Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis

Anna Lene Seidler, Mason Aberoumand, Kylie E Hunter, Angie Barba, Sol Libesman, Jonathan G Williams, Nipun Shrestha, Jannik Aagerup, Heike Rabe, et al.

Publication date
09-12-2023

Document Version
Accepted version

Published in
The Lancet

Link to external publisher version
https://doi.org/10.1016/S0140-6736(23)02468-6

Umbilical cord clamping strategies at preterm birth: a systematic review and individual participant data meta-analysis comparing deferred cord clamping, cord milking and immediate cord clamping

Authors

Anna Lene Seidler, Mason Aberoumand, Kylie E Hunter, Angie Barba, Sol Libesman, Jonathan G Williams, Nipun Shrestha, Jannik Aagerup, James X Sotiropoulos, Alan A Montgomery, Gillian M L Gyte, Lelia Duley*, Lisa M Askie*, and iCOMP Collaborators†

*L Duley and L M Askie contributed equally to this manuscript
†Collaborators are listed at the end of this manuscript

Affiliations

University of Sydney, Sydney, NHMRC Clinical Trials Centre, NSW, Australia (A L Seidler PhD, M Aberoumand MAppStat, K E Hunter MPH, A Barba MSciMed, S Libesman PhD, J G Williams PhD, N Shrestha PhD, J Aagerup MPH, J X Sotiropoulos MD, Prof L M Askie PhD);
Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, United Kingdom (Prof A A Montgomery PhD, Emeritus Prof L Duley MD);
National Childbirth Trust, London, United Kingdom (G M L Gyte MPhil)

Summary

Background

Umbilical cord clamping strategies at preterm birth may impact important outcomes. We aimed to compare the effectiveness of deferred clamping, cord milking, and immediate clamping in reducing neonatal mortality and morbidity at preterm birth.

Methods

We conducted a systematic review and individual participant data (IPD) meta-analysis. We searched medical databases and trial registries (until 24 February 2022; updated 6 June 2023) for randomised trials comparing deferred (also known as delayed) clamping, cord milking, and/or immediate clamping for preterm births (<37 weeks' gestation). Authors of eligible studies were invited to join the iCOMP collaboration and share IPD. Data were checked, harmonised, re-coded, and assessed for risk of bias following pre-specified criteria. The primary outcome was death before hospital discharge. We performed intention-to-treat one-stage IPD meta-analyses accounting for heterogeneity to examine treatment effects overall and in pre-specified subgroup analyses.

PROSPERO registration: CRD42019136640.

Findings

We included IPD from 48 randomised trials with 6,367 infants. Deferred clamping, compared to immediate clamping, reduced death before discharge (OR 0·68 95%CI 0·51-0·91, high-certainty evidence [assessed with GRADE], 20 studies, n=3,260, 232 deaths). Number needed to treat was 40 (95%CI 26-143). For cord milking compared to immediate clamping, there was no clear evidence of a difference in death before discharge (OR 0·73, 95%CI 0·44-1·20, low certainty, 18 studies, n=1,561, 74 deaths). Similarly, for cord milking compared to deferred clamping, there was no clear evidence of a difference in death before discharge (OR 0·95, 95%CI 0·59-1·53, low certainty, 12 studies, n=1,303, 93 deaths). There was no evidence of subgroup differences for the primary outcome, including by gestational age, mode of delivery, multiple birth, study year, and perinatal mortality rate.

Interpretation

This study provides high-certainty evidence that deferred clamping, compared to immediate clamping, reduces death before discharge in preterm infants. This effect appears consistent across several participant- and trial-level subgroups. These results will inform international treatment recommendations.

Funding

Australian National Health and Medical Research Council.

Panel: research in context

Evidence before this study

Due to immaturity of multiple organs and body systems, infants born preterm (<37 weeks' gestation) are at higher risk of death and major morbidities. Waiting to clamp the umbilical cord for at least 60 seconds (called 'deferred' or 'delayed' cord clamping) is now recommended practice for term infants and has been proposed alongside other strategies, such as cord milking, to improve the outcomes of preterm infants. Previous systematic reviews and meta-analyses of randomised trials comparing cord clamping strategies at preterm birth (by Cochrane, the International Liaison Committee on Resuscitation (ILCOR), and others) found some indication for differential cord management strategies improving preterm survival. For instance, the most recent review by ILCOR (searches up to July 2019) found that deferred clamping 'may slightly improve infant survival but may make no difference' and effects of cord milking on survival were inconclusive. However, these reviews were limited by reliance on published trial-level summary data, meaning unpublished trials or outcomes were not included, outcomes were not harmonised across trials, and subgroup differences could not be evaluated. We searched medical databases and trial registries up to 6 June 2023 without language restrictions for randomised trials of cord clamping strategies in preterm infants. Search terms included "umbilical cord", "clamp$", "milk$", "preterm" and "premature". All identified published and unpublished trials were invited to share individual participant data.

Added value of this study

This individual participant data meta-analysis brought together data from 48 trials with 6,367 infants to compare different cord clamping strategies. The main added value of the current analysis is the high-quality rigorous approach providing robust evidence overall and for several secondary questions. Individual participant data led to greater data availability, hence more power to assess safety and effectiveness outcomes. It also enabled more complex and accurate analyses, including assessment of whether there were differential treatment effects for subgroups of participants. Comprehensive data quality and integrity checks, combined with the collaborative process of working with international investigators and advisors, improved the quality of our dataset.

Implications of all available evidence

This individual participant data meta-analysis showed with high certainty that deferred cord clamping reduces death before discharge for preterm infants. This effect appears robust across several participant- and trial-level subgroups (including gestational age at birth, mode of birth, multiple birth, sex, trial year and perinatal mortality rate). Our companion network meta-analysis published in the same issue showed a dose-response effect of longer deferral (more than two minutes) leading to larger reductions in death before discharge. Together, these results will challenge current practice, inform international recommendations and guide clinical practice for cord clamping strategies at preterm birth.

Main text

Background

Worldwide, over 13 million infants are born preterm (<37 weeks' gestation) annually. [1] Of these, almost one million die, [2] with high morbidity and healthcare costs for survivors. [3] For infants born at term, deferring umbilical cord clamping (or delayed clamping) improves haemoglobin/haematocrit levels, and reduces iron deficiency incidence. Deferred clamping is now recommended routine practice for term infants, [4] however, whether this practice is also beneficial for preterm infants is less clear.

Various cord clamping strategies have been proposed for preterm infants, including clamping the cord at different times, milking the intact or cut cord, or, when necessary, providing respiratory support with the cord intact. Cord clamping stops blood flow between the placenta and infant, whilst deferring clamping allows longer continuation of this flow after birth, and waiting until after the lungs are aerated may smoothen the transition from foetal to neonatal respiration. [5,6] Cord milking increases blood transfer from the placenta to the infant in a short timeframe, but may have harmful effects in preterm infants. [7]

Over 100 randomised trials have compared different cord clamping strategies at preterm birth, [8] and systematic reviews have reached different conclusions. Earlier reviews for all preterm infants found a reduction in mortality for deferred compared with early clamping. [9,10] A more recent review restricted to those born <34 weeks' gestation, reported deferring clamping 'may slightly improve infant survival but may make no difference' compared with early clamping. [11] Evidence on cord milking was inconclusive. [11] This uncertainty about the optimal cord clamping strategy, particularly for high-risk infants such as those born very preterm or needing resuscitation, has led to varying recommendations on cord management at preterm birth in national and international guidelines (Appendix p.1). [12-16]

Individual participant data (IPD) meta-analysis is the gold standard for combining data from randomised trials. IPD refers to de-identified participant-level data, with many advantages for meta-analysis, including more exact statistical modelling for rarer outcomes and more powerful and reliable subgroup analyses to examine hypotheses about differential individual-level treatment effects. [17] This manuscript presents results from pairwise comparisons and subgroup analyses. Results from a complementary network meta-analysis are published in a companion article in this issue. [18] The aim of this study was to conduct a systematic review and IPD meta-analysis to evaluate the effects of deferred cord clamping, cord milking and immediate clamping on mortality and morbidity for preterm infants.

Methods

Overview

Methods were pre-specified in a published protocol, [19] PROSPERO record (CRD42019136640), and a statistical analysis plan, time-stamped before any analyses, including minor changes from the protocol based on data availability (Appendix p.3). We followed PRISMA-IPD reporting guidelines[20] (Appendix

p.134). This review was supported by a Patient and Public Involvement representative (GG) with lived and research experience through monthly meetings and reviewing relevant outputs. The study protocol was approved by The University of Sydney Human Research Ethics Committee (approval number 2018/886).

Search strategy and selection criteria

We systematically searched medical databases (Medline, Embase, CENTRAL) and trial registries (ClinicalTrials.gov, WHO ICTRP) until 24 February 2022 (updated 6 June 2023) following recommended guidelines[21] (Appendix p.140). Additionally, we consulted our network, searched reference lists of relevant reviews , and conference proceedings. Eligible participants were people giving birth preterm (<37 weeks' gestation) and their infants. Henceforth, we will use the terms 'mother' and 'maternal' to respectfully refer to people of any gender giving birth. For studies including both term and preterm births, only preterm births were included. We included randomised controlled trials evaluating any cord management intervention to enhance umbilical blood flow or facilitate respiratory transition, and immediate cord clamping. There were no date, peer-review or language restrictions. Interventions were grouped into three prespecified comparisons (Appendix p.139): 1) any deferral of cord clamping versus immediate clamping (as soon as possible or within 15 seconds); 2) any cord milking (cord intact or cut) versus immediate clamping; 3) any cord milking versus deferred clamping. Cluster-randomised or quasi-random studies were excluded.

Each study was screened in duplicate, with conflicts resolved by a third reviewer. If eligibility was unclear, study authors were contacted. Chief Investigators of all eligible trials were invited to join the *i*ndividual participant data on *CO*rd *M*anagement at *P*reterm birth (iCOMP) Collaboration, to provide input into the protocol and statistical analysis plan and share their IPD.

Data collection and management

We followed an extensive, pre-specified data collection, processing, re-coding, cleaning, checking, querying, and merging process to ensure high-quality datasets (Appendix p.3). De-identified IPD were requested for pre-specified variables according to a standardised data coding form (Appendix p.3). Data were systematically checked for invalid, inconsistent, out-of-range and missing values. All variables and trial information were cross-checked against published reports and trial registry records. Each step was conducted by two reviewers, with discrepancies resolved by a third. Remaining inconsistencies were queried with investigators and resolved consulting our secretariat and advisors. Finalised IPD from all trials were combined into one dataset. If IPD could not be retrieved for a trial, we extracted summary data from published records in duplicate, following a purpose-built extraction form.

Outcomes and subgroup analyses

Our primary outcome was death before hospital discharge for all infants <37 weeks' gestation. Several participant-level and hospital/trial-level subgroups were pre-specified to assess differential treatment effects for this primary outcome. Pre-specified participant-level subgroups included gestational age at birth, singleton/multiple pregnancy, and mode of birth, with infant sex assessed post-hoc. We were unable to assess ethnicity due to sparse and heterogenous

data. Hospital/trial-level subgroups included study year, perinatal mortality rate, whether initial resuscitation was provided at bedside with cord intact, and planned position of the infant relative to the placenta (above/below).

We pre-specified secondary outcomes separately for preterm infants <32 weeks' and ≥32 weeks' gestation, since these infants have different morbidities and may respond differently to treatment. [22-26] Outcomes were categorised prospectively as key secondary outcomes, including any blood transfusion, hypothermia on admission, and intraventricular haemorrhage (any or severe) for both gestational age groups, as well as chronic lung disease, late-onset sepsis, necrotising enterocolitis, and patent ductus arteriosus in infants <32 weeks' gestation. Other secondary outcomes included haematologic measures, other morbidities of prematurity, and markers of illness severity. Pre-specified maternal outcomes included death and safety outcomes (e.g. postpartum haemorrhage).

All outcomes and subgroups are defined in the statistical analysis plan (Appendix p.3). Pre-specified long-term follow-up outcomes including neurodevelopmental outcomes and disability-free survival are currently being collected with anticipated analysis in 2024.

Risk of bias, integrity, certainty of evidence

Risk of bias was assessed for all studies using IPD, publications, and information provided by study authors with Cochrane criteria adapted for IPD. [27] We conducted separate risk of bias assessments for death before discharge, delivery room, and post-delivery room outcomes, since levels of blinding and missing data varied across these outcomes (Appendix p.164). Integrity and data quality were assessed following a pre-specified checklist collated from previous tools, [28,29] including items such as ethics approvals, incomplete data, implausible values, and publication retraction notices or expressions of concern (from Retraction Watch (http://retractiondatabase.org/), PubPeer (https://pubpeer.com/)) (Appendix p.3). Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[30,31] for the primary and key secondary outcomes, and an adaptation of the GRADE approach for subgroup analyses (Appendix p.265). All assessments were performed in duplicate, and adjudicated by a third reviewer.

Data analysis

All analyses were pre-specified in the statistical analysis plan (Appendix p.3) and performed in R software version 4.2. [32] We followed pre-specified decision criteria on whether to include published data when IPD were unavailable, comparing trial characteristics, effect sizes, risk of bias, and integrity. All analyses were intention-to-treat, and included all available data (including post-randomisation exclusions where possible, albeit not all trials contributed data to all outcomes due to no events. For each outcome, a one-stage meta-analysis approach assuming a common (fixed) treatment effect was employed, [33] with generalised linear mixed-effects models fitted using lme4 version 1.1.33. [34] Intercepts were stratified by trial to account for clustering. We adjusted for the pre-specified covariate gestational age, mean-centered by trial. Correlation of outcomes from multiple births were accounted for with random effects for each maternal intercept. We used mixed-effects logistic regression models to estimate odds ratios (OR) for dichotomous outcomes, since our full models failed to converge for risk ratios (RR). [35] For outcomes with low event rates (as expected for primary and most key secondary outcomes) OR and RR may be

interpreted virtually interchangeably. [36] We use mixed-effects linear regression models to estimate mean differences (MD) for continuous outcomes, and mixed-effects Poisson regression models to estimate rate ratios for count outcomes. We calculated 95% confidence intervals (CIs) using Wald approximation. To account for multiplicity issues, outcomes were assessed and interpreted as patterns of evidence instead of single significant results. [37] Numbers needed to treat with 95%CI were calculated for the primary outcome.

To estimate heterogeneity and assess how summary treatment effects changed, we performed random effects meta-analyses as sensitivity analyses and inspected forest plots. Participant-level subgroup analyses were performed by examining within-trial treatment-by-covariate interactions, [38] avoiding trial-level aggregation bias by centering covariates by trial. Trial-level subgroups were assessed with meta-regression. Pre-specified sensitivity analyses included: different outcome definitions, inclusion of aggregate data in simplified two-stage models, exclusion of high risk of bias trials. The study funder had no role in study design, analysis, interpretation, writing of the report or decision to submit.

Results

We identified 2,369 records (Figure 1). Of these, 992 were excluded after title and abstract screening, the remaining 435 records were reviewed in full (Figure 1). Of these, 122 trials were eligible. Sixty-one trials provided IPD (13 were unpublished at time of analysis, identified through trial registries), of which seven were excluded due to missing data, integrity issues (including major discrepancies between IPD and published data and lack of association between highly correlated variables i.e. gestational age and birthweight), or not fitting intervention categories. Of the remaining 61 eligible trials without IPD, aggregate data were available for 43, though 11 had major integrity or quality issues (e.g. no ethics approval information and implausible findings) and were thus excluded from all analyses. The remaining 32 aggregate data trials were compared to IPD, revealing systematic differences in baseline characteristics, higher risk of bias (overall high: 86% aggregate data trials versus 29% IPD trials), and increased integrity concerns (Appendix p.266). These differences likely explain larger effect sizes for two out of the three pre-specified comparison outcomes in the aggregate data trials [39] Thus, following our pre-specified decision rule and to avoid including lower quality data that may bias study results, our primary analysis only included trials providing IPD, with a total of 48 randomised trials including 6,367 infants. [7,40-82] Aggregate data were included in a sensitivity analysis for the primary outcome. Study characteristics (e.g., year, country of study, sample size) are summarised in Appendix p.282. Certainty of evidence tables are in Appendix p.314. Our updated search (June 2023) identified an additional five published small trials, [83-87] (combined n = 442); one of these was excluded due to integrity concerns (n=100) and four had no mortality data available for a planned sensitivity analysis (Appendix p.140).

For the first comparison, deferred versus immediate clamping, 21 eligible studies were included, with 3,292 infants (232 deaths). Median sample size was 65 (Interquartile range [IQR] 40-101). Median gestational age at birth was 29 weeks (IQR 27-33). Deferral of clamping ranged from 30 to ‘at least’ 180 seconds (with some trials encouraging deferrals up to 5 minutes where feasible). For the immediate clamping group, most trials (n=14) specified clamping within 10 seconds. Of all infants, 61% (1950/3169) were born by caesarean, 25% (670/2637) were multiples, and 56% (1287/2899) were male. Trials were conducted in high-income (n=9/21), upper-middle-income (n=5/21) and lower-middle-income (n=7/21) countries. [88]

Deferred clamping reduced death before discharge compared with immediate clamping (OR 0·68; 95%CI 0·51-0·91, high certainty of evidence, Figure 2). Number needed to treat was 40 (95%CI 26-143). There was no evidence that this effect differed according to any individual or trial-level characteristics (Table 1). For key secondary outcomes, in infants <32 weeks' gestation, deferred compared to immediate clamping reduced the receipt of blood transfusion (OR 0·59; 95%CI 0·47-0·73, high certainty), increased risk of hypothermia (<36·5°C) (OR 1·28; 95%CI 1·06-1·56, moderate certainty), and had no clear evidence of an effect on other key secondary outcomes (Table 2). Certainty of evidence in infants ≥32 weeks' gestation was mostly very low with no significant findings for key secondary outcomes, due to low event rates. There was an improvement in haematologic measures (haemoglobin, haematocrit) for deferred compared to immediate clamping in both infants <32 and ≥32 weeks' gestation (Appendix p.330). No differences were found for maternal outcomes; however, event rates were low (Appendix p.334).

For the second comparison, any cord milking versus immediate clamping, 18 eligible studies were included, with 1,565 infants (74 deaths). The cord was milked intact (2-4 times) in 12 trials with 886 infants, whilst four trials with 340 infants milked the cut cord once. Median sample size was 60 (IQR 45-122). Median gestational age at birth was 29 weeks (IQR 27-31). Of all infants, 64% (764/1196) were born by caesarean, 13% (152/1199) were multiples, and 56% (882/1564) were male. Trials were conducted in high-income (n=10/18), upper-middle-income (n=4/18) and lower-middle-income (n=4/18) countries.

For the primary outcome death before discharge, there was no clear evidence of a difference for cord milking compared to immediate clamping (OR 0·73; 95%CI 0·44-1·20, low certainty, Figure 2). There was no evidence that this effect differed according to any of the pre-specified subgroups, albeit certainty of evidence was low or very low due to insufficient sample size (Table 1). Cord milking probably made no difference for any intraventricular hemorrhage (IVH) for infants <32 weeks' gestation (OR 1·02; 95%CI 0·76-1·38, moderate certainty), and probably reduced the receipt of blood transfusions for <32 weeks' gestation (OR 0·69; 95%CI 0·51-0·93, moderate certainty) and ≥32 weeks' gestation (OR 0·31; 95%CI 0·09-0·99, low certainty) (Table 2). For other key secondary outcomes there were no significant differences with low or very low certainty of evidence due to low event rates in either gestational age group (Table 2). For other secondary outcomes, there was improvement in haematologic measures (haemoglobin, haematocrit) for cord milking compared to immediate clamping in both gestational age groups (Appendix p.330). Maternal outcomes were not estimable or showed no difference with wide confidence intervals, due to few trials collecting maternal outcomes and low event rates.

For the third comparison, any cord milking versus deferred clamping, 15 eligible studies were included, with 1,655 infants (93 deaths). One trial with forty infants milked the cut cord once, whereas 14 studies with 2,1615 infants milked the cord intact (2-4 times). Deferral times ranged from 30 to 120 seconds. Median sample size was 44 (IQR 36-171). Median gestational age at birth was 30 weeks (IQR 28-33). Of all infants, 64% (1022/1593) were born by caesarean, 15% (231/1550) were multiples, and 54% (884/1651) were male. Trials were conducted in high-income (8/15), upper-middle-income (3/15) and lower-middle-income (4/15) countries.

For the primary outcome death before discharge, there was no evidence of a difference between cord milking and deferred clamping (OR 0·95; 95%CI 0·59-1·53, Figure 2), albeit certainty of evidence was low. There was no evidence of differential treatment effects for any of the pre-specified subgroups, but certainty was low or very low due to insufficient sample size (Table 1). Cord milking may increase the risk of severe IVH compared to deferred clamping (OR

2·20; 95%CI 1·13-4·31, low certainty, Table 2). There were no differences, with low or very low certainty, for all other key secondary outcomes due to low event rates (Table 2), and no noteworthy findings for other secondary and maternal outcomes (Appendices p.330, p.334).

For all comparisons, assessment of forest plots and random-effects sensitivity analysis revealed low heterogeneity of treatment effects across all analyses, implying consistent results across trials (Appendix p.335). For the primary outcome death before discharge, risk of bias for 12/49 (24%) trials was rated as high, 20/49 (41%) as some concerns, and 17/49 (35%) as low. For delivery room outcomes, risk of bias for 43/54 (80%) trials was rated as high, 5/54 (9%) as some concerns and 6/54 (11%) as low. For outcomes beyond the delivery room, risk of bias for 27/53 (51%) trials was rated as high, 14/53 (26%) as some concerns and 12/53 (23%) as low (Appendix p.164).

