NLS 5051 Consensus on Science (2)

B- FOR THE IPD NETWORK META-ANALYSIS:

Population: Preterm infants born at <37^{+0} weeks' gestation and their mothers.

Interventions:

1. Immediate (early) cord clamping (ICC) at ≤15 seconds, without cord milking or initiation of respiratory support or as defined by the trialist.
2. Short deferral of cord clamping for >15 s to <45 s without milking, with or without respiratory support.
3. Medium deferral of cord clamping for ≥45 to <120 s without milking, with or without respiratory support.
4. Long deferral of cord clamping for ≥120 s without milking, with or without respiratory support.
5. Intact cord milking immediately after birth (with the umbilical cord attached to placenta).

Comparisons: Between-intervention comparisons.

Outcomes:

9 (Critical)- Infant's mortality before hospital discharge.
7 (Critical)- Intraventricular hemorrhage (any).
6 (Important)- Blood transfusion (any).

Study Designs:

Randomized trials comparing umbilical cord management strategies at preterm birth were included. Interventions were grouped into the following nodes: immediate clamping, short deferral, medium deferral, long deferral, and intact cord milking. Trials with missing data, integrity issues or not fitting intervention categories were excluded. Cluster- or quasi-randomized trials were also excluded.

Timeframe:

All years and all languages were included. Medical databases including MEDLINE, Embase and CENTRAL, and clinical trial registries, including ClinicalTrials.gov were originally searched up to Feb 2022, and WHO ICTRP up to March 2022. The search was updated on June 6th, 2023.

***A priori* subgroups examined:**

Subgroup analyses were conducted for the primary outcome (death before discharge) and the two key secondary outcomes (IVH any grade and receipt of any blood transfusion). Gestational week at birth and highest level of available care were considered as effect modifiers to improve consistency of the NMA model.

There were subgroup analyses testing for effect modification for the pre-specified variables: gestational age at birth, mode of birth (vaginal/cesarean), type of pregnancy (singleton, multiple) and highest level of care available.

Details of the analyses can be found in the study protocol {Seidler 2020 e034595} and in more detail in the time-stamped statistical analysis plan.

PROSPERO registration:

The iCOMP review was registered with PROSPERO CRD42019136640 in 2019.

GRADE evaluation:

Certainty of evidence was assessed using the Confidence in Network Meta-Analysis (CINeMA) framework, which is based on the GRADE framework but is adapted for network meta-analysis. {Nikolakopoulou 2020 e1003082}

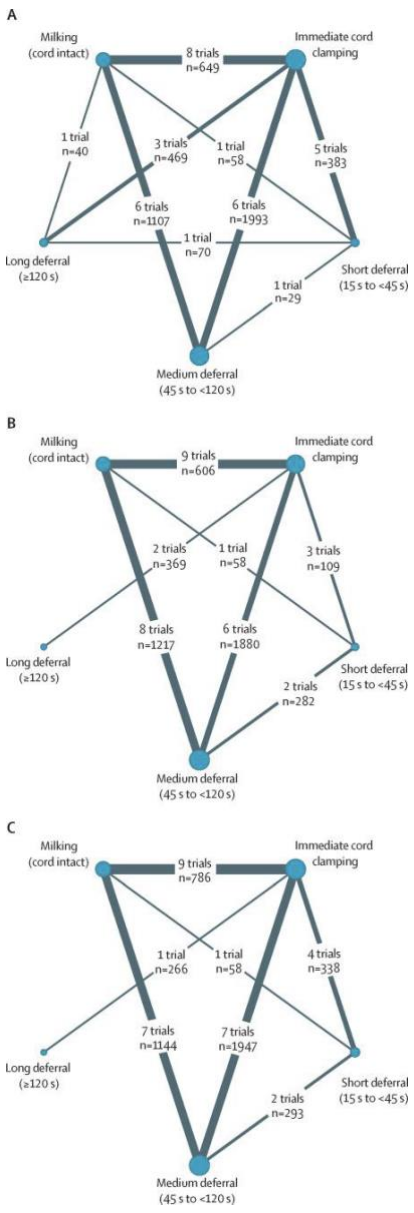
CONSENSUS ON SCIENCE:

The IPD network meta-analysis identified **47 eligible studies** (6,094 infants). Median sample size was 60 infants (IQR 40-127). The median gestational age at birth was 29.6 weeks (IQR 27.6 to 33.3). Of all infants, 54% were male, 61% were born by cesarean delivery, and 17% were multiples. The primary outcome was missing for 4 (<0.1%) infants. {Seidler 2023 2223}

The following five comparisons are included in the NMA (Figure 1).

1. Immediate (early) cord clamping (ICC).
2. Short deferral of cord clamping.
3. