant of adverse outcome for the child, as well as the family and health services.[1] Each year, 15 million babies are born too soon (before 37 weeks gestation) and the number is rising.[2-4] Of these, 1.1 million babies die, and preterm birth is now the second most common cause of death in children under five years of age.[2] Preterm birth is more common in low and middle-income countries.[2] There are stark inequalities in survival, with 95% survival in high-income countries compared to 30% in low-income countries for babies born at 28-32 weeks gestation.[3] Worldwide, preterm birth is a risk factor for half of all neonatal deaths.[3]

For those born preterm who survive, morbidity and health service costs are high compared to babies born at term. In the UK, hospital stay lasts 85 times longer for babies born before 28 weeks than for term infants; and 16 times longer for those born at 28-31 weeks.[5] Total cost to the UK public sector of very preterm birth (before 32 weeks) is estimated at £1 billion annually.[6] Of very premature infants (<28 weeks) who survive, 5-10% develop cerebral palsy; and 25% develop neurosensory disability.[1] Those without severe disability have increased risk of developmental, cognitive, and behavioural difficulties.[7-10] Teenagers and young adults born very preterm report poorer physical abilities and more chronic ill health than their peers born at term, although similar health-related quality of life.[11,12] Prematurity and its sequelae may have a negative psychosocial and emotional impact on parents and families.[1] Even modest improvement in outcome would be of substantial benefit to the children, their families, and health services.

Neonatal transition and blood transfer in preterm infants

Net transfer of blood from the placenta to the baby is known as 'placental transfusion'. If the umbilical cord is not clamped immediately at birth, blood flow between the baby and placenta may continue for a few minutes. Blood flow may continue without any net transfer, however, and sometimes net transfer may be to the placenta.[13]

As the baby is born, umbilical circulation slows and pulmonary vascular resistance falls, rapidly increasing pulmonary blood flow volume. Continued flow in the umbilical vein and arteries at birth may be part of the physiological mechanisms assisting the baby during this transition from fetal to neonatal circulation. For term births, umbilical blood flow may continue for up to five minutes or longer.[14,15] For preterm births, umbilical blood flow may continue for longer,[16] since a greater proportion of feto-placental circulating blood volume is still in the placenta (while at term two-thirds are in the infant with one third in the cord and placenta).[17]

Time of umbilical cord clamping

Animal and pilot human studies suggest that breathing and lung aeration before cord clamping can improve cardiovascular stability and oxygenation and reduce infant mortality, and intraventricular haemorrhage.[18-21] Other animal and pilot studies suggest that initial respiratory support for up to 5 minutes before cord clamping results in improved blood pressure and cerebral oxygenation and reduced cerebrovascular impairment compared with immediate cord clamping.[22,23] One potential mechanism of benefit of deferred clamping is allowing time for the infant to establish spontaneous breathing whilst still placentally supported, thus avoiding invasive interventions such as endotracheal intubation in the delivery room.

Without the assistance of video or extra equipment, clinicians record the time when the cord is clamped more accurately and consistently than the time when vigorous breathing begins. In unpublished data from an earlier study,[24] Katheria found that time of onset of breathing in preterm infants receiving gentle stimulation is related to time after birth – within a minute over 90% of preterm infants had begun spontaneous breathing (r squared=0.91, $P<0.001$) (personal communication). Thus the longer after birth the cord is clamped, the more likely is it that breathing has begun.

Cord milking

Cord milking (pinching the cord close to the mother and running the fingers towards the baby, usually several times) may be a way to increase preterm blood volume without deferring clamping.[25] However milking over-rides the infant's physiological control of its blood pressure and volume and disrupts umbilical flow. Animal data show that cord milking without allowing placental refill fails to provide placental transfusion, and milking can cause major haemodynamic disturbance.[26] A recent trial comparing deferred cord clamping with cord milking was stopped early in the subgroup of extremely preterm infants (23-27 weeks), as the incidence of severe intraventricular haemorrhage was higher in the cord milking group.[24] Hence, the effects of cord milking need further elucidation.

Other cord management issues

Initial neonatal care and stabilisation traditionally takes place on a resuscitation platform at the side of the room or in an adjacent room, away from the woman. For infants requiring resuscitation immediately at birth, this practice means the cord is usually clamped and cut immediately.

An alternate strategy is providing immediate neonatal care, including resuscitation if needed, with the cord intact beside the woman.[27,28] The recent Cord pilot trial[29] showed that neonatal stabilisation and resuscitation with cord intact is feasible and acceptable to parents and clinicians.[28,30-32]

Previous reviews of aggregate data

A 2012 Cochrane Review of timing of cord clamping for preterm births[33] included 15 trials, with 738 infants, one of which (with 40 infants) compared cord milking with immediate cord clamping.[34] There was heterogeneity in the timing of cord clamping and gestational age at recruitment, and data were insufficient for reliable conclusions about any of the primary outcomes of the review. A systematic review and meta-analysis published in 2018 (including 18 trials with 2834 participants) compared the effect of deferred (≥30 seconds) vs early (<30 seconds) clamping in preterm infants, and found a reduction the primary outcome hospital mortality by 32% (Risk Ratio = 0.68, 95% Confidence Interval = 0.52-0.90).[35] The main outcomes of this systematic review are summarised in Table 1. There was heterogeneity in the definition of 'early cord clamping' ranging from immediate or less than 5 seconds to 25 seconds, and 'late cord clamping, ranging from 30 seconds to 180 seconds, with most trials clamping after less than 60 seconds. Recruitment age varied from 22 weeks to 36+6 weeks. Most analyses of infant and maternal morbidity were substantially underpowered.[35] The review concludes that while there is high quality evidence that deferred cord clamping improves outcomes, individual participant data analyses of existing and new randomised controlled trials are urgently needed to further understand the benefits and potential harms of different cord management strategies, and to understand whether differential treatment options are advantageous for key subgroups of infants.[35]

Current guidelines and practice for cord management at birth

These uncertainties in optimal cord clamping strategies are reflected in varying guidelines. The World Health Organisation (WHO) recommends late cord clamping[36] unless resuscitation is required, the National Institute for Health and Clinical Excellence (NICE) recommends waiting for 30 seconds to 3 minutes if mother and baby are stable,[37] and the International Resuscitation Council (ILCOR) recommends a delay in cord clamping of at least 1 minute. NICE recommends positioning the baby positioned at or below the level of the placenta whilst deferring clamping, whilst WHO and ILCOR make no such recommendations. If the baby is assessed as requiring resuscitation (which is the case in many preterm infants),[38] WHO recommends immediate clamping,[39] NICE recommends to consider cord milking before clamping, and ILCOR

concludes that there is insufficient evidence to make any recommendations.[38] There is little information about actual practice for cord clamping.[40]

The current study

Overall, there is uncertainty about the optimal cord management strategy which has led to wide practice variation. It is also unclear whether there should be differential cord management strategies for key subgroups of infants, e.g. those for which resuscitation and/or stabilisation is deemed necessary, extremely preterm infants, or those with growth restriction. This uncertainty has led to 112 planned, ongoing or published trials (in more than 15,000 preterm babies) that are comparing a range of cord management strategies. Individual participant data (IPD) meta-analysis is the gold standard for combining such trial data. IPD will provide larger statistical power for estimation of treatment effects of rarer secondary endpoints and will enable reliable subgroup analyses to examine hypotheses about differences in treatment effect, exploring interactions between treatment- and participant-level characteristics.[41] A network meta-analysis (NMA) facilitates data synthesis when there is a range of interventions available and permits comparisons across all interventions, although some interventions may not have been directly compared in trials.[42] Indirect evidence for these comparisons is obtained by inferring the relative effectiveness of two competing treatments through a common comparator.[43] Network meta-analysis produces estimates of relative effects for each intervention compared with every other intervention in the network. These effect sizes can be used to obtain rankings of the effectiveness of the interventions.[44] Using individual participant data in a network meta-analysis (as opposed to aggregate data) can improve precision, increase information, and reduce bias.[45]

Objectives

The aims of this study are to:

1) evaluate the effectiveness of strategies of cord management on neonatal mortality and morbidity and to evaluate differential treatment by participant characteristics using individual participant data meta-analysis;
2) evaluate, compare and rank the effect of different cord management strategies for preterm births on mortality using network meta-analysis.

Methods and analysis

We will conduct a systematic review of randomised trials with individual participant data pairwise and network meta-analysis, and a nested prospective meta-analysis. The lead investigator for all

potentially eligible studies will be contacted and invited to collaborate and join the **i**ndividual participant data **C**o**r**d **M**anagement at **P**reterm birth (iCoMP) Collaboration. Eligible trials identified up to August 2018 are listed in Table 2. The Collaboration will undertake this project according to the methods recommended by the Cochrane Collaboration Individual Participant Data, Cochrane Multiple Interventions Group, and Prospective Meta-Analysis Methods Groups.[41,46,47] The protocol is registered at PROSPERO, the International Prospective Register of Systematic Reviews.[48] PRISMA-IPD and PRISMA-NMA statements will be followed for reporting.

Eligibility criteria

Types of studies

Studies will be included if they are randomised trials, quasi-random studies will be excluded. Studies must compare at least two of the interventions of interest (defined below).

Trial participants

Participants will be women giving birth preterm (before 37 completed weeks' gestation) and/or their babies. Individually randomised studies will be eligible for inclusion if the unit of randomisation was either the woman, or the baby. Women and babies will be included regardless of whether mode of delivery was vaginal or Caesarean, and whether the birth was singleton or multiple. Babies will be included regardless of whether or not they received immediate resuscitation at birth.

Types of interventions and comparators

Part 1: individual participant data pairwise meta-analysis

For the pairwise meta-analysis we will include all trials that compare an intervention to enhance umbilical blood flow or allow more time for physiological transition to the comparator immediate cord clamping. This includes interventions assessing cord management strategies for timing of cord clamping, and other strategies to influence umbilical flow and physiological transition (such as lowering the baby below the level of the placenta whilst cord intact, and umbilical cord milking or stripping). Studies will be included if they compare strategies to maintain 'physiological' umbilical flow (i.e. none or minimal intervention) and placental transfusion, and if they examine strategies that aim to alter umbilical blood flow and placental transfusion (such as using gravity by lowering the baby, or cord milking or stripping). Trials will be included regardless of whether initial neonatal care is provided with the umbilical cord intact, or not.

Different strategies (i.e. cord clamping and milking) will be analysed in separate subgroups to assess comparability between the groups by assessing subgroup effects and heterogeneity. They will then be collapsed into one 'cord management intervention' group if they are deemed comparable based on the previous subgroup assessments. If they are deemed non-comparable they will be analysed and interpreted separately.

Part 2: individual participant data network meta-analysis

For the network meta-analysis we will include as interventions of interest cord management strategies for timing of cord clamping, and other strategies to influence umbilical flow and placental transfusion.

Thus, interventions of interest include:

- Immediate cord clamping (within 30 seconds)
- Short deferral of cord clamping (>30 to ≤ 45 seconds) without milking
- Medium deferral of cord clamping (45 to ≤ 90 seconds) without milking
- Long deferral of cord clamping (≥ 90 seconds) without milking
- Umbilical cord milking or stripping before cord clamping
- Umbilical cord milking or stripping after immediate cord clamping
- Umbilical cord milking or stripping after deferred cord clamping
- Physiological clamping after onset of breathing

If we identify other interventions not listed above we will include them if they are addressing cord management or related strategies to influence umbilical flow and placental transfusion. Again, trials will be included regardless of whether initial neonatal care is provided with the umbilical cord intact, or not. Studies evaluating collection and storage of residual placental blood that is then used for transfusion after birth will be excluded. All possible comparisons between eligible interventions are displayed in Figure 1.

Nodes that specify different timings of cord clamping were defined according to what timing is classified as immediate clamping, short deferral, medium deferral or long deferral according in the literature to date (as shown in Table 2), and after discussion with clinicians. Different timings are commonly compared in head-to-head comparisons, hence, their classification as different intervention nodes. Similarly, nodes that specify cord milking were classified after a review of current milking techniques described in the literature and after discussion with clinicians.

If insufficient data are available, categories will be collapsed where possible. For instance, milking before and after cord clamping could be collapsed into one single cord milking category, or medium and long delay could be collapsed into a medium to long delay category. We consider the interventions of interest to be jointly randomisable (i.e. a participant could, in principle, be randomised to any one of the interventions of interest).

Types of outcome measures

Included trials must report at least one of the clinical outcomes included in this review as specified in the 'measures' section below to be included.

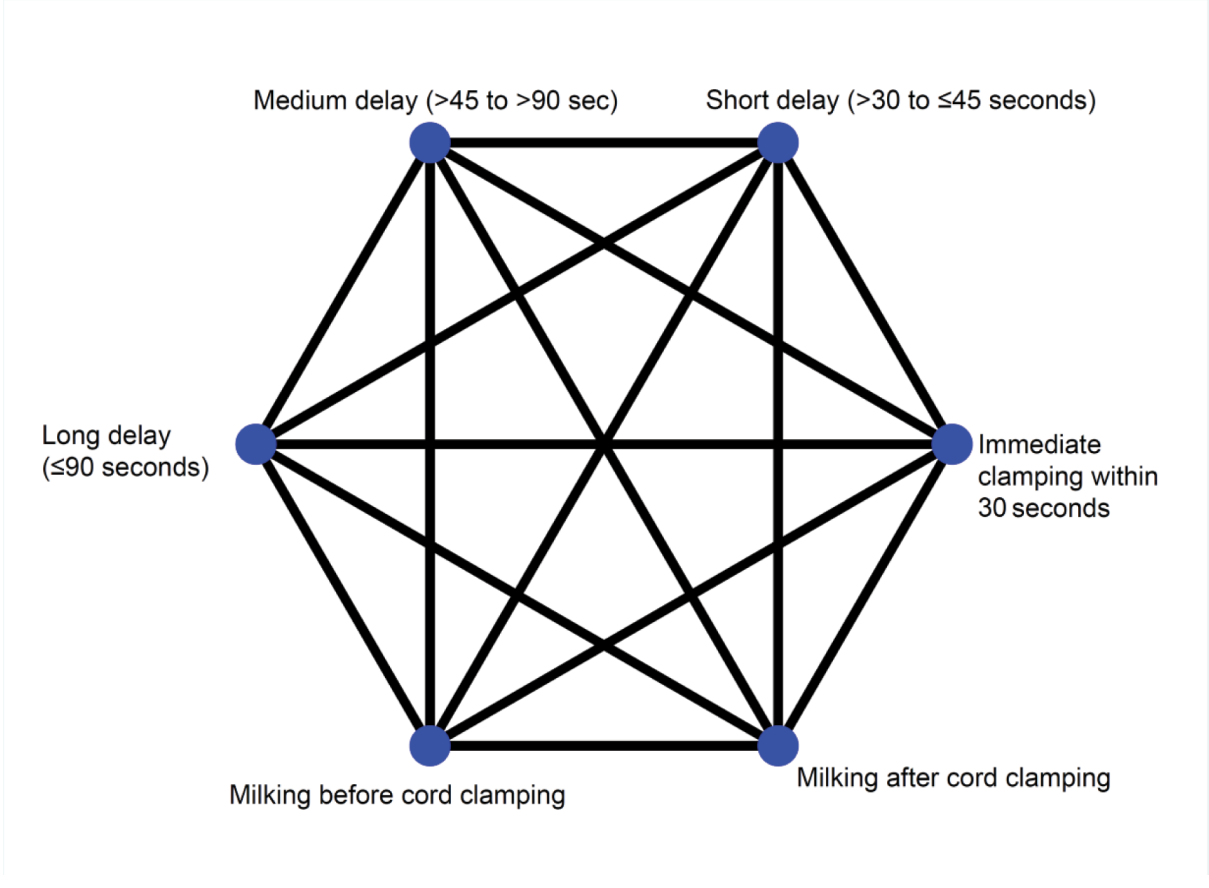

Figure 1. Network of possible comparisons between cord management interventions

Eligibility for nested prospective meta-analysis

Studies are only included in the nested prospective meta-analysis if the investigator/s were blind to outcome data by intervention group at the time the main components of the protocol (i.e. objectives, aims and hypotheses, eligibility criteria, subgroup and sensitivity analyses and main outcomes) were initially agreed in January 2015. Other planned or completed eligible trials will

be included in the first cycle of this IPD meta-analysis if their expected last participant enrolment is before end March 2019.