Results were consistent across all pre-specified sensitivity analyses (Appendix p.335), including combining IPD with aggregate data from trials not providing IPD, different outcome definitions, excluding trials with high risk of bias, and different analysis methods (e.g. two-stage model). We could not conduct pre-specified sensitivity analysis excluding trials with low treatment adherence, since many did not report adherence. Pre-specified subgroup analyses of whether initial resuscitation was provided at bedside with cord intact, planned position of the infant relative to the placenta, and non-linear interactions of gestational age could not be performed due to insufficient data or convergence issues.

Discussion

This is the most comprehensive review to date of umbilical cord clamping strategies at preterm birth. Using thoroughly cleaned and checked IPD, we found high-certainty evidence that deferred compared to immediate clamping leads to a moderate reduction in death before discharge for preterm infants; 40 infants (95%CI 26-143) would need to receive deferred instead of immediate clamping to prevent one additional death. This effect appears robust across several individual- and trial-level subgroups. Certainty of evidence for cord milking compared to immediate and deferred clamping was low, due to smaller sample sizes.

Compared to immediate clamping, both deferred clamping and cord milking were associated with less blood transfusion, and improved haematologic markers (haemoglobin, haematocrit). This supports hypotheses that deferred clamping and cord milking increase net blood transfer from placenta to infant. [89-92] Additionally, deferring clamping until after the lungs are aerated may stabilise the transition from fetal to neonatal circulation. [6,93-95]

Deferred clamping increased hypothermia (<36·5°C) on admission to the NICU compared to immediate clamping in infants <32 weeks' gestation. Although the mean temperature difference was only -0·13°C (95%CI -0·20 to -0·06), this suggests that particular care should be taken to keep infants warm when deferring clamping. This may involve strategies such as improved skin-to-skin care, drying and wrapping the infant with the cord intact, or bedside warming trollies. Generally, the available evidence indicates that routine procedures such as drying and stimulating infants should not be delayed and can occur with the cord intact. [42,96,97]

Umbilical cord milking compared to deferred clamping doubled the odds of severe IVH, albeit no difference was found for all grade IVH. This finding was driven by events in infants born <28 weeks' gestation. An increased IVH risk for interventions abruptly interrupting umbilical arterial flow leading to a hypertensive surge was a major hypothesis preceding the first deferred cord clamping trials three decades ago.[98] This hypothesis was subsequently supported by animal studies, which also showed that these hypertensive surges are greatly mitigated by lung aeration.[99,100] Yet, the finding was graded low certainty of evidence due to imprecision and concerns about risk of bias. No differences in all grade IVH or severe IVH were found when comparing cord milking to immediate clamping, even when restricting the population to infants <28 weeks in a post-hoc sensitivity analysis (Appendix p.335).This finding contrasts with a previous network meta-analysis that found a reduction in IVH for cord milking compared to immediate clamping.[101] Our review included more trials and infants due to inclusion of unpublished data and more recent searches. Also, we excluded three studies included in the previous review: one was quasi-randomised, and two had serious integrity concerns (post-randomisation exclusions, unusual data patterns, missing data). Otherwise, our results generally align with previous studies, whilst resolving previous uncertainties. For instance, in the most recent systematic review commissioned by ILCOR, the 95% CI for mortality crossed the line of no effect,[11] whilst our review provides high-certainty evidence that deferred clamping reduces death before discharge in preterm infants.

Our review has many strengths. IPD led to greater data availability and the ability to harmonise outcomes, hence more power to assess safety and effectiveness outcomes resulting in high certainty evidence for mortality, and revealing differences for secondary safety outcomes such as hypothermia. IPD enabled more complex and accurate analyses (e.g. accounting for correlations among multiple births), including ability to examine and demonstrate robustness of treatment effect across key subgroups. IPD also allowed intention-to-treat analysis for all trials. This is important, as failure to comply with the allocated intervention is more common for deferred cord clamping and is related to outcome since clinicians may be tempted to quickly cut the cord of the sickest infants so they can be moved for stabilisation or resuscitation. Analysing these interventions per-protocol would likely skew results to be more favourable for the deferred clamping group. We conducted extensive data processing, quality and integrity checks, of all included data.[28,102] Proportion of missing data was low (0·34%) for our primary outcome death before discharge (Appendix p.353).[103]

Limitations include that, despite extensive efforts, we were unable to retrieve data for all eligible trials, due to data being unavailable from older studies, researchers not responding to our requests, or in one case an ethics board refusing data sharing. This resulted in 32 trials with publications for which we had no IPD, of which only 16 reported mortality. Thus, for our primary outcome death before discharge, we did not have IPD for 19% of infants (n = 1268, 16 trials). The trials we could not retrieve tended to have higher risk of bias and integrity concerns, and be older than those providing IPD. Our results were robust when including aggregate data in sensitivity analyses. Statistical power was limited for several outcomes leading to low or very low certainty of evidence for comparisons of cord milking, for most outcomes in infants >32 weeks' gestational age (due to low event rates), and for maternal outcomes (e.g., postpartum haemorrhage). Large observational or registry studies may assess maternal safety for deferred clamping at preterm birth in future. Interventions were unblinded for all trials, increasing risk of bias, albeit this may be less concerning for the objective outcome mortality than other outcomes.

Certain features of included studies should be considered when applying results in clinical practice. Many studies excluded at-risk populations (e.g. multiple gestation, infants assessed as requiring resuscitation), potentially limiting generalisability to the most vulnerable infants. Exclusion criteria across studies are summarised in Appendix p.356. Many trials did not collect data on intervention adherence. Of those that did, adherence was frequently low (<75% for deferred clamping arm), due to infants randomised to deferred clamping not receiving per-protocol deferral earlier clamping or milking instead. This was likely due to practitioners being uncomfortable to delay advanced resuscitation measures for the most unwell infants, limiting generalisability.

Although several trials were conducted in middle-income-countries, all were conducted in hospitals with a NICU. Hence there is insufficient evidence from low-resource settings, and these results should not be generalised to such settings, or only with considerable caution. High-quality trials assessing cord clamping strategies in low-resource settings are needed.

To allow longer deferral of clamping for infants assessed as needing immediate resuscitation at birth, more trials are providing respiratory support, if needed, beside the mother with the cord intact. This occurred for seven trials in the deferred clamping group (831 infants). Furthermore, several large ongoing trials examining such strategies have committed to sharing their data with the iCOMP Collaboration, with combined results anticipated in 2025. [80,104-106]

Our findings are the best evidence to date that deferred clamping is beneficial for preterm infants, making this study highly relevant to clinicians, parents, and guideline developers. Findings should be interpreted and implemented in conjunction with our companion network meta-analysis, [18] which examined how long to wait before cord clamping, and found that longer deferral (>2 minutes) resulted in the largest mortality reduction (OR 0·31; 95%CI 0·11-0·81), with a 91% probability of longer delays being the best cord management strategy to prevent death before discharge. This finding was rated as moderate certainty evidence, and each of the included trials were relatively small (none were statistically significant independently). Large ongoing trials assessing long deferral will add further insights.[104,107]

In conclusion, we combined 54 trials of cord clamping strategies with IPD from 6,833 preterm babies across three comparisons. We found high-certainty evidence that deferred clamping reduces death before discharge in preterm infants, and this effect is consistent across different population groups. Effects of cord milking on mortality were inconclusive, but severe IVH is a potential safety risk. Together with our companion network meta-analysis, [18] these results will inform updated guidelines and practice on cord management at preterm birth.

Author contributions

Funding acquisition was undertaken by ALS, LMA, LD, AAM. ALS and MA contributed to writing – original draft. ALS, MA, AB, JXS, JAA, JGW, KEH, NS, SL were part of the project team responsible for formal analysis, investigation, data curation, writing - initial review and editing, visualization, project administration, and had access to all the included data from all trials. Only the project team authors that were all located at the data management and analysis centre (NHMRC Clinical Trials Centre) had access to all raw individual participant data, since data sharing agreements with participating trials and our ethics approval stipulated data to be securely hosted locally. ALS, SL, MA accessed and verified the data. All members of the project team were independent from all trials. ALS, MA,

AAM, AB, GMLG, JXS, JAA, JGW, KEH, LD, LMA, NS, SL were members of the iCOMP Secretariat which provided supervision for all the prior mentioned activities, conceptualization, and methodology. ACT, ACW, GRP, HGL, RJS, KPR, MK, PGD, RR, SD, SBH, TPAD were members of the iCOMP Advisory Group which contributed to conceptualization, and methodology. AG, AK, AK, AAG, AT, ACK, ABtP, AKC, BU, BS, CHB, CPM, CT, CR, DC, DAB, EO, EMD, GRM, GC, HKA, HR, HA, IN, JQL, JSD, JSM, JBJ, JK, KDF, KW, KEM, MG, MdV, MMG, MIM, MPM, MKM, NAE, NN, NKD, OA, PP, RK, SA, SS, SSB, SH, SB, SP, TS, VCM, VS, VL, VD, WEN, WAC, WOTM were iCOMP trial investigators and provided resources, were involved in data curation for their trial and were invited to review and contribute to methodology, and results from formal analysis and visualization. All authors were invited to virtual meetings held throughout the project to receive updates and provide input. All authors were involved in the decision to submit the manuscript and contributed to writing – review and editing.

Declaration of interests

iCOMP trial representatives comprised of principal investigators of studies included in this meta-analysis. Trial representatives did not input on study eligibility, data integrity assessments, data extraction or risk of bias assessments for their own studies. Trial representatives did not make final decisions on certainty of evidence ratings. ACT acts as an unpaid council member for the Australian Medical Association (NSW) and the Royal Australasian College of Physicians. ALS is recipient of AustralianNational Health and Medical Research Council (NHMRC), Project and Investigator grants (funds paid directly to the University of Sydney). ABtP holds Concord patent P110521EP10 where LUMC receives royalties and is Chair of the Scientific Advisory Board Concord Neonatal. DB is recipient of grants from NHMRC and the Medical Research Future Fund (MRFF), Australia (funds paid directly to their institution). HL is the chair of the Newborn Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) who may use this evidence to inform updates to clinical practice guidelines. JXS received travel grants and scholarships from the Association of Interdisciplinary Meta-science and Open-Science (AIMOS), Pediatric Academic Societies (PAS and the Perinatal Society of Australia and New Zealand (PSANZ). JD receives grants from the National Institutes of Health (NIH), UK, Canadian Institutes of Health Research (CIHR), and Research Nova Scotia IWK Health. JD acts on the Data Safety Monitoring Committee (DSMC) for the CAPE trial (ISRCTN 12033893). JM acts on the DSCM for a trial related to umbilical cord management (NCT03631940). KDF was loaned LifeStart Trolleys from Inspiration free of charge and donated NeoPuff devices and mask from Fisher & Paykel for NCT02742454. KEM is recipient of MRFF and CIHR grants, and acts on the DSMB for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Network (NICHD), the AGREE study and the FAST Therapy trial. JSD is also recipient of steroid medication for research purposes from Organon Pharmaceuticals, and is a SurePulse advisory board member. KEH is recipient of NHMRC funding paid directly to the University of Sydney. MK acts on the DSMC for the ACE-DUCT trial. OA acts on the CORD-CHD trial DSMC. PD receives NHMRC salary support paid via their institution. RDR receives royalties for two books; “IPD Meta-Analysis” and “Prognosis Research in Healthcare”. RJS receives research funding paid to the University of Sydney from NHMRC, Roche, Bristol Myers Squibb, Astra Zeneca, MSD and Pfizer. RJS receives consulting fees from Detsamma Investments Pty Ltd paid directly to the University of Sydney. SH is a board member for the Japan Resuscitation Council, Member of the Neonatal Life SUpport Task Force, ILCOR and Director of Neonatal Resuscitation Committee for Japan Society of Perinatal and Neonatal Medicine. SD receives fees from the Association of the British Pharmaceutical Industry (ABPI) for delivering the NICE/DSU/ABPI Masterclass on evidence synthesis (2019, 2021, 2022). WAC acts on the DSMB for the NIAMS study, SALMON study and the editorial boards for *Neonatology* and *Pediatric*

Research. WOTM receives NHMRC funding paid to the University of Sydney and received travel and accommodation to present a keynote presentation at the 11th International Conference on Clinical Neonatology, Turin, July 2023.

