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Umbilical cord clamping strategies at preterm birth: a systematic review and network meta-analysis with individual participant data

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Summary

Background

Deferred (also known as delayed) cord clamping at preterm birth improves survival, but the optimal timing remains unclear. We compared umbilical cord clamping strategies, including alternative timings for clamping and cord milking.

Methods

For this systematic review with individual participant data network meta-analysis (IPD-NMA), we searched medical databases and trial registries (until 24 February 2022; updated 6 June 2023) for randomised trials comparing cord clamping strategies for preterm births (<37 weeks). IPD were harmonised and assessed for risk of bias and quality. Interventions were grouped into immediate clamping, short deferral (≥15 to <45 seconds), medium deferral (≥45 to <120 seconds), long deferral (≥120 seconds), and intact cord milking. The primary outcome was death before hospital discharge. We calculated one-stage, intention-to-treat Bayesian random-effects IPD-NMA. This study was registered with PROSPERO (CRD42019136640).

Findings

We included IPD from 47 trials for 6,094 participants. Of all interventions, long deferral reduced death before discharge the most (compared to immediate clamping: odds ratio=0·31; 95% credibility interval 0·11-0·81, moderate certainty) with a 91% probability of being the best option. Credibility intervals for medium and short deferral and cord milking crossed the line of no effect. Risk of bias was low for 33% of trials, 47% had some concerns and 20% were rated high. Heterogeneity was low, with no indication of inconsistency.

Interpretation

This study found that long deferral of clamping likely leads to a large reduction in death before discharge in preterm infants. Long deferral lasts for at least two minutes, or in some studies longer if lung aeration has not occurred. In infants assessed as requiring immediate resuscitation, this finding may only be generalisable if there are provisions for such care with the cord intact. These results are based on thoroughly cleaned and checked IPD and will inform future guidelines and practice.

Funding

Australian National Health and Medical Research Council.

Panel: research in context

Evidence before this study

Worldwide, almost 13 million babies are born preterm annually, and almost one million die. Deferral of umbilical cord clamping can reduce death in preterm infants. Our systematic review and individual participant data pairwise meta-analysis published in the same issue showed with high certainty that deferred cord clamping reduced death before discharge by one third. Yet, the question of how long to wait before clamping the cord remains unanswered. Current recommendations in practice guidelines range from deferral for 30 seconds to at least 60 seconds, and some recommend considering cord milking as an alternative. To resolve this question, we performed a systematic review and individual participant data network meta-analysis to compare and rank different timings of deferred cord clamping, intact cord milking, and immediate clamping. We searched medical databases and clinical trial registries up to 24 February 2022 (updated 6 June 2023) including terms such as “umbilical cord”, “clamp$”, “milk$”, “preterm” and “premature” without language restrictions. All published and unpublished randomised controlled trials examining cord clamping strategies in preterm infants were eligible and investigators were invited to share individual participant data.

Added value of this study

Whilst previous reviews have looked at any deferral of cord clamping, this individual participant data network meta-analysis compares different timings of cord clamping and cord milking in preterm infants (<37 weeks’ gestation), combining high-quality individual participant data from 47 trials with 6,094 participants. Network meta-analysis allows comparison and ranking of different intervention strategies, including different timings of deferral and intact cord milking, in the same analysis. Using individual participant data in network meta-analysis enables more precise, reliable and informative results, by maximising data quality and availability, examining and adjusting for covariates across trials, and standardising analyses. This study shows that longer deferral of cord clamping (≥120 seconds) has a high probability (91%) of being the best strategy for preventing death before discharge in preterm infants, showing a large reduction for this treatment group compared to immediate clamping (odds ratio 0·31; 95% credibility interval 0·11-0·81, moderate certainty).

Implications of all available evidence

This network meta-analysis found that longer deferral of cord clamping likely leads to larger reductions in death before discharge. In infants assessed as requiring immediate interventions (e.g. resuscitation), this finding may only be generalisable if there are provisions to provide such care with the cord intact. Our study shows that there is no longer equipoise for immediate cord clamping, since this treatment had a high probability of being ranked worst for the primary outcome of death before discharge and also for the key secondary outcome of receiving any blood transfusion. Preliminary qualitative research has found deferring cord clamping can be a positive experience for mothers, as it allows an immediate, prolonged connection with their newborns. In combination, these results may lead to a change in clinical practice to defer cord clamping in preterm infants for longer time periods. This will require multidisciplinary teams of midwives, obstetricians and paediatricians working together to defer clamping whilst ensuring the baby is warm, breathing and cared for.

Main text

Background

Infants born preterm (<37 weeks' gestation) have a high risk of mortality and severe morbidity due to immaturity of organs and body systems. [1,2] Deferring umbilical cord clamping is an effective intervention to reduce mortality for preterm infants, with our pairwise individual participant data (IPD) meta-analysis[3] showing reductions in odds of death before discharge by one third, compared to immediate clamping. This effect appears robust across key subgroups[3] and suggests that preterm infants benefit from continued umbilical flow at birth. [4] However, the question of how long to wait before clamping the cord remains unanswered.

For preterm infants, the transition from foetal to neonatal respiration may take longer than at term. [5,6] Deferring cord clamping may provide more time for the newborn to aerate its lungs, thus providing a smoother transition to neonatal respiration than if the cord is clamped too soon. [5,6] However, some infants, especially those born extremely preterm, may require immediate assistance with lung aeration or advanced resuscitation, [7] which may be logistically challenging with the cord intact. [8] In practice, there are many cord clamping strategies available, including different timings of clamping or umbilical cord milking, but little guidance on which to choose.

Global guidelines for preterm cord clamping strategies vary considerably (Appendix p.1-2). Recommendations for when to clamp range from 30 to at least 60 seconds; some recommend cord clamping only when the lungs are aerated and others suggest cord milking. [9-15] Over 100 trials have compared strategies for cord clamping at preterm birth, yet, none of the previous systematic reviews had the capacity to compare different timings of deferral and cord milking. [16] Thus, the question of which cord clamping strategy works best remained unresolved.

Network meta-analysis (NMA) combines direct and indirect evidence to estimate comparative effectiveness of cord clamping strategies. [17] Combining IPD with NMA can improve precision, increase information and reduce bias. [18] The aim of this study was to conduct a systematic review and IPD-NMA to compare and rank different cord clamping strategies for preterm infants.

Methods

Overview

Methods were pre-specified in a published protocol, [19] PROSPERO record CRD42019136640, and a statistical analysis plan that was time-stamped prior to analyses, including minor changes from the protocol based on anticipated data availability (Appendix p.13-18). We followed PRISMA-IPD[20] and PRISMA-NMA[21] statements (Appendix p.134-150). This review was supported by a Patient and Public Involvement representative (GG) with lived and research experience who contributed to this review through monthly meetings and comments on 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), clinical trial registries (ClinicalTrials.gov, WHO ICTRP), reference lists and conference proceedings up to 24 February 2022; updated 6 June 2023. Full details of each search strategy are available in Appendix pp.151-176, and matched our companion IPD pairwise meta-analysis, [3] but inclusion criteria, outcomes and analysis strategy differed. We included all randomised trials comparing umbilical cord clamping strategies at preterm birth. Eligible participants were preterm babies (<37 weeks' gestation). If trials included

both term and preterm babies, only data for preterm babies (<37 weeks' gestation), were included. Interventions were grouped into five nodes: immediate clamping (as soon as possible or <15 seconds), short deferral (≥15 to <45 seconds), medium deferral (≥45 to <120 seconds), long deferral (≥120 seconds or for some trials longer if lung aeration had not occurred by the time cut-off), and any intact cord milking (i.e. milking before the cord was clamped). Some pre-specified nodes such as cut cord milking had to be collapsed/excluded due to limited data availability (Appendix pp.175-176). All intervention categories were pre-specified, randomised comparisons and based on pre-specified planned (not observed) deferral or milking. Trials were included regardless of whether initial neonatal care was provided with the cord intact. Cluster- and quasi-randomised trials were excluded.

Each trial was screened by at least two reviewers; uncertainties were resolved by a third reviewer or by contacting trial authors. There were no language restrictions. Lead investigators of eligible studies were invited to join the *i*ndividual participant data on *Co*rd *M*anagement at *P*reterm birth (iCOMP) Collaboration and share their IPD.

Data collection and management

We followed an extensive, pre-specified data collection and management process that has been described in detail elsewhere (Appendix p.19-25). Data were harmonised, re-coded, cleaned, and cross-checked against published records. All steps were performed in duplicate and queried with trial investigators, where necessary. If IPD could not be retrieved, summary data were extracted from publications.

Outcomes and subgroup analyses

The primary outcome was infant death before hospital discharge. Key secondary outcomes were intraventricular haemorrhage (IVH) (any grade) and blood transfusion (any). We examined subgroup differences testing for effect modification for the pre-specified variables gestational age at birth and mode of birth (vaginal/caesarean), and for infant sex as a post-hoc analysis. We were unable to assess effect modification for 'type of pregnancy (singleton, multiple)' since parameters could not be estimated due to lack of model convergence, 'highest level of care available', since all infants had access to a neonatal intensive care unit, and 'ethnicity' due to sparse and heterogenous data.

Risk of bias, integrity, and certainty of evidence

Risk of bias was assessed for all studies by adapting Cochrane criteria for IPD. [22] We conducted separate risk of bias assessments for death before discharge and the two key secondary outcomes (Appendix pp.177-228). We performed comprehensive, pre-specified data quality and integrity checks, including items such as retraction notices, ethics approval, implausible values, and randomisation (Appendix p.23-25). Certainty of evidence was assessed using the Confidence in Network Meta-Analysis (CINeMA) framework, [23,24] which is based on the GRADE framework but adapted for NMA.