Information sources and search strategy

The search strategy to identify potentially eligible studies will include a search of the register of trials developed and maintained by the Cochrane Collaboration Pregnancy and Childbirth Review Group. The Cochrane Pregnancy and Childbirth Group's Trials Register contains trials identified from: monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of MEDLINE (Ovid); weekly searches of Embase (Ovid); monthly searches of CINAHL (EBSCO); hand searches of 30 journals and the proceedings of major conferences; and weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts. Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.[49] We will identify ongoing trials that may be eligible by searching for published protocols in Medline and Embase, searching online registries of clinical trials, and personal contacts (for example, by asking collaborators to notify any unregistered studies they are aware of). The Chief Investigators of eligible trials will be invited to join the iCoMP Collaboration. They will also be asked if they know of any further planned, ongoing or completed studies.

Selection of studies for inclusion in the review

Two members of the iCoMP Secretariat (see project management section below) will independently assess all the potentially eligible studies identified for inclusion. Disagreements will be resolved by discussion or, if required, by consulting a third member. Studies that are not willing or able to provide IPD will be will be synthesised where possible using aggregate data.

Data collection, management and confidentiality

Data receipt

De-identified, individual participant level data for each randomised participant will be provided by each participating trial. These data will be backed-up and stored in a secure, centralised database.

Data processing

Data checking: Range, internal consistency, consistency with published reports and missing items will be checked for each trial. Trial details such as randomisation methods and intervention timing will be cross-checked against any published reports, trial protocols and data collection sheets. Integrity of the randomisation process will be examined by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of prognostic factors across treatment groups (taking into account stratification factors). Inconsistencies or missing data will be discussed with the individual trialists and any problems will be resolved by consensus. Each trial will be analysed individually and the resulting analyses and trial data will be sent to the trialists for verification before inclusion in the iCoMP database. All trial specific outcomes generated from the individual participant data will be cross-checked against published information via a series of crosstabs.

Data re-coding: The outcome data may have been collected in different formats within the different trials. Therefore, the de-identified data collected from each of the participating trials will be extracted and re-formatted into a commonly coded dataset.

Data transformation and collating: Once the data from each of the trials are finalised, it will be combined into a common dataset, but a trial identifier code for each participant will be retained. New variables will be created from the combined dataset as required to address the hypotheses to be tested.

Risk of bias assessment and quality of evidence appraisal

Eligible studies will be assessed for risk of bias using the criteria described in the Cochrane Handbook:[50] random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. The quality of evidence will be assessed using the GRADE approach[51] for the pairwise comparisons, and the rating approach suggested by Salanti and colleagues for network meta-analysis that is implemented in the CINeMA application.[52]

Measures

Part 1: individual-participant data pairwise meta-analysis

Outcomes

All outcome measures are listed in Table 3. The primary outcome will be death of the baby at any time. As outcomes for babies born very preterm (before 32 weeks gestation) are different to those born moderately preterm (32 to 37 weeks), separate analyses will be conducted for these two groups of infants for the secondary outcomes. Where possible, definitions will be standardised, otherwise outcomes will be used as defined by the trialists. Secondary outcomes will include measures of neonatal and maternal morbidity, and health service use. There will be efficacy outcomes that cord management strategies, compared with immediate clamping, may improve such as death, late onset sepsis and severe intraventricular haemorrhage, and there will be safety outcomes reflecting potential risks of not clamping immediately such as postpartum haemorrhage, hypothermia and polycythaemia.

Covariates and subgroups

Subgroup analyses will be conducted for the primary outcome of death and key secondary outcomes, if sufficient data are available. All included covariates and subgroups are listed in Table 3. The comparative effects of alternative cord management strategies may vary depending on key infant risk factors, but also depending on the level and type of neonatal care available at the hospital of birth. Thus, there will be subgroup analyses based on participant-level characteristics and based on hospital-level characteristics. If data are insufficient for subgroup analysis, categories will be collapsed.

Table 3. Measures for individual participant data pairwise meta-analysis

Outcomes	
For all infants	
Primary outcome	• Death (at any time for follow-up duration of the included trials)
For infants born before 32 weeks gestation	
Key secondary outcomes	• Death (within 7 days) • Severe intraventricular haemorrhage on cranial ultrasound (grade 3-4) • Necrotizing enterocolitis ≥ grade 2 (or trialist definition) • Late onset sepsis (where possible defined as clinical sepsis > 72 hour after birth) • Patent ductus arteriosus requiring treatment (medical and/or surgical) • Chronic lung disease (at 36 weeks postmenstrual age or trialist defined)
Other secondary outcomes	• All grades of intraventricular haemorrhage on cranial ultrasound • Respiratory support (mechanical ventilation, CPAP, low flow oxygen) • Duration of respiratory support • Retinopathy of prematurity requiring treatment (medical and/or surgical) • Drug treatment for hypotension • Blood transfusion (volume) • Hypothermia on admission to neonatal unit

	• Polycythaemia, haemoglobin, haematocrit
	• Jaundice requiring treatment
	• Birthweight
	• Length of stay in NICU
	• Long term developmental disability (assessed using the Bayley III, or similar tools):
	  o cerebral palsy (severe, moderate, mild)
	  o neurosensory disability (severe, moderate, mild)
	  o deafness (severe, moderate, mild)
	  o blindness (severe, moderate, mild)

For infants born at or after 32 weeks gestation	
Key secondary outcome	• Death (within 7 days) • Admission to Neonatal Intensive Care Unit (NICU)

Other secondary outcomes	• Length of stay in NICU
	• Duration of respiratory support (mechanical ventilation or CPAP)
	• Chronic lung disease (receiving supplemental oxygen at 36 weeks postmenstrual age)
	• Late onset sepsis (> 72 hour after birth)
	• Patent ductus arteriosus requiring treatment (medical and/or surgical)
	• Drug treatment for hypotension
	• Blood transfusion
	• Hypothermia on admission to neonatal unit or postnatal ward
	• Long term developmental disability (assessed using the Bayley III, or similar tools):
	  o cerebral palsy (severe, moderate, mild)
	  o neurosensory disability (severe, moderate, mild)
	  o deafness (severe, moderate, mild)
	  o blindness (severe, moderate, mild)

For all women	
Secondary outcomes	• Maternal death • Postpartum blood loss ≥500ml • Postpartum infection requiring antibiotics • Manual removal of placenta • Retained placenta (>30 minutes) • Not breast feeding when baby discharged from hospital • Postnatal depression • Blood transfusion
Covariates/ Subgroups	
Based on participant-level characteristics	
	• Gestation at birth: <37 completed weeks to 32 weeks; 28 to <32 weeks; 26 to <28 weeks, <26 weeks • Type of pregnancy: singleton; multiple • Mode of birth: caesarean before onset of labour; caesarean after onset of labour; vaginal • Spontaneous onset of labour: spontaneous onset or prelabour ruptured membranes; not spontaneous onset or prelabour ruptured membranes; not known whether spontaneous onset of labour or prelabour ruptured membranes • Time of breathing onset (seconds or before/after cord clamping/milking) • Assessed as needing resuscitation and/or stabilisation (yes/no) • Gender (male, female, uncertain/other) • Intrauterine growth restriction: yes, no (trialist defined) • Suspected maternal antenatal/intrapartum sepsis (trialist defined): yes/no

Based on hospital / trial-level characteristics	
	• Highest level of neonatal unit available at site: neonatal intensive care unit, neonatal unit (some capacity to provide ventilation), special care baby unit (no ventilation available), no neonatal unit or special care baby unit • Type of uterotonic drug (if any) • Planned timing of uterotonic drug: before cord clamping; after/at cord clamping; timing mixed or not known • Planned position of the baby relative to the placenta whilst cord intact: level with placenta (between level of woman's bed and her abdomen/anterior thigh); more than 20 cm below level of placenta; position mixed or not known • Need for immediate resuscitation at birth: infants requiring immediate resuscitation at birth excluded; infants requiring immediate resuscitation at birth included; unclear whether infants requiring immediate resuscitation at birth included or excluded • Type of consent

Part 2: individual participant data network meta-analysis

Outcome

The primary outcome for the network meta-analysis will be death of the baby at any time (during the follow-up duration of the trials).

Covariates and subgroups

All variables listed in Table 3 will be considered as covariates to improve consistency of the NMA model. There will be subgroup analyses comparing babies born before and after 32 weeks, and comparing babies in need of immediate resuscitation versus not in need of immediate resuscitation.