Acknowledgements

Support for developing the protocol and establishing the collaborative group was received from the UK National Institute of Health Research (grant number RPPG060910107). Funding to undertake data collection and data analysis for the iCOMP Collaboration has been provided by the Australian National Health and Medical Research Council (NHMRC) via a Project Grant (GNT1163585) and ALS was supported by an NHMRC Investigator Grant (GNT2009432). We would like to acknowledge the following persons for contributions to iCOMP, including assistance with screening, study operations, data processing, and providing guidance: Neil Finer, Angeles Linde, G Justus Hofmeyr, Thomas Love, Ka King, and Elona Rey-Costa.

Role of the funding source

The funders had no role in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Data sharing statement

Individual participant data collected for this study, including a data dictionary, will be made available following a moderated access process, where a proposal needs to be approved by the original data custodians (i.e. the trial investigators) and a cross-institutional data access agreement needs to be signed. Statistical analysis plan and protocol are already publicly available. Please contact ALS (lene.seidler@sydney.edu.au) or the iCOMP collaboration (icomp.study@sydney.edu.au) to request data access.

iCOMP Collaborators

Anna Lene Seidler, Mason Aberoumand, Kylie E Hunter, Angie Barba, Sol Libesman, Jonathan G Williams, Nipun Shrestha, Jannik Aagerup, James X Sotiropoulos, Alan A Montgomery, Gillian M L Gyte, Aashim Garg, Aditi Kumar, Aidan C Tan, Amir Kugelman, Angela C Webster, Anu A George, Anu Thukral, Anup C Katheria, Arjan B te Pas, Ashish KC, Berndt Urlesberger, Bernhard Schwaberger, Carl H Backes, Catalina De Paco Matallana, Chamnan Tanprasertkul, Chayatat Ruangkit, Deepak Chawla, Douglas A Blank, Emel Okulu, Eugene M Dempsey, Govindu Ram Mohan, Graeme R Polglase, Guillermo Carroli, Heidi K Al-Wassia, Heike Rabe, Helen G Liley, Hytham Atia, Islam Nour, Jiang-Qin Liu, John Kattwinkel, Jon S Dorling, Judith S Mercer, Justin B Josephsen, Karen D Fairchild, Kedra Wallace, Kellie E Murphy, Kristy P Robledo, Manizheh M Gharehbaghi, Margarita de Veciana, Maria Goya, Martin Kluckow, Melissa I March, Michael P Meyer, Mukul K Mangla, Nahed E Allam, Nehad Nasef, Niraj K Dipak, Ola Andersson, Peter G Davis, Pharuhad Pongmee, Richard D Riley, Robert John Simes, Ronny Knol, Saadet Arsan, Shashank Shekhar, Sheila S Belk, Shigeharu Hosono, Shiraz Badurdeen, Simone Pratesi, Sofia Dias, Stuart B Hooper,

Tanushree Sahoo, Thomas P A Debray, Varanattu C Manoj, Venkataseshan Sundaram, Victor Lago, Vikram Datta, Walid El-Naggar, Waldemar A Carlo, William O Tarnow-Mordi, Lelia Duley, Lisa M Askie

iCOMP Collaborators Affiliations

University of Sydney, Sydney, NHMRC Clinical Trials Centre, NSW, Australia (A L Seidler PhD, M Aberoumand MAppStat, K E Hunter MPH, A Barba MSciMed, S Libesman PhD, J G Williams PhD, N Shrestha PhD, J Aagerup MPH, J X Sotiropoulos MD, A C Tan MD, Prof A C Webster PhD, Prof R J Simes PhD, K P Robledo PhD, Prof W O Tarnow-Mordi MBBCh, Prof L M Askie PhD);
Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, United Kingdom (Prof A A Montgomery PhD, Emeritus Prof L Duley MD);
National Childbirth Trust, London, United Kingdom (G M L Gyte MPhil);
AIIMS, Jodhpur, India (A Garg MD, S Shekhar MD);
AIIMS, Bhubaneswar, India (A Kumar MD, T Sahoo MD);
Rambam Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel (Prof A Kugelman MD);
University of Sydney, Sydney, NSW, Australia (Prof M Kluckow MBBS);
Malankara Orthodox Syrian Church Medical College Hospital, Kolenchery, India (A A George MD);
AIIMS, New Delhi, India (A Thukral MD, M K Mangla MD);
Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States (A C Katheria MD);
Willem-Alexander Children's Hospital, Leiden University Medical Centre, Leiden, Netherlands (Prof A B te Pas MD);
University of Gothenburg, Gothenburg, Sweden (A KC PhD);
Division of Neonatology, Medical University of Graz, Graz, Austria (Prof B Urlesberger MD, B Schwaberger MD);
Nationwide Children's Hospital, Colombus, OH, United States (C H Backes MD);
Hospital Clínico Universitario "Virgen de la Arrixaca", Faculty of Medicine, Universidad de Murcia, Murcia, Spain (C De Paco Catallana PhD);
Thammasat University Research Unit in Advanced clinical data statistics analysis and innovative research in obstetrics and gynecology group, Khlong Nueng, Thailand (C Tanprasertkul PhD);
Ramathibodi Medical School, Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Samut Prakan, Thailand (C Ruangkit MD);
Government Medical College Hospital, Chandigarh, India (D Chawla MD);
Monash Newborn, Monash Health, Clayton, VIC, Australia, The Ritchie Centre, Hudson Institute of Medical Research & Department of Paediatrics, Monash University, Clayton, VIC, Australia (D A Blank MD);
Ankara University Faculty of Medicine, Ankara, Türkiye (E Okulu MD, Prof S Arsan MD);
INFANT Centre, University College Cork, Cork, Ireland (Prof E M Dempsey MD);
St John's Medical College, Bengaluru, India (Dr G Ram Mohan MD);

The Ritchie Centre, Hudson Institute of Medical Research and Department of Obstetrics and Gynaecology, Monash University, Clayton, VIC, Australia (Prof G R Polglase PhD, Prof S B Hooper PhD);
Centro Rosarino de Estudios Perinatales, Rosario, Argentina (G Carroli MD);
King Abdulaziz University, Jeddah, Saudi Arabia (H K Al-Wassia MD);
Brighton and Sussex Medical School, Brighton, United Kingdom (Prof H Rabe MD);
Mater Mother's Hospital, Brisbane, QLD, Australia. Mater Research, Faculty of Medicine, University of Queensland, South Brisbane, QLD, Australia (Prof H G Liley MBChB);
Faculty of Medicine, Zagazig University, Zagazig, Egypt (H Atia MD);
Department of Pediatrics, Faculty of Medicine, University of Mansoura, Mansoura, Egypt. Neonatal Intensive Care Unit, Mansoura University Children's Hospital, Mansoura, Egypt (I Nour PhD);
Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University, Shanghai, China (J Q Liu PhD);
University Hospital Southampton and University of Southampton Biomedical Research Centre, Southampton, United Kingdom (Prof J S Dorling MBChB);
University of Rhode Island, Kingston, RI, United States (Prof J S Mercer PhD);
Saint Louis University, St. Louis, MO, United States (J B Josephsen MD);
University of Virginia School of Medicine, Charlottesville, VA, United States(Prof J Kattwinkel MD, Prof K D Fairchild MD);
University of Mississippi Medical Center, Jackson, MS, United States (Dr K Wallace PhD, S S Belk MD);
University of Toronto, Toronto, ON, Canada (K E Murphy MD);
Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran (Prof M M Gharenhbaghi MD);
Eastern Virginia Medical School, Norfolk, VA, United States (Prof M de Veciana MD);
Maternal-Fetal Medicine Unit, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain (M Goya PhD);
University Hospitals Cleveland, Cleveland, OH, United States (M I March MD);
Middlemore Hospital and University of Auckland, Auckland, New Zealand (M P Meyer MBChB);
Al-Azhar University, Cairo, Egypt (N E Allam MD);
Faculty of Medicine, University of Mansoura, Mansoura, Egypt (Prof N Nasef PhD);
Max Superspeciality Hospital, Vaishali, India (N K Dipak MD);
Lund University, Lund, Sweden (O Andersson MD);
The Royal Women's Hospital, University of Melbourne, Parkville, VIC, Australia (Prof P G Davis MD);
Ramathibodi Medical School, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (P Pongmee MD);
Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom (Prof R D Riley PhD);
Erasmus Medical Centre - Sophia Children's Hospital, Rotterdam, Netherlands (R Knol MD);
Jichi Medical University Saitama Medical Center, Saitama, Japan (Prof S Hosono MD);

Murdoch Children's Research Institute, Parkville, VIC, Australia (S Badurdeen MD);
Careggi University Hospital, Florence, Italy (Prof S Pratesi MD);
University of York, York, United Kingdom (Prof S Dias PhD);
Smart Data Analysis and Statistics, Utrecht, Netherlands (T P A Debray PhD);
Jubilee Mission Medical College and Research Institute, Thrissur, India (Prof V C Manoj MD);
Postgraduate Institute of Medical Education and Research, Chandigarh, India (V Sundaram MD);
University Hospital La Fe, Valencia, Spain. CEU University, Valencia, Spain V Lago MD);
ABVIMS and Dr RML Hospital, New Delhi, India (V Datta MD);
Dalhousie University, Halifax, NS, Canada (W El-Naggar MD);
University of Alabama, Birmingham, AL, United States (Prof W A Carlo MD)

References

1. Ohuma EO, Moller A-B, Bradley E, et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. *Lancet* 2023; **402**(10409): 1261-71.
2. Perin J, Mulick A, Yeung D, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet Child Adolesc Health* 2022; **6**(2): 106-15.
3. Gomersall J, Berber S, Middleton P, et al. Umbilical Cord Management at Term and Late Preterm Birth: A Meta-analysis. *Pediatrics* 2021; **147**(3).
4. El-Naggar W, Davis PG, Soll RF, et al. Cord Management at Birth for Term and Late Preterm infants. . International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support Task Force, Feb 2021. Available from: http://ilcor.org (accessed 29 August 2023).
5. Hooper SB, Te Pas AB, Lang J, et al. Cardiovascular transition at birth: a physiological sequence. *Pediatr Res* 2015; **77**(5): 608-14.
6. Bhatt S, Alison BJ, Wallace EM, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol* 2013; **591**(8): 2113-26.
7. Katheria A, Reister F, Essers J, et al. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. *JAMA* 2019; **322**(19): 1877-86.
8. Seidler AL, Hunter KE, Barba A, et al. Optimizing cord management for each preterm baby – Challenges of collating individual participant data and recommendations for future collaborative research. *Semin Perinatol* 2023: 151740.
9. Fogarty M, Osborn DA, Askie L, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2018; **218**(1): 1-18.