Data analysis

All analyses were pre-specified in the statistical analysis plan (Appendix p.64-75) and performed in R software version 4.2. [25] All analyses were intention-to-treat, and any post-randomisation exclusions were re-included where possible. We employed random-effect network meta-analyses using a one-stage generalised linear modelling approach within a Bayesian Framework. Distributions were estimated using Markov Chain Monte Carlo simulation using *JAGS*[26] and *R2jags*. [27] Detailed model specifications and analysis code are provided in Appendix p.268-277. [28,29] We chose a Bayesian

framework for this analysis, since frequentist frameworks are less suited to incorporate pre-specified complex model features, including accounting for small clusters (multiple births), multi-arm trials and adjusting for key covariates. For uninformative priors (as was the case in our analysis), frequentist and Bayesian network meta-analysis approaches have been shown to produce comparable results in simulation studies. [30] Further explanation of network meta-analysis terminology and principles is available elsewhere. [31-33]

Direct and indirect treatment effects were linked in a single network using the consistency equation. Correlations among multiple pregnancies were accounted for with nested random intercepts. Prognostic factors gestational age, multiple gestation, and mode of birth were adjusted for within each trial. Each binary outcome used a linear model with Bernoulli likelihood and logit link. Uninformative priors in log units (normal distribution, mean = 0, standard deviation = 100) were placed on treatment effects, prognostic factors and effect modifiers. Convergence was monitored with visual inspection of trace plots and confirmed when rhat <1·05, meaning the model was stable in its distribution estimation.

For each model, we report posterior mean relative effect odds ratios (OR) with 95% credible interval (CrI), along with the posterior mean rank of each treatment with 95% CrI, and the rank probability plots (rankograms). Transitivity was examined by comparing the distributions of effect modifiers across treatments. To assess consistency, the conflict of direct and indirect evidence was checked globally using unrelated mean effects and locally using node-splitting. Heterogeneity was estimated with prediction intervals and by inspecting the between-trial heterogeneity parameter, τ^2. We assumed a common heterogeneity parameter (τ^2), which assumes the variance between trials is shared for all treatment contrasts. This enables the model to account for between study variance whilst enhancing the estimation of heterogeneity. Robustness to bias of the best treatment ranking was examined using a contrast-based threshold analysis. [34,35] The funder of this study had no role in study design, data collection, analysis, interpretation, or writing of the report.

Results

Our search identified 2,369 citations and we reviewed 435 full-text articles (Figure 1). Overall, 122 completed studies appeared eligible, but 31 of these were unpublished. We retrieved IPD for 61 studies (13 unpublished). Of the 61 studies, five were excluded due to missing data (e.g. data for >60% of eligible participants provided due to lost records), or integrity issues (e.g. major discrepancies between IPD and published data, lack of association between variables known to be highly correlated, i.e. gestational age and birthweight). Another nine studies were excluded as they did not fit our intervention categories or network (e.g. not connected to network, both interventions within same category, combining two intervention categories). Aggregate data from publications were available for 14 trials. Following our pre-specified decision criteria, we did not combine IPD with aggregate data in our primary analysis due to higher risk of bias, integrity concerns, larger effect sizes for aggregate data trials compared to IPD trials, and inability to perform the same rigorous analyses (Appendix pp.229-249). [36] Instead, we performed a sensitivity analysis combining aggregate data with IPD for the primary outcome. Our updated search (June 2023) identified an additional five published small trials, but these did not contribute to our analyses (1 had integrity issues, 4 had no data for our primary outcome) (Appendix pp.155-174).

Thus, this network meta-analysis included 47 trials with IPD for 6,094 infants. Study characteristics (e.g., year, country of study, sample size) can be found in Appendix pp.250-266. The median trial sample size was 60 (IQR 40 to 127). In total, 2,048 participants were randomised to immediate cord clamping, 2,869 to different timings of deferred clamping and 1,177 to intact cord milking. The

median gestational age at birth was 29·6 weeks (IQR 27·6 to 33·3), 54% (n=3070) of infants were male, 61% (n=3487) were born by caesarean and 17% (n=981) were multiples. The primary outcome was missing for 4/6,094 (<0·1%) infants. Baseline characteristics by intervention group are in Appendix p.261.

Figure 2 shows the network of eligible comparisons for each outcome. For death before discharge, 30 trials (4,712 infants) reported at least one event and were available in the network. Direct comparisons were available for all but one intervention pair (long versus medium deferral). Compared to immediate clamping, long deferral (≥120 sec) reduced death before discharge (OR 0·31; 95%CrI 0·11-0·80, moderate certainty, number needed to treat = 18, 95%CrI 6-90, Figure 3). Credibility intervals for medium and short deferral crossed the line of no effect: medium deferral (OR 0·76; 95%CrI 0·48-1·39, low certainty) and short deferral (OR 0·82; 95%CrI 0·41-1·73, very low certainty). Intact cord milking also crossed the line of no effect (OR 0·75; 95%CrI 0·41-1·43, very low certainty). Figure 4 shows ranking probabilities of different interventions. Long deferral had a 91% probability of being the best treatment to prevent death before discharge, while medium deferral and intact cord milking had a high probability of being second or third best. Immediate clamping had <1% probability of being the best treatment for preventing death before discharge, and a 53% probability of being the worst treatment. There was no indication of substantial heterogeneity (τ=0·20, 95% CrI 0·01-0·67). Long deferral versus immediate clamping would be expected with more than 95% probability to repeat a benefit of long deferral in a future study, since the prediction interval did not cross the line of no effect, when accounting for heterogeneity across studies (Figure 3). There was largely no effect modification for participant characteristics, including gestational age (Appendix pp.284-285), albeit there was some indication that short and long deferral may have had stronger effects on death before discharge compared to immediate clamping for vaginal instead of caesarean births. This finding was not evident for medium deferral.