Data analysis

The full, detailed Statistical Analysis Plan will be agreed on by the Collaboration before any analyses are undertaken. Analyses will include all randomised participants with available data, and the primary analyses will be based on intention-to-treat without imputation of missing data. Missing data will be described and reasons for missing data explored. The impact of missing data on conclusions about the comparative effects on the primary outcomes may be explored in sensitivity analyses if appropriate.

Part 1: individual-participant data pairwise meta-analysis

For each outcome, a one-stage approach to analysis will be employed to include individual participant data from all eligible trials in a multilevel random or mixed effects regression model. Aggregate data will be included were individual participant data is unavailable. Heterogeneity of treatment effects across trials will be estimated using confidence and prediction intervals, with further inclusion in secondary models of participant-level and trial-level covariates to explain the sources of heterogeneity. Forest plots will be presented by trial for each of the primary outcomes, and for any secondary outcomes where there is evidence of heterogeneity across trials.

We will use a generalised linear modelling framework, with the choice of outcome distribution and link function dependent on outcome type. For example, binomial with log link will be used to estimate risk ratios for the binary primary outcome of death or serious morbidity, and Gaussian with identity link for differences in mean duration of ventilation, with log-transformation of the data if appropriate. We will follow a similar approach for secondary outcomes. For estimation of subgroup effects on the primary outcomes, we will present forest plots of pooled treatment effects according to pre-specified subgroup variables, and estimate effects by including appropriate interaction terms between subgroup variable and treatment arm in the regression models. The results of all comparative analyses will be presented using appropriate estimates of treatment effect along with 95% confidence intervals and two-sided p-values.

Part 2: individual participant data network meta-analysis

We will calculate a two-step random-effects network meta-regression model to compare and rank all available treatments using direct and indirect comparisons using a Bayesian model and assuming an independent interaction between treatment effects and covariates. We will obtain probability rankings of the effect of all interventions on the primary outcome death and for key secondary outcomes if data permits. If there are statistically significant interactions between covariates and treatment effects, we will provide probability rankings of intervention effects by subgroup for these covariates. Heterogeneity will be measured by the heterogeneity parameter τ^2. Residual inconsistency will be measured by comparing effect estimates between the direct and indirect comparisons. A judgement of excessive heterogeneity or inconsistency would prevent the interpretation and reporting of the network meta-analysis.

Assessment of compliance with the allocated intervention

Compliance with the interventions will be described for each trial. For studies of early versus deferred cord clamping this will be based on i) the time to cord clamping in each allocated group and ii) the difference in time between early and deferred clamping. For studies comparing cord milking with no milking, this will be based on i) time to cord clamping in the allocated groups ii) reported compliance with cord milking in both groups.

Adjustments for multiple testing (to be added)

Planned sensitivity analyses

To assess whether results are robust to trial quality and different methods of analysis the following sensitivity analyses will be conducted for the primary outcome, if data are sufficient:

- Excluding studies with high risk of bias, defined as those assessed as high or unclear risk of bias for sequence generation and/or concealment of allocation, and/or high risk of bias for loss to follow up for pairwise and network meta-analysis;
- For trials comparing early cord clamping with deferred clamping: analysis of outcomes weighted by degree of separation between groups (observed between-arm difference in mean timing of clamping) for pairwise meta-analysis;
- Analysis of outcomes weighted by degree of separation in haemoglobin (at 24 hours) achieved between intervention and control groups for pairwise meta-analysis (as a surrogate for net placental transfusion);
- For trials with deferred cord clamping, we will perform an additional dose-response analysis assessing intended time of cord clamping deferral as a continuous variable;
- An exploratory analysis will be based, not as intention-to-treat, but on actual timing of cord clamping for individual participants for pairwise and network meta-analysis.

Project management

Membership of the iCoMP Collaboration will include representatives from each of the trials contributing data to the project, the Secretariat, and invited experts in individual participant data systematic reviews, network meta-analysis and prospective meta-analysis who will form an Advisory Group. The Secretariat will be responsible for data management and analysis and communication within the Collaboration, including newsletters and email updates.

Ethical issues

Participants in the individual trials have previously consented to participation in their respective trial. The data will be available through an agreement between all Chief Investigators of the included trials, and ethics approval for each of the trials has been given by their respective Research Ethics Committees. The trialists remain the custodians of their own data and retain the right to withdraw their data from the analysis at any time. Individual participant data will be de-identified before being shared with the iCoMP Collaboration. Ethics approval for this project has been granted by the University of Sydney Human Research Ethics Committee (Project number: 2018/886).

Publication policy <will be updated>

The key methods for this meta-analysis protocol were agreed by the iCoMP Collaborators in January 2015, before unblinding of any outcome data from the studies included in the nested prospective meta-analysis. This manuscript was discussed at the first iCoMP Collaborators meeting held at the Pediatric Academic Societies meeting in San Diego, in April 2015. At this meeting it was agreed the protocol should be expanded to a retrospective systematic review and individual participant data and network meta-analysis with a nested prospective meta-analysis. The protocol was then revised based on further discussion, and circulated to members of the collaborative group for further comment and agreement prior to submission.

Participating trialists in the prospective meta-analysis, when reporting results from their own trials, will endeavour to include a statement that their trial is part of this prospective meta-analysis in any published manuscripts or conference abstracts. Any reports of the results of this meta-analysis will be published either in the name of the collaborative group, or by representatives of the collaborative group on behalf of the iCoMP Collaboration, as agreed by members of the collaborative group. Reports will be circulated to the collaborative group for comments and approval before submission for publication.

Discussion

There is an urgency to conduct this systematic review and individual participant data pairwise and network meta-analysis so we can make sense of the many small trials now being undertaken,

inform clinical practice and identify the most promising interventions for further evaluation. This meta-analysis offers an opportunity to reliably test important hypotheses that cannot be resolved by any of the individual trials, either alone or in simple combination. Coordinating international efforts in this way will help achieve consensus on the most important substantive clinical outcomes to assess in any future trials. Unequivocal synthesized results, together with the identification of key determinants (e.g. effect modifiers) will be critical for translating evidence from the results of this meta-analysis into practice. Figure 2 gives an idea of the network of direct comparisons available from the trials that we have identified to date. We plan to complete study identification and individual participant data collection by mid-2019, and conduct the analysis and disseminate the results by end-2020.

This study is only possible because trialists around the world have agreed to collaborate to share the individual participant data from their cord management trials. This collaborative approach will enable us to move beyond the traditional 'one-size-fits-all' approach in medicine, towards precision medicine to find the optimal treatment from a range of treatment options for each individual woman and her baby, based on their individual characteristics and risk factors.