10. Rabe H, Gyte GML, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2019; (9): CD003248.
11. Seidler AL, Gyte GML, Rabe H, et al. Umbilical Cord Management for Newborns <34 Weeks' Gestation: A Meta-analysis. *Pediatrics* 2021; **147**(3): e20200576.
12. Wyckoff MH, Singletary EM, Soar J, et al. 2021 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Neonatal Life Support; Education, Implementation, and Teams; First Aid Task Forces; and the COVID-19 Working Group. *Circulation* 2022; **145**(9): e645-e721.
13. Aziz K, Lee HC, Escobedo MB, et al. Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020; **142**(16_suppl_2): S524-S50.
14. World Health Organization. Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. 2014: Geneva.
15. National Institute for Health and Care Excellence. Preterm labour and birth. NICE guideline NG25. 2015 (last updated 10 June 2022): London. Available at https://www.nice.org.uk/guidance/ng25 (accessed August 2023).
16. Madar J, Roehr CC, Ainsworth S, et al. European Resuscitation Council Guidelines 2021: Newborn resuscitation and support of transition of infants at birth. *Resuscitation* 2021; **161**: 291-326.
17. Riley RD, Tierney JF, Stewart LA, eds. Individual Participant Data Meta-Analysis for Healthcare Research: Wiley; 2021.
18. Seidler AL, Libesman S, Hunter KE, et al, on behalf of the iCOMP Collaboration. Individual Participant Data on Cord Management at Preterm birth (iCOMP): a systematic review and network meta-analysis with individual participant data *submitted to Lancet* 2023.
19. Seidler AL, Duley L, Katheria AC, et al. Systematic review and network meta-analysis with individual participant data on cord management at preterm birth (iCOMP): study protocol. *BMJ Open* 2020; **10**(3): e034595.
20. Stewart LA, Clarke M, Rovers M, et al. PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015; **313**(16): 1657-65.
21. Hunter KE, Webster AC, Page MJ, et al. Searching clinical trials registers: guide for systematic reviewers. *BMJ* 2022; **377**: e068791.
22. Manuck TA, Rice MM, Bailit JL, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. *AJOG* 2016; **215**(1): 103.e1-.e14.
23. Blencowe H, Cousens S, Chou D, et al. Born Too Soon: The global epidemiology of 15 million preterm births. *Reprod Health* 2013; **10**(1): S2.
24. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. *Semin Fetal Neonatal Med* 2004; **9**(6): 429-35.
25. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. *Dev Med Child Neurol* 2018; **60**(4): 342-55.
26. Stoll BJ, Hansen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *JAMA* 2015; **314**(10): 1039-51.
27. Tierney JF, Riley RD, Rydzewska LHM, Stewart LA. Chapter 4: Running an IPD Meta-Analysis Project. In: Riley RD, Tierney JF, Stewart LA, eds. Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research: Wiley; 2021.

28. Hunter KE, Shrestha N, Barba A, et al. Data integrity assessment of clinical trials in neonatology for individual participant data meta-analyses: a case study of cord management in preterm infants. *Pediatric Academic Societies (PAS) Annual Meeting,* Washington DC, USA, April 2023 (poster).
29. Hunter KE. Assessment of data integrity for individual participant data meta-analyses: a case study. *Association for Interdisciplinary Meta-research and Open Science (AIMOS) Conference,* Melbourne, November 2022.
30. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**(7650): 924-6.
31. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook.
32. R Core Team. R: A language and environment for statistical computing. 2021: R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
33. Part II Fundamental Statistical Methods and Principles. In: Riley RD, Tierney JF, LA S, eds. Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research: Wiley; 2021.
34. Bates D, Maechler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *J Stat Software* 2015; **67**(1): 1-48.
35. Riley RD, Debray T. Chapter 6: The One-stage Approach to IPD Meta-Analysis. In: Riley RD, Tierney JF, Stewart LA, eds. Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research: Wiley; 2021.
36. Cummings P. The Relative Merits of Risk Ratios and Odds Ratios. *Arch Pediatr Adolesc Med* 2009; **163**(5): 438-45.
37. Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005; **365**(9470): 1591-5.
38. Riley RD, Fisher DJ. Chapter 7: Using IPD Meta-Analysis to Examine Interactions between Treatment Effect and Participant-level Covariates. In: Riley RD, Tierney JF, Stewart LA, eds. Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research: Wiley; 2021: 163-98.
39. Seidler AL, Aberoumand M, Riley R, et al. Should aggregate data be included where individual participant data are unavailable? Lessons from a large individual participant data meta-analysis. Cochrane Colloquium; 2023 4-6 September; London; 2023.
40. Tarnow-Mordi W, Morris J, Kirby A, et al. Delayed versus Immediate Cord Clamping in Preterm Infants. *N Engl J Med* 2017; **377**(25): 2445-55.
41. Kamal D, Abel-Fattah A, Saleh D, et al. Delayed cord clamping in premature fetuses: Randomised clinical trial. *Reprod Health Popul Sci* 2019; **44**: 66-87.
42. Duley L, Dorling J, Pushpa-Rajah A, et al. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2018; **103**(1): F6-f14.
43. Ranjit T, Nesargi S, Rao PN, et al. Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age. *Indian J Pediatr* 2015; **82**(1): 29-34.
44. Backes CH, Huang H, Iams JD, Bauer JA, Giannone PJ. Timing of umbilical cord clamping among infants born at 22 through 27 weeks' gestation. *J Perinatol* 2016; **36**(1): 35-40.
45. García C, Prieto MT, Escudero F, et al. The impact of early versus delayed cord clamping on hematological and cardiovascular changes in preterm newborns between 24 and 34 weeks' gestation: a randomized clinical trial. *Arch Gynecol Obstet* 2023.

46. Oh W, Fanaroff AA, Carlo WA, Donovan EF, McDonald SA, Poole WK. Effects of delayed cord clamping in very-low-birth-weight infants. *J Perinatol* 2011; **31**: S68-71.
47. Yunis M, Nour I, Gibreel A, et al. Effect of delayed cord clamping on stem cell transfusion and hematological parameters in preterm infants with placental insufficiency: a pilot randomized trial. *Eur J Pediatr* 2021; **180**(1): 157-66.
48. Gregoraci A, Carbonell M, Linde A, et al. Timing of Umbilical Cord Occlusion, Delayed vs Early, in Preterm Babies: A Randomized Controlled Trial (CODE-P Trial). *Eur J Obstet Gynecol Reprod Biol* 2023; **289**: 203-7.
49. Datta V, Kumar A, Yadav R. A randomized controlled trial to evaluate the role of brief delay in cord clamping in preterm neonates (34-36 weeks) on short-term neurobehavioural outcome. *J Trop Pediatr* 2017; **63**(6): 418–24.
50. Chu K, Whittle W, Windrim R, Shah P, Murphy K. The DUC trial: A pilot randomized controlled trial of immediate vs. delayed umbilical cord clamping in preterm infants born between 24 and 32 weeks gestation. *Am J Obstet Gynecol* 2011; **204**: S201.
51. Rana A, Agarwal K, Ramji S, Gandhi G, Sahu L. Safety of delayed umbilical cord clamping in preterm neonates of less than 34 weeks of gestation: a randomized controlled trial. *Obstet Gynecol Sci* 2018; **61**(6): 655-61.
52. Kugelman A, Borenstein-Levin L, Riskin A, et al. Immediate versus delayed umbilical cord clamping in premature neonates born < 35 weeks: a prospective, randomized, controlled study. *Am J Perinatol* 2007; **24**(5): 307-15.
53. ChiCTR. Delayed cord clamping prevents respiratory distress of infants delivered by selective cesarean section, a randomized controlled trial. https://www.chictr.org.cn/showproj.html?proj=30199 (accessed August 25, 2023).
54. Sahoo T, Thukral A, Sankar MJ, et al. Delayed cord clamping in Rh-alloimmunised infants: a randomised controlled trial. *Eur J Pediatr* 2020; **179**(6): 881-9.
55. Gharehbaghi MM, Yasrebinia S, Gharabaghi PM. Umbilical Cord Clamping Timing in Preterm Infants Delivered by Cesarean Section. *Int J Pediatr* 2020; **8**(4): 11095-101.
56. Finn D, Ryan DH, Pavel A, et al. Clamping the Umbilical Cord in Premature Deliveries (CUPiD): Neuromonitoring in the Immediate Newborn Period in a Randomized, Controlled Trial of Preterm Infants Born at <32 Weeks of Gestation. *J Pediatr* 2019; **208**: 121-6.e2.
57. Ruangkit C, Bumrungphuet S, Panburana P, Khositseth A, Nuntnarumit P. A Randomized Controlled Trial of Immediate versus Delayed Umbilical Cord Clamping in Multiple-Birth Infants Born Preterm. *Neonatology* 2019; **115**(2): 156-63.
58. Salae R, Tanprasertkul C, Somprasit C, Bhamarapravatana K, Suwannarurk K. Efficacy of delayed versus immediate cord clamping in late preterm newborns following normal labor: a randomized control trial. *J Med Assoc Thai* 2016; **99**(4): S159-S65.
59. Okulu E, Haskologlu S, Guloglu D, et al. Effects of Umbilical Cord Management Strategies on Stem Cell Transfusion, Delivery Room Adaptation, and Cerebral Oxygenation in Term and Late Preterm Infants. *Front Pediatr* 2022; **10**: 838444.
60. Chellappan MV, Divakaran D, George N, et al. Long Term Effects of Milking of Cut Umbilicial Cord in Very Preterm Neonates: A Randomised Controlled Trial in Southern India *Arch Dis Child* 2022; **107**.
61. Mercer JS, Erickson-Owens DA, Vohr BR, et al. Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial. *J Pediatr* 2016; **168**: 50-5.e1.