For IVH (any grade), 27 trials (4,283 infants) reported at least one event and were available for analysis (Figure 2). Trials were available for all head-to-head intervention comparisons, except long deferral, where only one trial, with immediate clamping as comparator, had data available (due to no events or missing data for other comparisons). There was no clear difference for IVH across any of the comparisons (Figure 3), and major uncertainties around ranking of interventions (any intervention may have been the best or the worst) for this outcome (Appendix pp.279-280,283). Certainty of evidence was very low for all comparisons, due to imprecision and within-trial bias.

For any blood transfusion, 29 trials (4,746 infants) reported at least one event and were available for analysis. Again, there were direct comparisons between all intervention groups, except long deferral, for which only one trial with events compared long deferral to immediate clamping. Compared to immediate clamping, short and medium deferral and intact cord milking all reduced any blood transfusion by about 50% (Figure 2). For short deferral the OR was 0·44 (95%CrI 0·17-0·90, moderate certainty), for medium deferral OR was 0·45 (95%CrI 0·23-0·75, moderate certainty) and for intact cord milking OR was 0·56 (95%CrI 0·31-0·90, low certainty) (Figure 2). The prediction intervals were large for all comparators due to substantial heterogeneity (τ=0·57, 95%CrI 0·08-1·09), and crossed the line of no effect, which led to downgrading of certainty of evidence (Figure 3, Appendix pp.280-281, 304). For long deferral, evidence was inconclusive due to insufficient evidence (OR 0·55; 95%CrI 0·12-2·43, very low certainty). Immediate clamping had <1% probability of being the best treatment (Appendix pp. 280, 284).

For the primary outcome of death before discharge, 10/30 trials (33%, 2374 infants) were rated as 'low risk of bias', 14 (47%, 1820 infants) as 'some concerns' and 6 (20%, 518 infants) as 'high risk'. For the secondary outcome IVH, 7/27 trials (26%, 485 infants) were rated as 'low risk of bias', 6

(22%, 953 infants) as 'some concerns' and 14 (52%, 2845 infants) as 'high risk'. For blood transfusion, 4/29 trials (14%, 270 infants) were rated as 'low risk of bias', 8 (28%, 1226 infants) as 'some concerns', and 17 (59%, 3250 infants) as 'high risk'. These ratings have been incorporated in the certainty of evidence assessments (Appendix pp.301-304).

Our sensitivity analyses revealed no substantive differences in results when examining different clustering approaches, heterogeneity priors, outcome definitions and model specifications (Appendix p.268). Results were also consistent when excluding high risk of bias trials, changing cut-offs for timing of deferral, and including aggregate data from publications in an unadjusted two-stage network meta-analysis model for the primary outcome death before discharge (Appendix p.267). Threshold analysis revealed treatment contrasts for death before discharge were robust to plausible bias (Appendix p.287-293). There was no substantial indication of network inconsistency; direct and indirect effect estimates were consistent across comparisons (Appendix p.267).

Discussion

This is the first IPD-NMA comparing different timings of deferred cord clamping, intact cord milking and immediate clamping in preterm infants. We analysed IPD from 47 trials incorporating 6,094 participants across five comparisons of alternative cord clamping strategies. Waiting at least two minutes led to a large reduction in death before discharge (OR 0·31, 95%CrI 0·11-0·80), with a 91% probability that this is the best treatment to prevent death before discharge for preterm infants. This reduction in mortality increased with length of deferral. However, CrIs for medium and short deferral crossed the line of no effect, as did CrIs for intact cord milking. Immediate clamping had a very low (<1%) probability of being ranked the best treatment for preventing death before discharge.

Until recently, it was standard practice to clamp the cord immediately after birth, so the preterm baby could be dried, wrapped, and if necessary, stimulated and resuscitated. [37,38] Our study shows that there is no longer equipoise for immediate clamping, since this treatment had a high probability of being ranked worst for the primary outcome of death before discharge and also for the key secondary outcome of receiving any blood transfusion. Instead, we found the highest reduction of mortality for long deferral of cord clamping of at least two minutes. This is different to current standards that recommend shorter deferral times, and will likely result in changed clinical practice worldwide. It is also consistent with findings in animals that deferring clamping until after lung aeration avoids the reduction in cardiac output caused by immediate clamping. [5,6]

We did not find any evidence of treatment effects for our key secondary outcome IVH (any grade), but certainty of evidence was very low due to low event rates. This contrasts with a previous NMA using aggregate data from published studies[16] that found an improvement in IVH for both umbilical cord milking (combining cut and intact milking) and deferred clamping (any timing), compared to immediate clamping. This difference in results may be explained by several factors. Our analysis used IPD rather than aggregate data accounting for the correlation of outcomes between multiple births; and we excluded several studies with quasi-randomisation or integrity concerns that were included in the previous NMA. We also included additional recent and unpublished studies. For our other key secondary outcome of any blood transfusion, the odds were halved for short and medium deferral, and for intact cord milking, compared to immediate clamping. The evidence was inconclusive for long deferral, with only one trial reporting this outcome.

Our companion pairwise meta-analysis[3] has shown, with high certainty, that deferring cord clamping reduces death before discharge for preterm infants, and this finding appears robust across several

participant- and trial level subgroups. Additionally, our pairwise analysis showed improved haematologic markers and decreased blood transfusion for deferred clamping and cord milking. The present NMA significantly complements these findings by assessing the comparative effects of different deferral times and intact cord milking. Whilst there appears to be a dose-response effect of deferral time for reducing death before discharge, the outcome for reducing blood transfusions appears stable across different deferral times and cord milking, with comparable effect sizes.

This study has many strengths that stem from assembling a large dataset of high-quality IPD to compare different timings of cord clamping and intact cord milking. The collaborative process involved close communication with global study investigators which greatly improved data quality and interpretation. We used innovative data quality and integrity tools, to ensure only high-quality data were included in the analyses. [41,42] Importantly, using IPD allowed us to use advanced modelling techniques, for instance by adjusting for covariates and for correlations among multiple births, which reduced heterogeneity in the network. [43] Levels of missing data were low for our primary outcome of death before discharge (<0·1%).

A limitation of this study was the inability to retrieve IPD for all eligible studies resulting in 16% (303 infants, 13 trials) of the potential mortality data being sourced only from publications. However, our retrieval rates were higher than for most IPD meta-analyses, [44 44] and our results were consistent in a sensitivity analysis including aggregate data (Appendix p.245-249). We also deviated from our original statistical analysis plan by analysing the data in *R2jags* instead of the pre-specified package *multinma*, as *multinma* did not allow us to account for clustering of multiples. Model building principles remained the same. Some pre-specified intervention categories, such as cut cord milking, were excluded from the network due to insufficient data provided by the few studies connecting this intervention to the network. [29] Risk of bias resulted in lower certainty of evidence for some comparisons.

Treatment adherence (i.e. whether the infant received the intervention they were randomised to) was underreported in most studies. When it was reported, it was frequently low for infants randomised to deferred clamping (<75%), mostly due to these infants receiving shorter deferrals, immediate clamping, or milking instead. It is likely that the most unwell infants often did not receive their allocated intervention due to the assumed need for immediate care. [45] Intention-to-treat analysis means this does not lead to confounding. Yet, generalisability is limited since it is not clear if these infants would have benefited most from a cord clamping intervention, or were correctly assessed as requiring care urgently and clamped early. Additionally, many studies excluded at-risk populations (exclusion criteria summarised in Appendix p.305-314). Future studies should collect in-depth adherence measures and focus on recruiting the sickest babies. Although several trials were conducted in middle-income countries, all of them were conducted in hospitals with neonatal intensive care units. Therefore, findings may not be generalisable to low-resource settings.

Table 1 provides details of the five trials with at least one event included in the 'long deferral' intervention category for the primary outcome death before discharge. These five trials all had a time-based criterion for deferral of clamping (three studies ≥ 120 seconds; two studies ≥180 seconds), albeit two trials combined the time-based criterion with a physiological criterion (e.g. waiting at least 120 seconds or longer until lung aeration has been established/until cord has ceased pulsing). Trials in this intervention category included infants across all gestational ages, with 28% (n=160) of infants being <28 weeks' gestational age (Appendix p.317). There was no indication of differential effects across gestational ages. Importantly, none of the 'long deferral' trials left infants assessed as requiring immediate resuscitation on the cord without providing respiratory support. Two trials did not provide the allocated intervention to infants requiring resuscitation. [46,47] The other

three trials provided initial resuscitation and stabilisation with the cord intact using mobile resuscitation equipment.[48-] It is important to note that individual trials were relatively small and none of them were statistically significant independently; the comparison between long deferral and immediate clamping only reached statistical significance when trials were combined. Large ongoing trials assessing long deferral will add further insights and more precise effect estimates.[50-53]

The utility of resuscitation with the cord intact is an important ongoing debate.[54] Our findings suggest that this practice may be beneficial, but further evidence is required. Several large trials are underway that will contribute data for an update of these analyses by late 2025.[50-53,55] For infants assessed as requiring resuscitation, future studies may also consider exploring potential differential or synergistic effects of resuscitation with the cord intact with various initial inspired oxygen concentration and oxygen titration strategies.[55,56] During deferred cord clamping, it is critical that infants receive the necessary interventions to effectively aerate and ventilate their lungs.