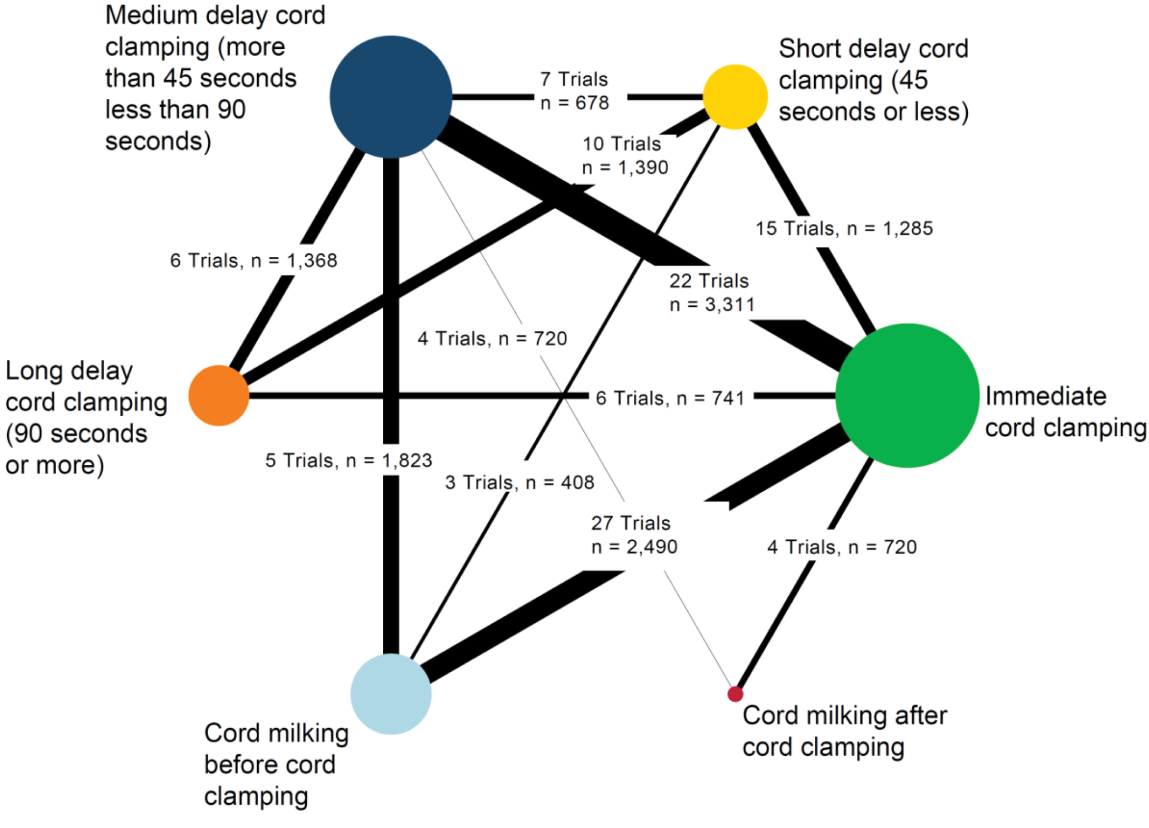

Figure 2. Illustration of network of currently available trials comparing different cord management strategies.

Funding

Developing the protocol and establishing the collaborative group was supported by the UK National Institute of Health Research with a grant entitled The Preterm Birth Programme (number RPPG060910107). It presents independent research commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG- 0609-10107). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. Funding for individual trials remains the responsibility of the trialists themselves. Funding to undertake the data collection and data analysis for the iCoMP Collaboration will be provided by the Australian National Health and Medical Research Council (APPID1163585).

<full list of iCoMP collaborators will be added>

List of abbreviations

iCoMP – **i**ndividual participant data on **Co**rd **M**anagement at **P**reterm birth
UK – United Kingdom
WHO – World Health Organization
NICE – National Institute for Health and Clinical Excellence
PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analysis
IPD – individual participant data
NMA – network meta-analysis
CPAP – continuous positive airway pressure
NICU – neonatal intensive care unit
NIHR – National Institute for Health Research

Competing interests

None known.

Non-financial competing interests

<List of all collaborating CIs> are Chief Investigators for potentially eligible trials.

Authors' contributions <needs to be updated>

LD and LA conceived the idea. LD, ALS and LA drafted the protocol with input from all authors. All authors have agreed the final manuscript.

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Table 1: Fogarty review[35] of immediate versus deferred cord clamping for preterm births

Outcome	Number of trials	Number of participants	Risk ratio	95% confidence interval
All infants born <37 wk				
Hospital mortality	18	2538	0.68	0.52 to 0.90
Apgar score				
<4 at 1 minute	2	1600	0.82	0.67 to 1.00
<8 at 5 minutes	3	1683	1.03	0.91 to 1.17
Cardiorespiratory support at resuscitation	10	748	0.89	0.71 to 1.11
Intubation in the delivery room	6	532	0.96	0.82 to 1.13
Temperature on admission (°C, mean)	11	2317	-0.02[$]	-0.07 to 0.3[$]
Intraventricular haemorrhage				
any (grade 1 to 4))	19	2871	0.87	0.75 to 1.00
severe (grade 3 or 4)	11	2300	0.87	0.59 to 1.27
Periventricular leukomalacia	8	1977	0.71	0.39 to 1.27
Combined periventricular leukomalacia or porencephaly or echodense intraparenchymal lesions or ventriculomegaly	6	1920	0.77	0.56 to 1.06
Mechanical ventilation	9	686	0.95	0.84 to 1.07
Chronic lung disease ≥ 36 wk	7	1951	1.02	0.93 to 1.12
Patent ductus arteriosus	12	2397	0.96	0.84 to 1.09
Necrotising enterocolitis	12	2397	0.88	0.65 to 1.18
Late onset sepsis	10	2146	0.95	0.80 to 1.13
Severe retinopathy of prematurity	5	1893	0.74	0.51 to 1.07
Peak haematocrit %	2	1587	2.73[$]	1.94 to 3.52[$]
Blood transfusion	13	2595	0.81	0.74 to 0.87
Polycythemia (haematocrit >65%)	13	2529	2.65	1.61 to 4.37
Partial exchange transfusion	4	1743	0.14	0.01 to 2.74
Serum bilirubin peak (mean)	15	2358	4.43[$]	1.15 to 7.71[$]
All infants born ≤28 wk gestation				
Hospital mortality	3	996	0.70	0.51 to 0.95
Severe (grade 3 or 4) intraventricular haemorrhage	3	967	0.80	0.51 to 1.25
Chronic lung disease ≥ 36 wk	3	869	0.99	0.91 to 1.09
Necrotising enterocolitis	4	977	0.87	0.61 to 1.24
Late onset sepsis	3	925	1.07	0.87 to 1.31
Severe retinopathy of prematurity	2	839	0.72	0.47 to 1.09
Blood transfusion	2	941	0.91	0.85 to 0.97

[$] *mean difference*

SCBU=Special Care Baby Unit

Table 2: Eligible randomised trials to date for the pairwise and network meta-analysis with individual participant data on Cord Management at Preterm Birth (iCoMP) February 2019

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Argentina[53] (Carroli)	n/a	2016/2020	700	24-30 weeks GA	DCC – at 90 sec	Early cord clamping <30 sec	Sepsis (proven and very probable)
Australia[54] (Badurdeen)	n/a	2018/2020	120 (not all preterm)	Infants greater than 32 weeks GA*	DCC: at least 1 minute	ICC	Average heart rate between 60-120 seconds after birth
Australia[55] (McDonnell)	1997	1994/1994	46	26 to 33 weeks	DCC: 30 sec	ICC	Venous haematocrit
Australia[56] (Kamlin)	n/a	2014/2015	27 (not all preterm)	32-42 weeks GA*	Arm 1: DCC - at 90-180 sec Arm 2: DCC – 10 sec after crying and breathing established	Early cord clamping <60 sec	Heart rate 90 sec after birth (measured by pulse oximetry and digital microphone enabled stethoscope)
Australia[57] (Tarnow-Mordi)	n/a (Pilot for Tarnow-Mordi 2017)	2009/2010	100	<32 weeks GA	Arm 1: Cord milking - cord cut long (3 cm from placenta/ introitus), milked during resuscitation Arm 2: DCC – at 30-60 sec infant below level of introitus/placenta. If baby in extremis, immediate clamping. Arm 3: DCC at 30 – 60 sec + milking	Immediate cord clamping within 10 sec	Haemoglobin 6 hours after birth
Australia[58] (Tarnow-Mordi)	2017	2010/2019	1634	<32 weeks GA	DCC - ≥60 sec, baby positioned below placenta	ICC within 10 sec	Composite: Mortality or major morbidity (IVH, chronic lung disease, ROP, NEC, late onset sepsis) at 36 weeks

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Austria[59] (Urlesberger)	n/a	2018/2021	80 (not all preterm)	>=28 weeks*	DCC 30 cm, cord milking after long clamping at 30cm, 1x 10cm/sec	Standard care (cord cutting)	Cerebral blood volume (CBV) (within 15 min after birth) Changes in CBV (ml/100g brain)
Bangladesh[60] (Yasmeen)	2015	2012/2013	40	Neonate delivered at less than 37 weeks of GA	DCC: cord clamped at 3 minutes	DCC: cord clamped at 1 minute	Haemoglobin (Hb), iron and ferritin
Canada[61] (El-Naggar)	2019	2011/2018	73	24-31 weeks GA	Cord milking x3, at or below the level of the placenta, ~20 cm milked, before clamping	ICC	Systemic blood flow (Superior vena cava flow at 4-6 hours)
Canada[62] (Murphy)	n/a	2007/2010	296	Singletons, 24-32 weeks GA	DCC – at 30-45 sec	ICC	Composite: IVH or late onset sepsis
China[63] (Dai)	2014	n/a	31	Preterm infants	Wait until cord pulsation ceased	ICC: 5-10 sec	NA
China[64] (Dong)	2016	n/a	90	<32 weeks	DCC: 45 sec	ICC: <10 sec	Routine blood test results, total amount of red blood cell transfusion, blood gas parameters, mean arterial pressure, bilirubin peak, total time of phototherapy, incidence rates of necrotizing enterocolitis, late-onset sepsis, intracranial haemorrhage, retinopathy, and bronchopulmonary dysplasia
China[65] (Hao)	n/a	2018/2019	48	Preterm infants with GA of 30 to 31 + 6/7 weeks	UCM	DCC	Cerebral haemodynamics