62. Josephsen JB, Potter S, Armbrecht ES, Al-Hosni M. Umbilical Cord Milking in Extremely Preterm Infants: A Randomized Controlled Trial Comparing Cord Milking with Immediate Cord Clamping. *Am J Perinatol* 2022; **39**(4): 436-43.
63. March MI, Hacker MR, Parson AW, Modest AM, de Veciana M. The effects of umbilical cord milking in extremely preterm infants: A randomized controlled trial. *J Perinatol* 2013; **33**(10): 763-7.
64. Hosono S, Mugishima H, Fujita H, et al. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**(1): F14-9.
65. Shen S-P, Chen C-H, Chang H-Y, et al. A 20-cm cut umbilical cord milking may not benefit the preterm infants < 30 week's gestation: A randomized clinical trial. *J Formos Med Assoc* 2022; **121**(5): 912-9.
66. Xie Y-j, Xiao J-l, Zhu J-j, Wang Y-w, Wang B, Xie L-j. Effects of umbilical cord milking on anemia in preterm infants: a multicenter randomized controlled trial. *Am J Perinatol* 2020; **39**(01): 031-6.
67. Hosono S, Tamura M, Kusuda S, Hirano S, Fujimura M, Takahashi S. One-time umbilical cord milking after cord cutting reduces the need for red blood cell transfusion and reduces the mortality rate in extremely preterm infants; a multicenter randomized controlled trial. *Pediatric Academic Societies Annual Meeting; 2015 April 25-28; San Diego, California*.
68. Katheria A, Poeltler D, Durham J, et al. Neonatal Resuscitation with an Intact Cord: A Randomized Clinical Trial. *J Pediatr* 2016; **178**: 75-80.e3.
69. El-Naggar W, Simpson D, Hussain A, et al. Cord milking versus immediate clamping in preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2019; **104**(2): F145-f50.
70. TCTR. The Effect of One-Time Umbilical Cord Milking and Early Cord Clamping in Preterm Infants: A Randomized Controlled Trial (One-Time Umbilical Cord Milking). https://www.thaiclinicaltrials.org/show/TCTR20170201003 (accessed August 28, 2023).
71. Alan S, Arsan S, Okulu E, et al. Effects of umbilical cord milking on the need for packed red blood cell transfusions and early neonatal hemodynamic adaptation in preterm infants born ≤1500 g: a prospective, randomized, controlled trial. *J Pediatr Hematol Oncol* 2014; **36**(8): e493-8.
72. George AA, Isac M. Effect of Umbilical Cord Milking on Maternal and Neonatal Outcomes in a Tertiary Care Hospital in South India: A Randomized Control Trial. *J Obstet Gynaecol India* 2022; **72**(4): 291-8.
73. Ram Mohan G, Shashidhar A, Chandrakala BS, Nesargi S, Suman Rao PN. Umbilical cord milking in preterm neonates requiring resuscitation: A randomized controlled trial. *Resuscitation* 2018; **130**: 88-91.
74. Lago Leal V, Pamplona Bueno L, Cabanillas Vilaplana L, et al. Effect of Milking Maneuver in Preterm Infants: A Randomized Controlled Trial. *Fetal Diagn Ther* 2019; **45**(1): 57-61.
75. ClinicalTrials.gov. Deferred Cord Clamping Compared to Umbilical Cord Milking in Preterm Infants. https://clinicaltrials.gov/study/NCT02996799 (accessed August 28, 2023).
76. Atia H, Badawie A, Elsaid O, Kashef M, Alhaddad N, Gomaa M. The hematological impact of umbilical cord milking versus delayed cord clamping in premature neonates: a randomized controlled trial. *BMC Pregnancy Childbirth* 2022; **22**(1): 714.
77. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical cord milking versus delayed cord clamping in preterm infants. *Pediatrics* 2015; **136**(1): 61-9.

78. Rabe H, Jewison A, Alvarez RF, et al. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. *Obstet Gynecol* 2011; **117**(2): 205-11.
79. Tanai T, Benjamaporn P, Prisana P, Sangkae C. Effect of delayed cord clamping versus cord milking in preterm infants: a randomized controlled trialL. *J Southeast Asian Med Res* 2018; **2**(1).
80. Pratesi S, Montano S, Ghirardello S, et al. Placental Circulation Intact Trial (PCI-T)—Resuscitation with the placental circulation intact vs. cord milking for very preterm infants: a feasibility study. *Front Pediatr* 2018; **6**: 364.
81. ClinicalTrials.gov. C-UCM and Cerebral Oxygenation and Perfusion. https://clinicaltrials.gov/study/NCT03748914 (accessed August 25, 2023).
82. CTRI. Delayed cord clamping versus milking of umbilical cord in term and near term neonates-A randomized controlled trial. http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=39871&EncHid=&userName=CTRI/2020/02/023364 (accessed August 28, 2023).
83. Sunil B, Sindhuraj MN, Athul P. Umbilical Cord Milking in Late Preterm Neonates and its Effects on Haematological and Haemodynamical Parameters- A Randomised Controlled Study. *J Clin Diagn Res* 2022; **16**(3): SC16-SC9.
84. Kumawat AK, Meena KK, Athwani V, et al. Effect of Umbilical Cord Milking in Term and Late Preterm Neonates: A Randomized Controlled Trial. *Perinatology* 2022; **22**(4): 258-65.
85. Kumar A, Singh BB, Kumar R. Randomized Comparative Clinical Assessment of the Umbilical Cord Clamping Timing in Preterm Infants delivered by Cesarean Section. *Int J Pharm Clin Res* 2022; **14**(8): 1014-9.
86. Bhikadiya M, Bhatt D, Nikhileshwar BA, Punasanvala P. A prospective study to determine the effectiveness of delayed umbilical cord clamping in preterm infants in a tertiary care hospital. *Int J Pharm Clin Res* 2022; **14**(9): 663-72.
87. Kilicdag H, Karagun BS, Antmen AB, Candan E, Erbas H. Umbilical Cord Management in Late Preterm and Term Infants: A Randomized Controlled Trial. *Am J Perinatol* 2021; **39**(12): 1308-13.
88. The World Bank Group. World Bank Open Data. https://data.worldbank.org/ (accessed 28 June 2023).
89. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. *J Perinatol* 2017; **37**(2): 105-11.
90. Lawton C, Acosta S, Watson N, et al. Enhancing endogenous stem cells in the newborn via delayed umbilical cord clamping. *Neural Regen Res* 2015; **10**: 1359–62.
91. Law GR, Cattle B, Farrar D, Scott EM, Gilthorpe MS. Placental blood transfusion in newborn babies reaches a plateau after 140 s: Further analysis of longitudinal survey of weight change. *SAGE Open Med* 2013; **1**.
92. Aladangady N, McHugh S, Aitchison TC, Wardrop CAJ, Holland BM. Infants' Blood Volume in a Controlled Trial of Placental Transfusion at Preterm Delivery. *Pediatrics* 2006; **117**(1): 93-8.
93. Nevill E, Meyer MP. Effect of delayed cord clamping (DCC) on breathing and transition at birth in very preterm infants. *Early Hum Dev* 2015; **91**(7): 407-11.
94. Ersdal HL, Linde J, Mduma E, Auestad B, Perlman J. Neonatal Outcome Following Cord Clamping After Onset of Spontaneous Respiration. *Pediatrics* 2014; **134**(2): 265-72.
95. Hooper SB, Polglase GR, te Pas AB. A physiological approach to the timing of umbilical cord clamping at birth. *Arch Dis Child Fetal Neonatal Ed* 2015; **100**(4): F355-F60.

96. Dekker J, Hooper SB, Martherus T, Cramer SJE, van Geloven N, te Pas AB. Repetitive versus standard tactile stimulation of preterm infants at birth - A randomized controlled trial. *Resuscitation* 2018; **127**: 37-43.
97. Guinsburg R, de Almeida MFB, Finan E, et al. Tactile Stimulation in Newborn Infants With Inadequate Respiration at Birth: A Systematic Review. *Pediatrics* 2022; **149**(4).
98. Hofmeyr GJ, Bex PJ, Skapinker R, Delahunt T. Hasty clamping of the umbilical cord may initiate neonatal intraventricular hemorrhage. *Med Hypotheses* 1989; **29**(1): 5-6.
99. Bhatt S, Alison BJ, Wallace EM, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. *J Physiol* 2013; **591**(8): 2113-26.
100. Viaroli F, Cheung P-Y, O'Reilly M, Polglase GR, Pichler G, Schmölzer GM. Reducing Brain Injury of Preterm Infants in the Delivery Room. *Front Pediatr* 2018; **6**.
101. Jasani B, Torgalkar R, Ye XY, Syed S, Shah PS. Association of Umbilical Cord Management Strategies With Outcomes of Preterm Infants: A Systematic Review and Network Meta-analysis. *JAMA Pediatr* 2021; **175**(4): e210102-e.
102. Hunter KE, Webster AC, Clarke M, et al. Development of a checklist of standard items for processing individual participant data from randomised trials for meta-analyses: Protocol for a modified e-Delphi study. *PLoS One* 2022; **17**(10): e0275893.
103. Tarnow-Mordi WO, Robledo K, Marschner I, et al. To guide future practice, perinatal trials should be much larger, simpler and less fragile with close to 100% ascertainment of mortality and other key outcomes. *Semin Perinatol* 2023; **47**(5): 151789.
104. Knol R, Brouwer E, van den Akker T, et al. Physiological-based cord clamping in very preterm infants: the Aeration, Breathing, Clamping 3 (ABC3) trial—study protocol for a multicentre randomised controlled trial. *Trials* 2022; **23**(1): 838.
105. Winter J, Kattwinkel J, Chisholm C, Blackman A, Wilson S, Fairchild K. Ventilation of Preterm Infants during Delayed Cord Clamping (VentFirst): A Pilot Study of Feasibility and Safety. *Am J Perinatol* 2017; **34**(02): 111-6.
106. Ekelöf K, Sæther E, Santesson A, et al. A hybrid type I, multi-center randomized controlled trial to study the implementation of a method for Sustained cord circulation And VEntilation (the SAVE-method) of late preterm and term neonates: a study protocol. *BMC Pregnancy Childbirth* 2022; **22**(1): 593.
107. ClinicalTrials.gov. VentFirst: A Multicenter RCT of Assisted Ventilation During Delayed Cord Clamping for Extremely Preterm Infants. https://clinicaltrials.gov/study/NCT02742454 (accessed August 29, 2023).

Figures

Figure 1. PRISMA flow chart.