When considering implementation of our findings into practice, several factors are important. Deferring cord clamping may seem counter-intuitive to some clinicians, since their intuition may be to rush the baby aside and intervene immediately. Providing support, particularly respiratory support, to preterm infants during this critical phase is a delicate process with a small therapeutic range, so appropriate training and equipment are important. Additionally, available evidence suggests that routine procedures such as drying and stimulating infants should not be delayed and can occur while deferring clamping.[57,58] A multidisciplinary approach involving midwives, obstetricians, neonatologists, paediatricians and parents is required to undertake successful deferral of cord clamping whilst ensuring the baby is warm, breathing and cared for. This may also improve treatment adherence with deferred cord clamping interventions. Preterm birth is stressful for parents, so their experiences should guide practice. In one cord clamping trial, parents randomised to deferred clamping reported more positive experiences than those randomised to immediate clamping, with parents reporting feeling positive about staying close and attached to their baby for longer after birth.[59] Whilst these results are encouraging for implementing longer deferrals and may reduce some perceived barriers to implementation, more research assessing parent's perspectives is desirable and may be incorporated into future trials. Generally, cord clamping approaches and neonatal care decisions should be discussed and planned with parents before birth, if possible. A recently funded stepped-wedge implementation trial will provide additional insights on barriers and enablers of deferred cord clamping.[60]

To conclude, we found that long deferral of cord clamping by at least two minutes likely leads to a large relative reduction in death before discharge for preterm infants. Results are not generalisable to infants assessed as requiring immediate resuscitation, unless potentially when resources and equipment are available to provide initial respiratory support with the cord intact. Ongoing trials will provide further information. Our results will likely lead to a change in clinical practice to defer cord clamping in preterm infants for longer time periods. This will require multidisciplinary teams working together to undertake successful deferral of cord clamping whilst ensuring the baby is receiving high-quality care.

Author contributions

Funding acquisition was undertaken by ALS, LMA, LD, AAM. ALS and SL 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, JSD, JSM, JBJ, JK, JQL, KDF, KW, KEM, MMG, MdV, MMG, MIM, MPM, MKM, NAE, NN, NKD, OA, PP, RK, SA, SS, SSB, SB, SH, SP, SC, TT, 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

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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

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.

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Figures

Figure 1. PRISMA flow chart.

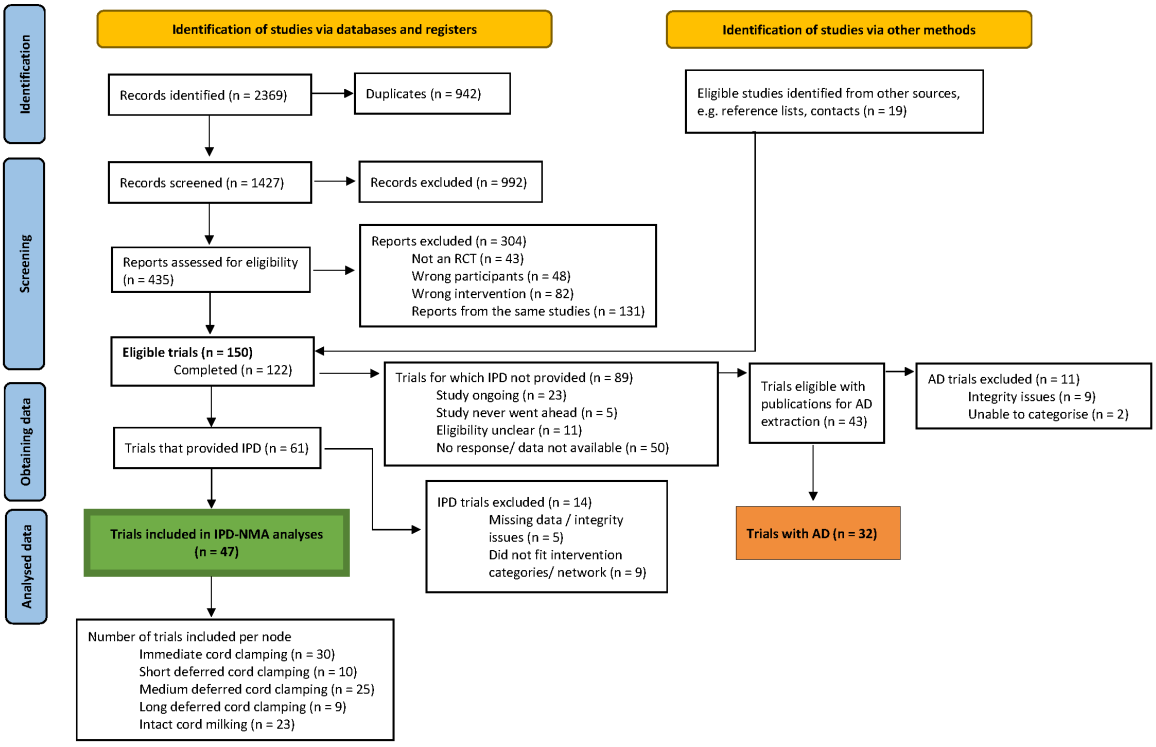


Figure 1. PRISMA flow chart.