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
China[66] (Hu)	2015 (master's thesis)	n/a	120	28-35 weeks GA Vaginal birth	1. DCC 30 sec 2. DCC 60 sec 3. DCC 120 sec	ICC < 10 sec	Haematocrit and haemoglobin levels at 24 hours and 1 week after birth
China[67] (Hua)	2010	2009/2011	176 (49 of those preterm)	Any GA*	<u>Normal birth</u> Arm 1: DCC – wait until cord ceases pulsing Arm 2: DCC – at 90 sec <u>Asphyxia</u> Arm 1: DCC – wait until cord ceases pulsing, resuscitate on bed site with cord intact	<u>Normal birth</u> Immediate clamping <10 sec <u>Asphyxia</u> Immediate clamping <10 sec, resuscitate after on irradiation table	Haemoglobin 1 month after birth
China[68] (Li)	2018	2017/2017	102	Neonates who were delivered vaginally between 28 0/7 and 36 6/7 week and complicated by premature prolonged rupture of membranes	UCM: milked four times at a speed of 10cm/sec, then clamped	ICC: clamped and cut immediately	Incidence of certain or probable infection in neonates
China[69] (Liu)	n/a	2019/2019	948 (not all preterm)	Neonates with GA between 34 weeks 0 day and 38 weeks 6 days*	DCC: 60 sec	ICC: within 10 sec	Rate of respiratory distress within 24 hours after birth
China[70] (Shi)	2017	n/a	60 preterm (and 460 term)	Single foetus deliveries*	DCC	ICC 5-10 sec	Hemoglobin (newborn cord blood &after 24 h), neonatal complications, bleeding volume, third labour time, incidence of placental adhesion and peeling
China[71] (Xie)	n/a	2017/2019	300	Singletons, <34 weeks GA	UCM: X2-3, 25cm/2 sec, below placenta level, before clamping	ICC	Concentrations of Haemoglobin &Haematocrit, serum ferritin level (48 hours after birth)

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Egypt[72] (Allam)	n/a	2018/2019	210	Premature babies at 30-34 weeks GA	ECC: first 5 sec	DCC: until cord stops pulsing or 1-2min	Fetal haemoglobin, neonatal death
Egypt[73] (Nour 2017a)	n/a	2017/2019	90	Preterm infant <34 weeks GA	UCM: cord milked three times at 10cm/sec	ICC	Peripheral venous CD34 at admission
Egypt[74] (Nour 2017b)	n/a	2017/2018	90	Preterm infant <34 weeks GA	Group A: ICC, with placental insufficiency Group B: DCC, with placental insufficiency	Normal placenta with DCC: 60 sec	Peripheral venous CD34 at admission
Germany[75] (Nelle)	1998	n/a	19	PT <1500g*	DCC: 30 sec, 30 cm below placenta	ICC	Mean Blood Pressure (mmHg, Dinamap), left ventricular output (LVO, ml/kg/min), mean cerebral blood flow velocity (CBFV) in the Arteria carotis interna (ACI, m/s; Doppler-ultrasound), hemoglobin (Hb, g/dl), hematocrit (Hct, %), systemic and cerebral hemoglobin transport(HbT), systemic vascular resistance (SVR; mmHg/kg/min-1)
Germany[76] (Rabe 2011)	2011	2006/2008	40	<33 weeks	DCC: 45 sec	DCC: 20 sec	Feasibility, effects on post-partal adaption and anaemia of prematurity
India[77] (Agarwal)	2018	2013/2014	100	<34 weeks GA	DCC: at 120 sec	ICC ≤30 sec	Hyperbilirubinemia and polycythemia within first 7 days

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
India[78] (Aghai 2014)	2018	2014/2016	101 (not all preterm)	>35 weeks GA, baby depressed*	UCM: X3 before cord clamping, below placenta level	ICC	Feasibility (Number neonates cord milking), resuscitation efforts (ventilation, intubation, chest compression), short term resuscitation outcomes (5 min Apgar, severity Hypoxic Ischemic Encephalopathy, blood gas 1 hour)
India[79] (Aghai 2018)	n/a	2018/2020	1400 (not all preterm)	Depressed neonates born between 35-42 weeks*	UCM: milked four times, milking 30cm over 2 sec	ICC: immediately after birth	Number of infants with moderate to severe HIE or death
India[80] (Anusha)	n/a	2017/2019	148	Neonates with birth weight less than 1500g*	DCC: 30 sec	ICC: within 10 sec	Haemodynamic stability, haematological status, serum ferritin, and requirement of blood transfusion
India[81] (Bhriguvanshi)	n/a	2017/not specified	236	Neonate > 28 weeks GA, requiring resuscitation*	UCM: milked three times towards baby at 10cm/sec, then clamped	ICC: within 30 sec	Haemoglobin (Hb) and hematocrit (Hct)
India[82] (Chopra)	2018	2013/2015	142	growth retarded babies (IUGR)born at and above 35 weeks of GA*	DCC: 60 sec	ICC: 10 sec	Hemoglobin and ferritin levels
India[83] (Datta)	2017	2012/2013	120	34-36 weeks GA	DCC: at 30-60 sec	ICC: <20 sec	Neurobehavioural Assessment of Preterm Infant (NAPI) at 37 weeks post-conceptional age
India[84] (Dhaliwal)	2014	n/a	300	34-37 weeks GA	DCC: 60 sec	ICC: <10 sec	Risk of neonatal mortality & abnormal neurological examination at 40 weeks GA
India[85] (Dipak)	2017	2013/2014	78	27-31 weeks GA	1. DCC: 60 sec DCC 60 sec with intramuscular ergometrine	ICC: 10 s	Hematocrit 4 h after birth

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
India[86] (George/Isac)	n/a	2017/2018	180 (not all preterm)	Mothers with a period of gestation between 34 and 40 6/7 *	UCM: milking whole length at 10cm/sec, three times, then clamped	ICC: no details	Infant haemoglobin (Hb) and hematocrit (Hct)
India[87] (Gupta)	n/a	2018/2020	110	Preterm newborn babies born at <34 weeks	DCC	ICC	Ferritin and PCV
India[88] (Ram Mohan)	2018	2014/2015	54	Preterm, requiring resuscitation	UCM: 20-25 cm umbilical cord x3, within 30 sec of birth	No milking	Haemoglobin at 6 weeks
India[89] (Ranjit)	2015	2010/2010	100	30-36[6]	ICC	DCC: >2min	Hematocrit and serum ferritin, at 6 weeks
India[90] (Kumar Mangla/ Thukral)	n/a	2016/2016	84 (not all preterm)	Late preterm and term neonates*	Deferred UCM: cord clamped at 60 sec	UCM: Cord milking in 10 sec	Venous haematocrit at 48 hours of life
India[91] (Upadhyay 2010)	2013	2010/2011	170 (not all preterm)	>35 weeks GA*	UCM	Non UCM	Haemoglobin and serum ferritin at 1 and 1.5 months
India[92] (Upadhyay 2013)	2015	2013/2014	200	32-36 weeks GA, vaginal or caesarean	UCM: X3, 10cm/sec	ICC: <30 sec	Haemoglobin and ferritin at 1.5 months
India[93] (Varanattu)	n/a	2018/2019	250	Preterm infants <32 weeks GA	UCM: milked three times over 20 sec period towards infant at 20cm/2sec with 2 second pause between.	ICC: clamped immediately	Haemoglobin levels at birth and IVH (incidence and severity)
India[94] (Venkataseshan)	2018	2012/2013	434	30-33 weeks GA	DCC: 60 sec below placenta. If baby depressed, immediate clamping keeping cord long, milked x3 during resuscitation	ICC: within 10 sec	Mortality and/or abnormal neurological examination at 40 weeks postnatal age
Iran[95] (Armanian)	2017	2015/2015	60	≤34 weeks GA	DCC: at 45 sec	ICC: <10 sec	Time of cord clamping

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Iran[96] (Haghshenas)	2017	2014/2015	54	<32 weeks GA, caesarean, birth weight < 1500g	DCC: at 30-45 sec	ICC: <10 sec	IVH (days 3 to 7), survival infant (up to 28 days)
Iran[97] (Hemmati)	n/a	2012/2013	114	26-34 weeks GA	DCC: at 30-45 sec	ICC: 10-15 sec	IVH, 3-4 and 7-10 days
Iran[98] (Mirzaeian)	n/a	2017/2018	160	Neonates with a GA of 28 to 34 weeks	UCM: milked three times in 20 sec	ICC	Amount of transfused blood, bilirubin levels
Iran[99] (Sekhavat)	2008	n/a	52	Infants born 26-34 weeks GA	DCC: 30-60 sec	ICC: 10-15 sec	higher blood pressure (BP), hematocrit (Hct) and blood glucose (BS)
Iran[100] (Shahgheibi)	n/a	2017/2018	90	Women with preterm labour	DCC: 180 sec	DCC: 30 sec	Blood parameters, weaning from ventilator, NICU discharge time
Ireland[101] (Dempsey)	n/a	2015/2016	45	<32 weeks GA	Arm 1: DCC – at 60 sec on mobile resuscitation trolley at/below placenta level Arm 2: UCM – Cord stripped 3 times at 20cm/2 sec at/below placenta level	ICC: <20 sec	Neonatal: Brain activity (6 & 12 hours post-partum, EEG and NIRS) Maternal: hemoglobin at 24-36 hours post-partum
Israel[102] (Kugelman)	2007	2004/2005	65	<35 weeks GA	DCC: 30-45 sec	ICC: 5-10 sec	initial serum complement (C3 and C4) and immunoglobulins (IgG, IgM)
Japan[25] (Hosono 2008a)	2008	2001/2002	40	24-28 weeks GA, singletons	UCM: 20 cm of the cord, 2-3x, before clamping, 20cm/2sec	ICC	Probability of not needing transfusion, determined by Kaplan–Meier analysis number of RBC transfusions
Japan[103] (Hosono 2008b)	n/a	2008/2016	566	24-28 weeks GA	UCM: cord cut 30 cm from infant, cord milked x1	ICC: <30 sec	1) Probability needing transfusion and death 2) Amount of blood transfusion first 4 weeks

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Korea[104] (Song)	2017	2012/2015	66	Neonate delivered between 24 0/7 and 32 6/7 weeks	UCM: milked four times at speed of 20cm/2sec, with 2sec pause between	ICC: immediately after delivery	Short term safety: Apgar score, prevalence of hypothermia, early intubation, initial blood gas analyses, bilirubin levels, duration of phototherapy, use of cross-transfusion, and respiratory distress.
Nepal[105] (Andersson)	2017	2014/2017	540 (not all preterm)	34-41 weeks GA*	DCC: at ≤180 sec	ICC: ≤30 sec	Haemoglobin at 8±1 months
Nepal[106] (Ashish KC)	n/a	2016/2016	1510 (not all preterm)	Singletons, ≥33 weeks GA*	DCC: at ≥180 sec	ECC: <60 sec	Neonatal heart rate continuously until 10 min after birth and at 1,3&5 min
Netherlands[107] (Te Pas)	n/a	2019/2020	660	<30 weeks GA	Physiology-based cord clamping (PBCC): Resuscitation with cord intact, clamp when infant is stable (heart rate >100 bpm, oxygen>80%, supplemental oxygen <40%)	DCC: 30-60 sec, clamping before resuscitation	Intact survival at NICU discharge (without cerebral injury (IVH ≥ grade 2 and/or PVL ≥ grade 2 and/or periventricular venous infarction) and/or NEC (Bell stage ≥ 2)
Netherlands[108] (Ultee)	2008	n/a	37	34 to 36 weeks GA	DCC: 3 min	ICC: <30 sec	haemoglobin and ferritin levels (at 10 weeks)
Pakistan[109] (Malik)	2013	2009-2009	80	30-37 weeks GA	DCC: 120 sec	DCC: 30 sec	Hematocrit
Saudi Arabia[110] (Al-Wassia)	n/a	2017/2019	180	Preterm infants <32 weeks GA	UCM: milked 20cm segment over 2-3 sec three times	DCC: 60 sec	IVH

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Saudi Arabia[111] (Gomaa)	n/a	2016/2018	200	Infants 23 to 34 + 6/7 weeks GA	DCC: 45-60 sec before clamping, with baby at level or below placenta	UCM: milked 4-5 times from maternal end of cord to baby abdomen, 2 sec pause between milking	Haematological parameters of neonates - hematocrit (Hct) level
South Africa[112] (Hofmeyr 1988)	1988	n/a	38	<35 weeks	DCC: 1 min & ergometrine	ICC	PVH/ IVH
South Africa[113] (Hofmeyr 1993)	1993	n/a	86	<2000 g birthweight*	DCC 1-2 min	ICC	PVH/ IVH
South Africa[114] (Tiemersma)	2015	2012/2012	102 (not all preterm)	Birth weight <2500g ± 500g*	DCC: at 2-3 minutes	ICC: within 30 sec	Haemoglobin at 2 months
Spain[115] (De Paco Matallana)	n/a	2011/2014	100	24- 34 weeks GA	DCC: at 45-60 sec	ICC: <10 sec	Neonatal haemoglobin, haematocrit and bilirubin levels (within 7 days after birth)
Spain[116] (Domingo Puiggrós)	n/a	2014/2016	40	<34 weeks GA, caesarean	UCM: X3 at 20 cm/2sec	DCC: 30 sec	Haemoglobin (at 1 and 24 hours)
Spain[117] (Leal)	2019	n/a	138	24 + 0/7 until 36 + 6/7 weeks	UCM	ICC	Red blood cell transfusion, phototherapy
Spain[118] (Socias)	n/a	2014/2017	150	26-32 weeks GA	DCC – at 30-60 sec	ICC: <30sec	Red blood cell transfusions (number & volume), IVH, postpartum haemorrhage
Switzerland[119] (Baenziger)	2007	1996/1997	39	24-32 weeks	DCC: 60-90 sec, below placenta	ICC: <20 sec	Cerebral oxygenation
Taiwan[120] (Shen)	n/a	2015/2019	100	Preterm infants born at less than 30 weeks GA	UCM: milked one time, 20cm section at speed of 10cm/sec and clamped at 2-3cm.	ICC and no milking	Neonate's hemoglobin, hematocrit, and mean arterial pressure at admission
Thailand[121] (Chamnanvanakij)	2017	2015/2016	46	25-34 weeks GA	UCM: X3-4 , 30 cm, before clamping	DCC: at 60 sec	Haematocrit level (2 hours after birth)

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
Thailand[122] (Jomak)	n/a	2018/2018	110	Singleton preterm pregnancy at 24 weeks to 36 + 6 /7 weeks GA	ICC	DCC	Hematocrit (Hct)
Thailand[123] (Mungkornkaew)	2015	2014/2014	200 (not all preterm)	Singleton, GA 34-42 weeks*	DCC: 2 minutes	DCC: 1 minute	Fetal hematocrit, hemoglobin and microbilirubin
Thailand[124] (Panichkul)	n/a	2015/2016	170	34-36 weeks GA	DCC: at 60 sec	ICC: at 10 sec	Haematocrit 2 hours after birth
Thailand[125] (Ruangkit)	2019	2016/2017	100	Multiples, 28-36 weeks GA	DCC: at 30-60 sec	ECC: <10 sec	Haematocrit level at birth
Thailand[126] (Salae)	2016	2014/2015	86	34-36 weeks GA	DCC: at 2 minutes	ECC: within 30 sec	Haematocrit at 48 hours
Thailand[127] (Tanthawat)	n/a	2016/2016	40	<32 weeks GA	UCM: Cut cord at 30cm, cord milking x1, 10cm/sec.	ECC: <10 sec	Haemoglobin and Haematocrit level at admission
Turkey[128] (Alan)	2014	2011/2013	44	≤32 weeks GA ≤1500 g	UCM: at 25-30 cm,X3, 5cm/s, below placenta level	ICC: <10 sec	Packed red blood cell (PRBC) transfusion and hematologic and hemodynamic parameters
Turkey[129] (Gokmen)	2011	2008/2009	42	<32 weeks GA	DCC: 30-45 sec	ICC: 5-10 sec	peripheral hematopoietic progenitor cells (HPCs) and haematological parameters
Turkey[130] (Kilicidag)	2015	2012/2013	54	PT ≤ 32 weeks GA	UCM: X4 before clamping (20cm/2sec)	ICC	absolute neutrophil counts (ANCs) and the neutropenia frequency
Turkey[131] (Silahli)	2018	2015/2016	75	<32 weeks GA	UCM: at 20 cm, 3x, before clamping	ICC <10s	Thymic size
UK[132] (Aladangady)	2006	n/a	46	24-32^{6} weeks GA	DCC: 30-90 sec, below placenta, oxytocic agent, with ventilation/ resuscitation if necessary	ICC	Infants' blood volumes.