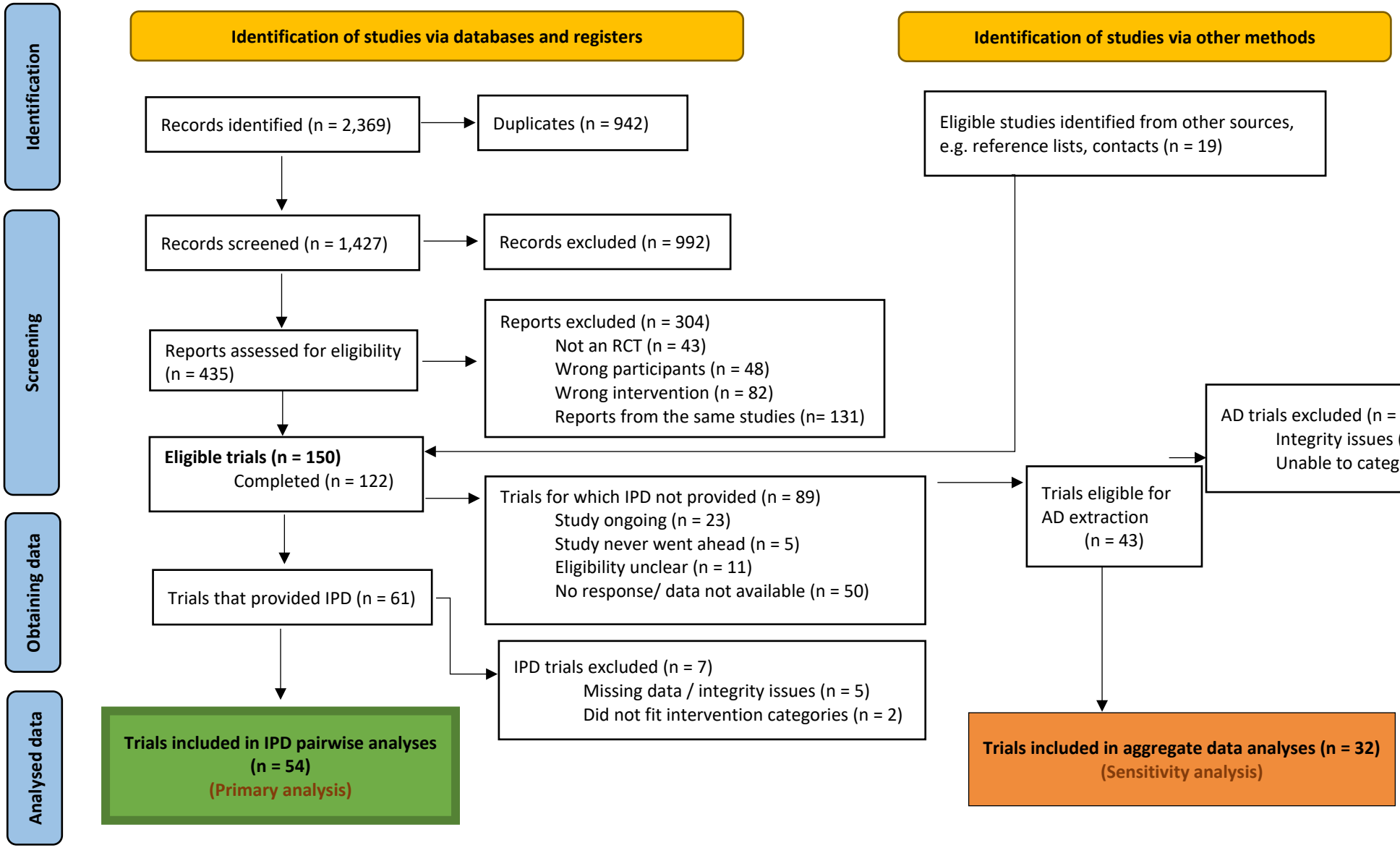
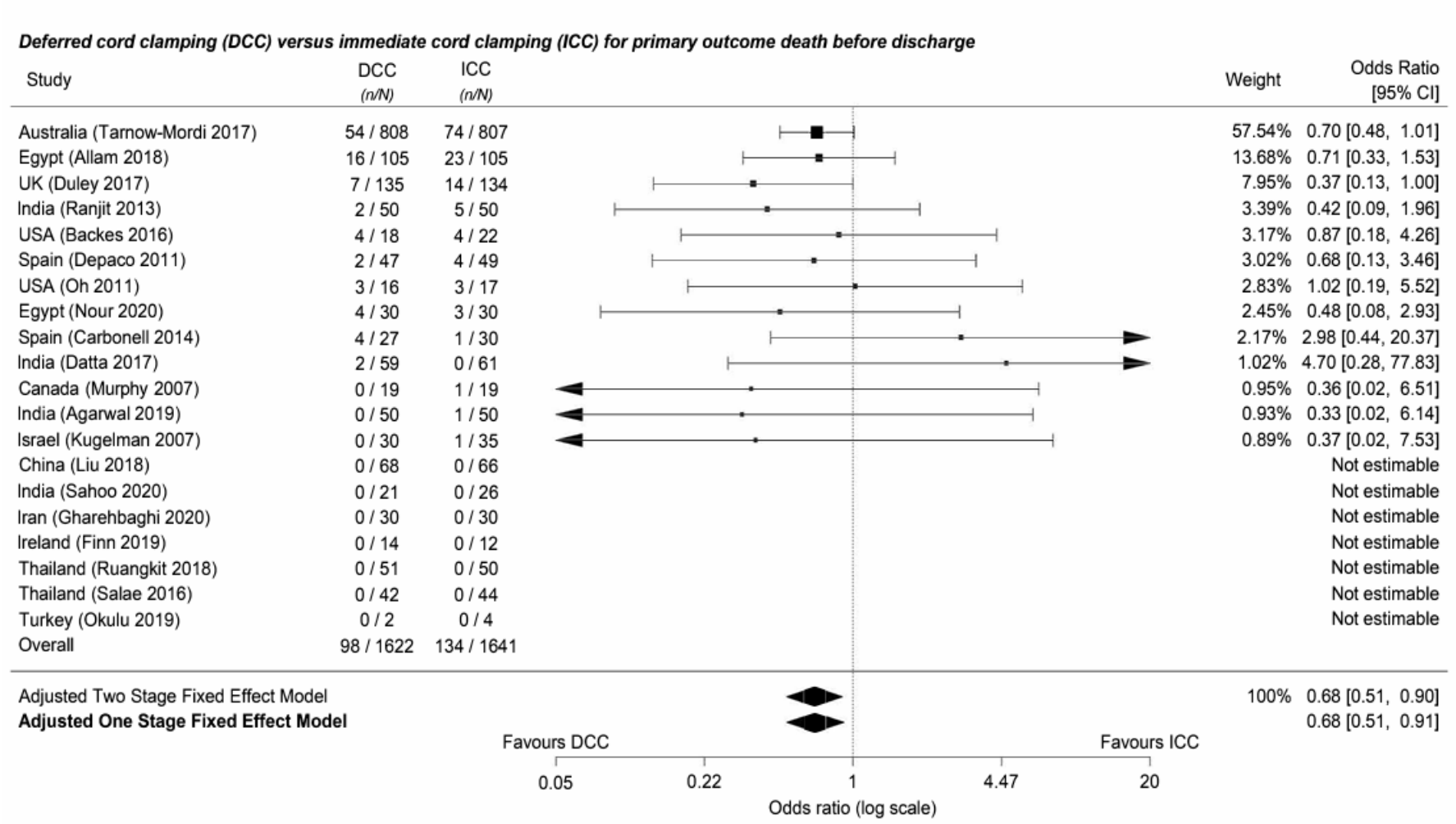
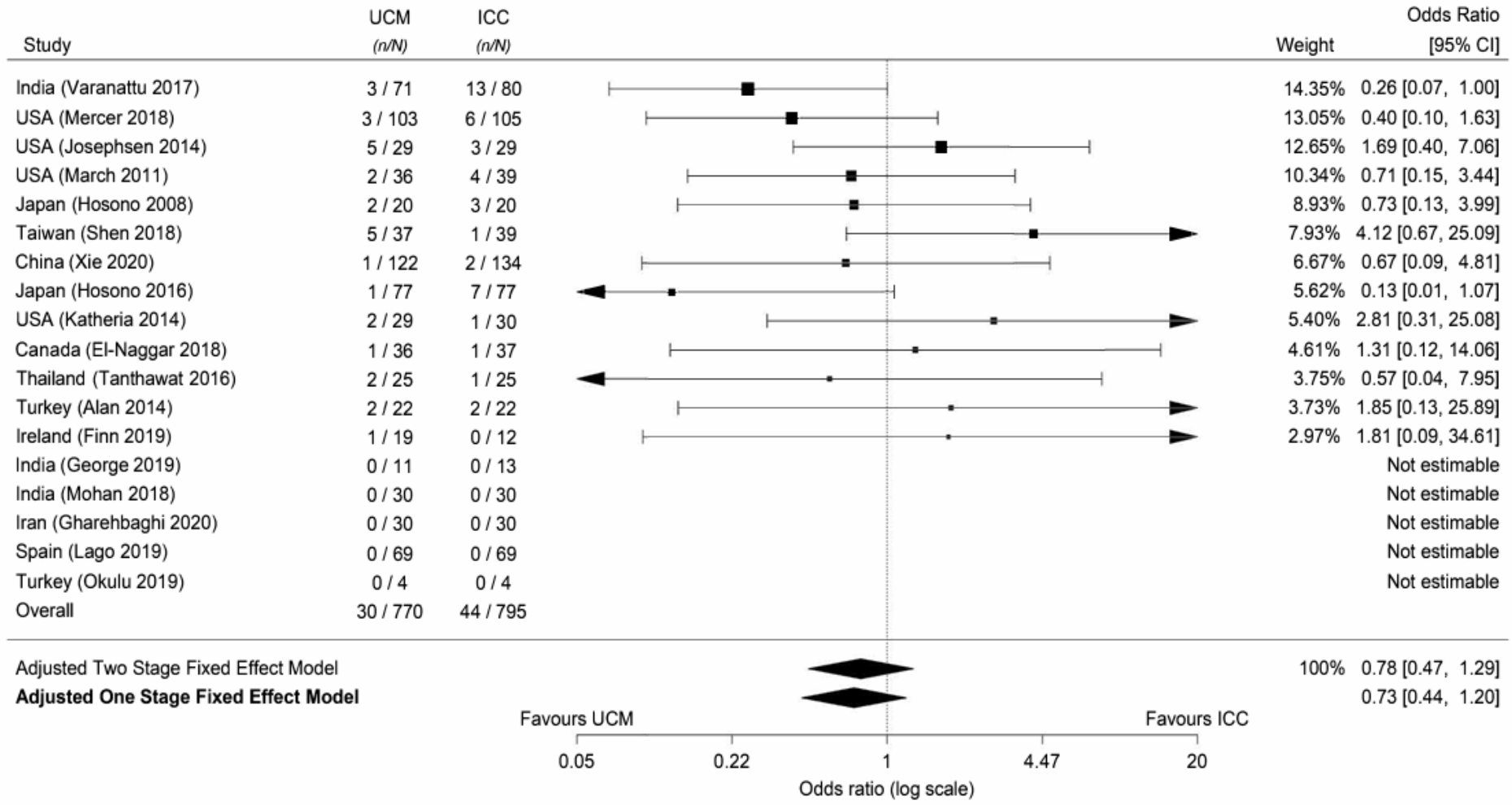
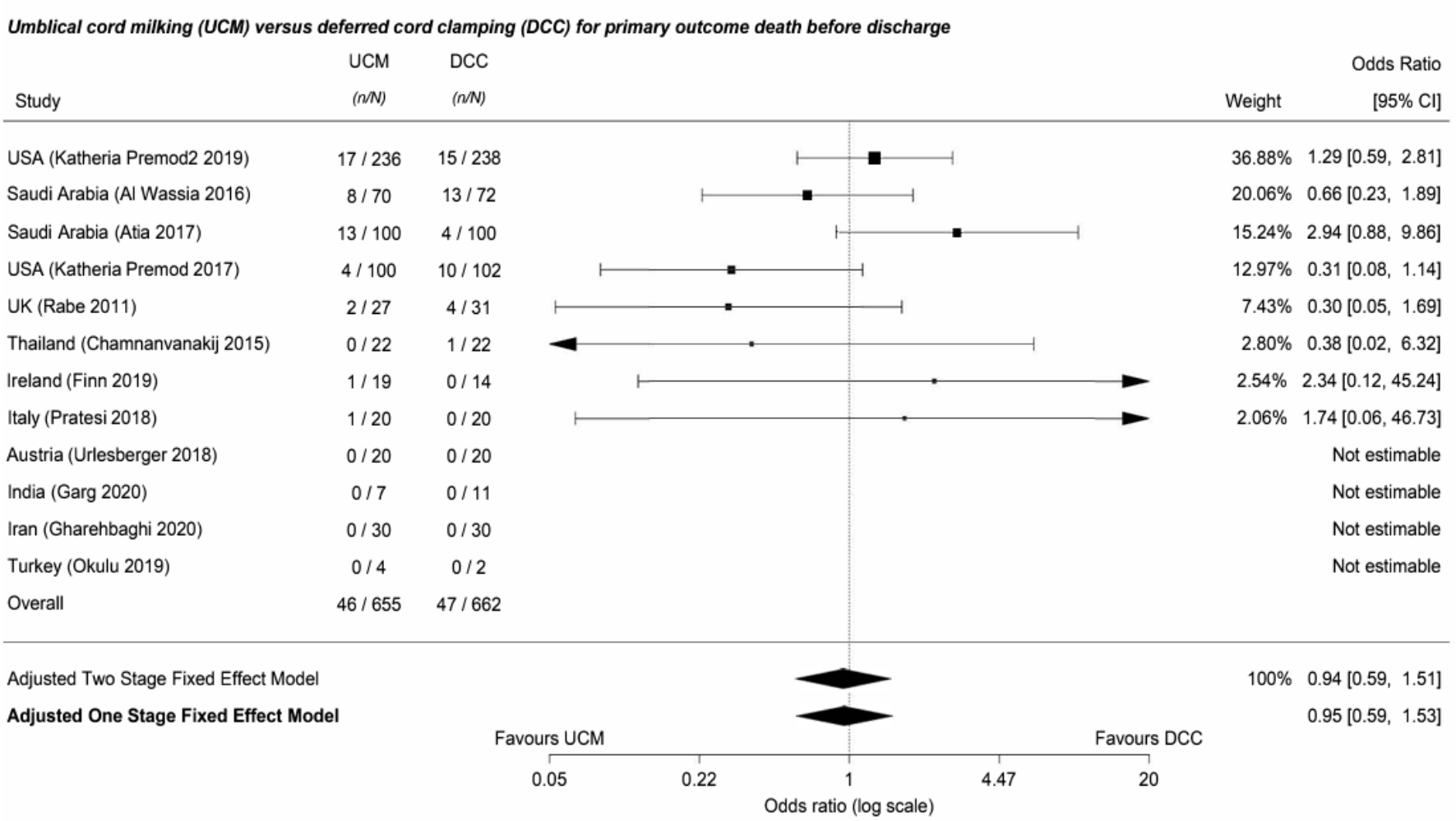