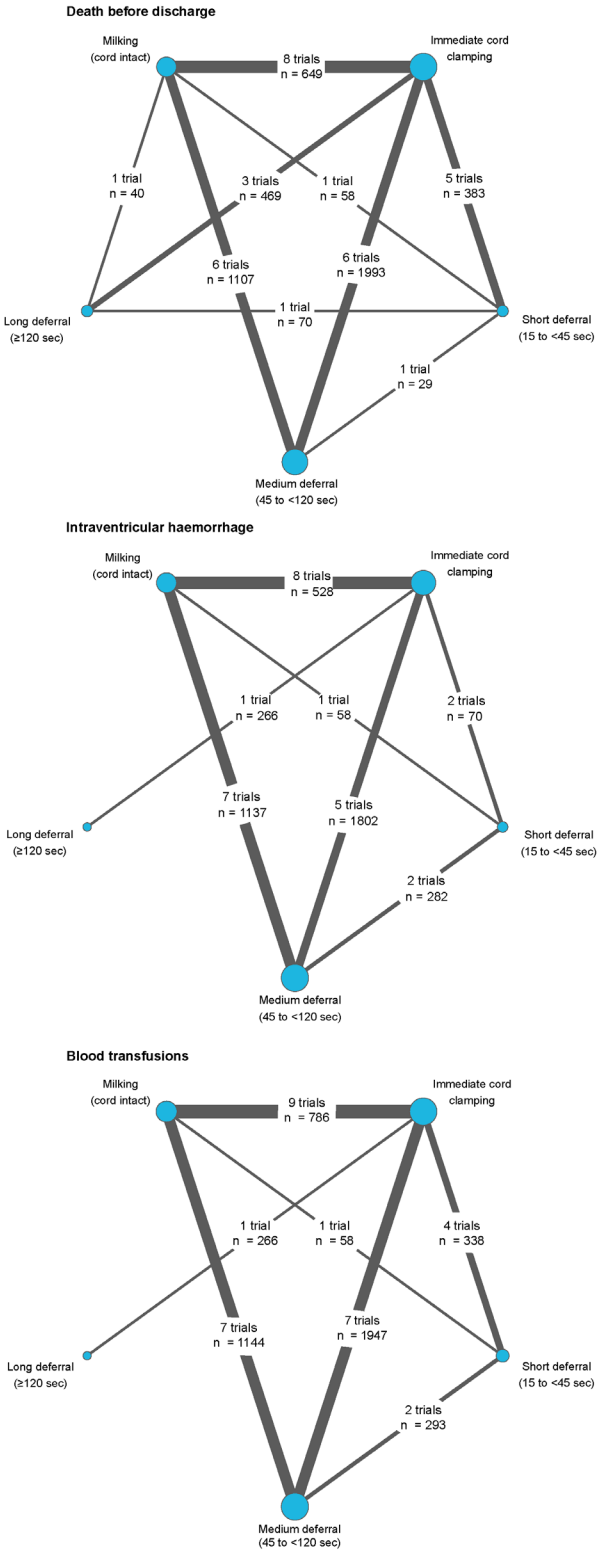
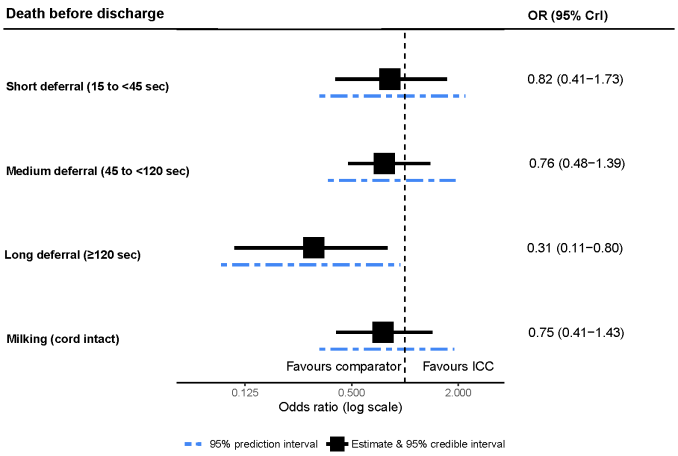
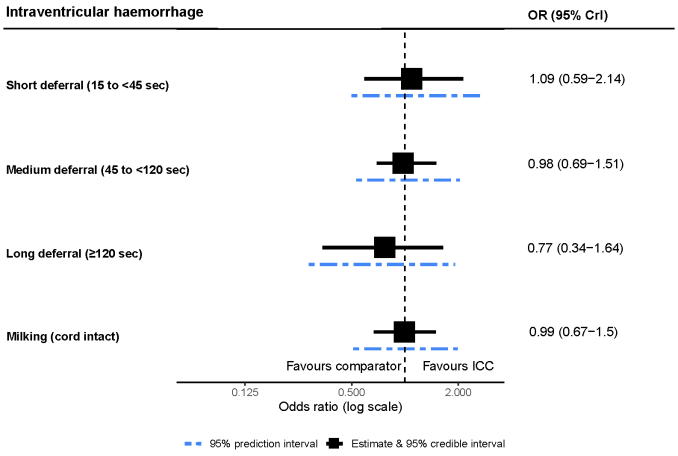


Figure 2. Network diagrams as panel.

Note: Each circular node represents an intervention. The diameter of the circular node captures the total number of infants in an intervention. The width of the line linking the nodes captures the number of trials making a direct comparison between two interventions.