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
UK[133] (Duley)	2017	2013/2017	260	<32 weeks GA	DCC: after at least 2 min	ECC: <20 sec	Feasibility: Recruitment, compliance, retention, completeness data, patient views
UK (Holland)	Not published	1998/2001		<33 weeks' gestation	DCC 40-90 s	ICC (?)	Median arterial/alveolar PO2 ratio over the first 24 hours of life
UK[134] (Kinmond)	1993	n/a	36	27-32 weeks GA, vaginal delivery	Conventional management (ICC): 10 sec median	DCC 30 sec, 20 cm below placenta	Initial packed cell volume, peak serum bilirubin concentrations, red cell transfusions, respiratory impairment
UK[135] (Rabe)	2011	2006/2008	58	Singletons, <34 weeks GA	UCM	DCC: Slight deferral in cord clamping time	Acceptability of cord clamping methods
UK[136] (Weeks)	n/a	n/a (protocol, not funded/started to date)	7242 (not all preterm)	All births*	DCC: clamped once it has stopped pulsating or at least 5 minutes after birth	ICC: within 30 sec of birth	Developmental delay and/or behaviour problem
USA[137] (Backes)	2016	2009/2013	40	22.5-27.6 weeks	DCC: 30-45 sec, Below placenta	ICC: 5-10 sec	Safety, feasibility, haematological and circulatory outcomes
USA[138] (Bauer)	n/a	2014/2019	400	24-29 weeks GA	Arm 1: DCC – at 45 sec and indomethacin within 6hrs Arm 2: DCC – at 45 sec and placebo within 6hrs	Arm 3: ICC and indomethacin Arm 4: ICC and placebo	Survival at 38 weeks with no severe IVH (grades 3/4) or PVL
USA[139] (Berens)	n/a	2018/2019	100 (not all preterm)	>35 weeks GA*	DCC: 60 sec	ECC: <15 sec	Neonatal bilirubin level [Time Frame: 24 hours after birth]

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
USA[140] (Bienstock)	n/a	2011/2013	22	24 - 32 weeks GA	UCM: X4 over 10 min	ICC	Haemoglobin (within 24 hours of birth and through NICU stay)
USA[141] (deVeciana)	2013	2009/2011	113	Singletons, 24-28 weeks GA	UCM: 10cm, immediately after delivery	ICC	Red blood cell transfusion (within 28 days of life)
USA[142] (Driggers)	n/a	2011/2013	2	Infants delivered at 24 to 28 + 6/7 weeks GA	DCC: 30 sec UCM: milking four times in 10 sec	ICC	Adverse neonatal event: composite of bronchopulmonary dysplasia, NEC, grade 3 or 4 IVH or PVL, or death
USA[143] (Elimian)	2014	2006/2011	200	Singletons, 24-34 weeks GA	DCC: at 30-35 sec	ICC: <5 sec	Need for blood transfusion
USA[144] (Garg)	n/a	2016/2018	5	<32 weeks GA	UCM: X2, before clamping	ICC	Cerebral oxygenation and function (first 24 hours of life)
USA[145] (Josephsen)	n/a	2012/2016	64	24-27 weeks GA	UCM: below level of placenta and ~20 cm cord milked x3 over 10-20 sec before clamping	ICC	Haemoglobin and haematocrit concentrations (within 4 hrs birth) Incidence and number blood transfusions until discharge
USA[146] (Katheria 2011)	2014	2011/2013	60	<32 weeks GA	UCM: milking X3, below placenta, about 20 cm of cord over 2 sec	ICC	Superior vena cava flow at 6 hours
USA[147] (Katheria 2013)	2015 & 2017	2013/2018	197	23-31 weeks GA	UCM: X4 at 20 cm/2 sec	DCC – at 45-60 sec	Superior vena cava flow at <12 hours
USA (Katheria 2017)	n/a	2017/2022	1200	Infants 23 to 32 + 6/7 weeks GA	UCM: milking four times at 20cm/2sec	DCC: at least 60 sec	Incidence of IVH or death

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
USA (Katheria 2019)	n/a	2019/2020	1000 (not all preterm)	Non-vigorous newborns born between 35-42 weeks GA*	UCM: milking four times, entire umbilical length over 2 sec.	ICC: average 20 sec	Admission to NICU
USA[148] (Kattwinkel)	n/a	2016/2021	940	23-28 weeks GA	Assisted Ventilation (face mask, Continuous Positive Airway Pressure or Positive Pressure Ventilation) prior to DCC at 120 sec	DCC: 30-60 sec, assisted ventilation only after cord clamping	IVH on head ultrasound (7-10 days)
USA (Krueger)	2015	2012/2013	67	Singletons, 22-31[6] weeks GA	DCC: (30 sec) with cord milking	DCC: (30 sec) without cord milking	Initial fetal hematocrit
USA[149] (Martin)	n/a	2012/2014	72	Singletons, 23-37 weeks GA	Arm 1: DCC – at 60 sec Arm 2: DCC – at 40 sec	ECC: 20 sec	IVH number and severity (15 months)
USA[150] (Mercer 2003a)	2003	1998/2001	32	24 to 32 weeks GA	DCC: 30-45 sec	ICC: 5-10 sec	Initial blood pressure
USA[151] (Mercer 2003b)	n/a	2003/2006	58	Singletons, <34 weeks gestation	DCC: 30-45 sec, below placenta	ICC	Acceptability of cord clamping methods
USA[152] (Mercer 2006)	2006	2003/2004	72	<32 weeks GA	DCC:30-45 sec	ICC: 5-10 sec	bronchopulmonary dysplasia (BPD) and suspected NEC (SNEC)
USA[153] (Mercer 2008)	2011 & 2016 & 2018	2008/2014	211	24-31 weeks GA	DCC & UCM - 30 - 45 sec, below placenta level, cord milking x1 at end of time, before clamping. If clamping cannot be deferred, cord milked x2-3	ICC: <10 sec	IVH, late onset sepsis
USA[154] (Oh)	2011	2000/2001	54	Singletons, 24-27 weeks GA	DCC: at 30-45 sec	ICC: <5 sec	Number of infants enrolled in the pilot within 6 months
USA[155] (Perlman)	n/a	2015/2019	150	28-34 weeks GA	DCC: at 60 sec	DCC: at 30 sec	Haematocrit 1 hour after birth

Trial Country (PI)	Publication year	Start year/ completion year	Sample size	Participants	Intervention	Comparator	Primary outcome/s
USA[156] (Smith)	n/a	2014/2018	240	23-34 weeks GA	UCM: X4, before clamping, below placenta level	DCC: at 30 sec, below placenta level	Haemoglobin & Haematocrit in NICU (~50 days)
USA (Strauss)	2008	n/a	158	Neonates ≤36 weeks GA	DCC: 60 sec	ICC	Red blood cell volume/mass, per biotin labelling
USA (Yared/Young)	n/a	2015/2016	39	Very low birth weight (500 to 1500 grams)*	DCC: at 60 sec	DCC: at 30 sec	IVH (during NICU admission up to 6 months)
Thailand Pongmee 2010	2010 (abstract)		43	<35 weeks GA	Milking 2x along 30 cm after cutting	ICC	Initial haematocrit, need for blood transfusion, morbidity
Medina 2014				Premature neonates	DCC		Haemodynamic parameters

* only those born <37 weeks gestation eligible

NEC = necrotising enterocolitis; GA = gestational age; DCC = deferred cord clamping; ROP = retinopathy of prematurity; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia; EEG = electroencephalogram; NIRS = near-infrared spectroscopy; cm = centimetres; sec = seconds, NICU = Neonatal intensive care unit; UCM = umbilical cord milking; ECC = early cord clamping; ICC = immediate cord clamping