Figure 2. Forest plots as a panel



Umblical cord milking (UCM) versus immediate cord clamping (ICC) for primary outcome death before discharge





Note: Effect estimates on the x-axis are odds ratios on the log scale. The black squares capture the treatment effect estimate. The 95% confidence intervals around this estimate are represented by the black line. Gestational age and correlation between multiple infants are adjusted for in this figure.

Table 1. Primary and key secondary outcomes for all comparisons

Outcomes	DCC vs ICC			UCM vs ICC			UCM vs DCC		
	Events/ number of infants (N trials)	Relative effect OR (95% CI)	GRADE	Number of infants (N trials)	Relative effect OR (95% CI)	GRADE	Number of infants (N trials)	Relative effect OR (95% CI)	GRADE
Primary outcome: all infants									
Mortality to discharge	232/3260 (N=20)	0·68 (0·51-0·91)	High	74/1561 (N=18)	0·73 (0·44-1·20)	Low	93/1303 (N=12)	0·95 (0·59-1·53)	Low
Key secondary outcomes (<32 weeks' GA)									
Intraventricular haemorrhage (IVH) (all grades)	444/2124 (N=13)	0·98 (0·79-1·22)	Low	264/1069 (N=15)	1·02 (0·76-1·38)	Moderate	210/1022 (N=9)	1·04 (0·75-1·44)	Low
IVH (severe)	100/2096 (N=11)	0·83 (0·54-1·26)	Low	65/939 (N=14)	0·78 (0·45-1·35)	Low	47/860 (N=7)	2·20 (1·13-4·31)	Low
Blood transfusion	1136/2128 (N=13)	0·59 (0·47-0·73)	High	616/1163 (N=15)	0·69 (0·51-0·93)	Moderate	414/985 (N=8)	1·07 (0·77-1·50)	Low
Chronic lung disease	922/1929 (N=10)	1·06 (0·87-1·30)	Low	239/836 (N=12)	0·96 (0·63-1·47)	Low	75/293 (N=4)	1·02 (0·56-1·87)	Very low
Hypothermia on admission	958/1995 (N=8)	1·28 (1·06-1·56)	Moderate	299/688 (N=8)	0·95 (0·69-1·31)	Very low	215/875 (N=7)	0·90 (0·64-1·26)	Low
Late-onset sepsis	551/2037 (N=9)	0·93 (0·74-1·17)	Low	189/977 (N=12)	1·07 (0·76-1·51)	Low	98/787 (N=6)	0·91 (0·57-1·48)	Low
Necrotising enterocolitis	173/2052 (N=11)	0·82 (0·59-1·13)	Low	59/1047 (N=13)	0·90 (0·52-1·56)	Low	58/976 (N=7)	0·95 (0·55-1·66)	Low
Patent ductus arteriosus (PDA) requiring medical treatment	588/1928 (N=8)	0·91 (0·73-1·14)	Low	292/893 (N=12)	1·25 (0·88-1·76)	Very low	122/631 (N=5)	0·88 (0·56-1·37)	Low
PDA requiring surgical treatment	520/1678 (N=7)	0·93 (0·73-1·19)	Low	57/888 (N=11)	0·84 (0·46-1·52)	Low	26/631 (N=5)	1·43 (0·63-3·25)	Low
Key secondary outcomes (≥32 weeks' GA)									
IVH (all grades)	4/478 (N=10)	0·52 (0·05-6·02)	Very low	6/192 (N=6)	6·05 (0·63-58·55)	Very low	14/250 (N=9)	1·62 (0·47-5·50)	Very low
IVH (severe)	Not estimable (0 events)			Not estimable (0 events)			Not estimable (0 events)		
Blood transfusion	61/729 (N=12)	0·97 (0·54-1·73)	Very low	16/330 (N=6)	0·31 (0·09-0·99)	Very low	19/251 (N=8)	1·67 (0·60-4·60)	Very low
Hypothermia on admission <36.5°C	143/396 (N=8)	0·95 (0·51-1·79)	Low	97/190 (N=2)	1·57 (0·84-2·93)	Very low	31/209 (N=5)	1·40 (0·54-3·69)	Very low
NICU admission	305/524 (N=9)	0·74 (0·42-1·30)	Very low	240/330 (N=6)	0·82 (0·34-1·95)	Very low	144/221 (N=7)	1·23 (0·60-2·52)	Very low

DCC = deferred cord clamping, ICC = immediate cord clamping, UCM = umbilical cord milking, OR = odds ratio, CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, IVH = intraventricular haemorrhage, PDA = patent ductus arteriosus, GA = gestational age, NICU = neonatal intensive care unit. All analyses presented in this table are adjusted for gestational age and correlation between multiple births (e.g. twins).

Table 2. Subgroup analyses for primary outcome of death before discharge for all comparisons

Subgroup for death before discharge	DCC vs ICC			UCM vs ICC			UCM vs DCC		
	Number of studies	Certainty of evidence (adapted GRADE)	Interaction OR 95% CI	Number of studies	Certainty of evidence (adapted GRADE)	Interaction OR 95% CI	Number of studies	Certainty of evidence (adapted GRADE)	Interaction OR 95% CI
Gestational age (weeks)*	13 RCTs	High	0·93 (0·78-1·11)	11 RCTs	Low	1·01 (0·97-1·05)	7 RCTs	Low	1·08 (0·80-1·47)
Multiple birth (singleton/ multiple)	4 RCTs	Low	1·11 (0·49-2·50)	7 RCTs	Very Low	1·52 (0·37-6·32)	4 RCTs	Very Low	1·26 (0·34-4·67)
Mode of delivery (caesarean/ vaginal)	4 RCTs	Low	0·69 (0·39-1·22)	13 RCTs	Very Low	0·59 (0·20-1·75)	8 RCTs	Low	0·83 (0·33-2·12)
Study start (year)*	13 RCTs	Low	1·00 (0·92-1·08)	13 RCTs	Very Low	0·98 (0·85-1·12)	8 RCTs	Low	0·89 (0·74-1·08)
Perinatal mortality rate (per 1,000)*	13 RCTs	Low	1·00 (0·97-1·02)	13 RCTs	Very Low	1·02 (0·99-1·04)	8 RCTs	Low	0·98 (0·88-1·09)
Sex(male/ female) – post hoc analysis	11 RCTs	Not assessed: post-hoc analysis	1·00 (0·64-1·86)	11 RCTs	Not assessed: post-hoc analysis	1.22 (0.44-3.37)	7 RCTs	Not assessed: post-hoc analysis	0·54 (0·20-1·48)

DCC = deferred cord clamping, ICC = immediate cord clamping, UCM = umbilical cord milking, GRADE = Grading of Recommendations Assessment, Development and Evaluation, OR = odds ratio, CI = confidence interval, RCT = randomised controlled trial. *Analysed as a continuous covariate
Note: The number of studies reflects the studies with available information for this subgroup comparison (with events across different subgroups). We calculated within-study interaction estimates for participant-level variables, and across-study interaction estimates for study-level variables.