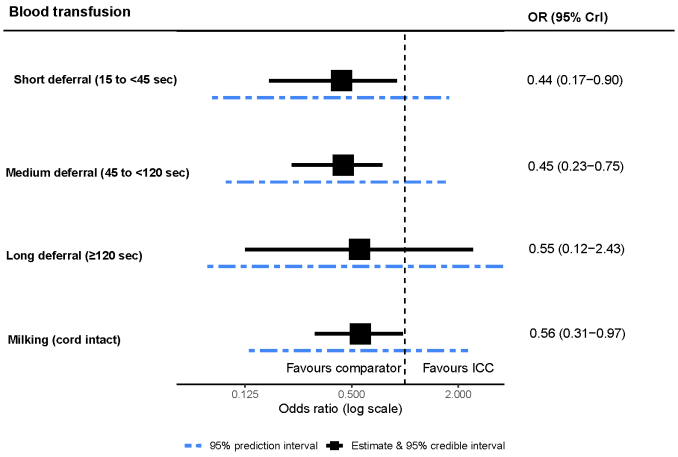


Figure 3. Forest plots for network meta-analysis of all trials for the outcomes death before discharge, intraventricular haemorrhage and blood transfusion*Note: In these forest plots, all 'comparator interventions' are compared against the 'reference' intervention immediate cord clamping (ICC). Effect estimates on the x-axis are odds ratios on the log scale. The black squares capture the treatment effect estimate. The 95% credible intervals around this estimate are represented by the black line. The dashed blue line captures the 95% prediction interval. Number of infants and events contributing to each node can be found in the Appendix (p.318-320)*

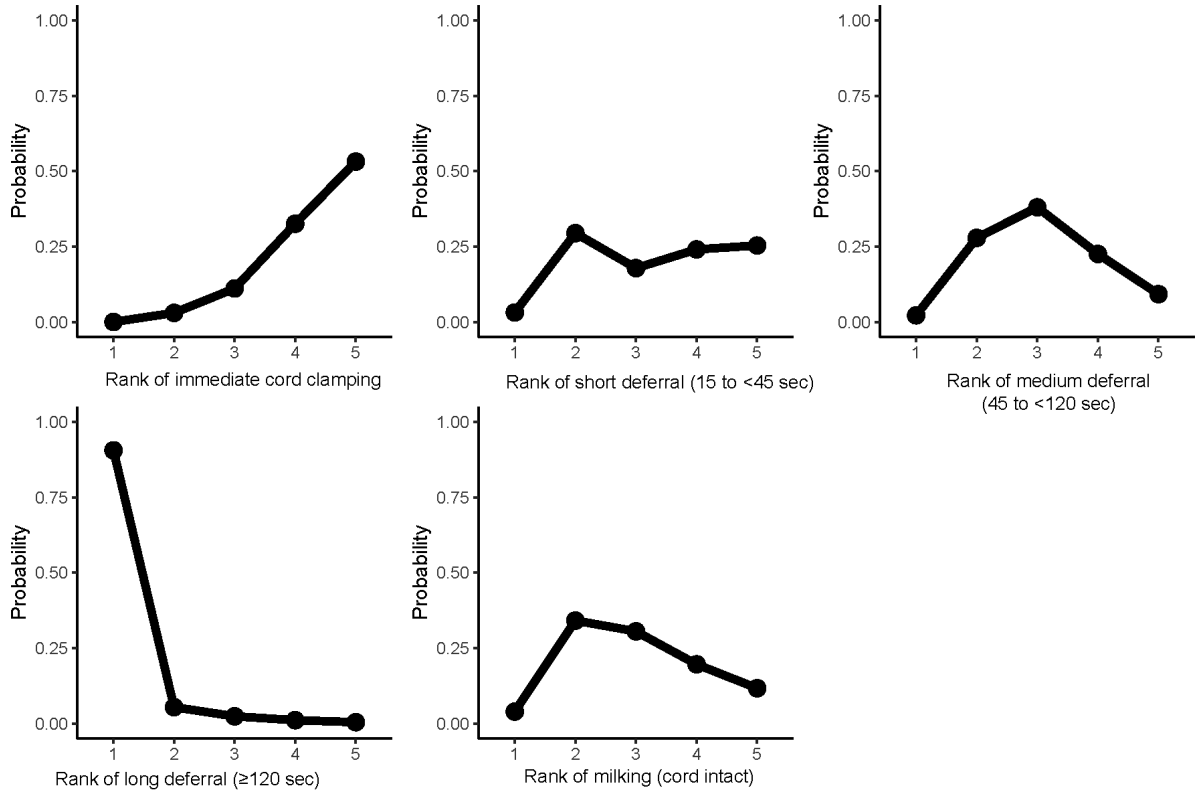


Figure 4. Rankogram for death before discharge.

Note: Each rankogram depicts the probability of an intervention being ranked the 1st, 2nd, 3rd, 4th and 5th best intervention for reducing death before discharge. Rank 1 is the best intervention and rank 5 is the worst intervention. For example, the top left panel evaluates immediate clamping and indicates there is a low probability that immediate clamping is ranked the best (1st) intervention and a higher probability that it is ranked the worst (5th) intervention.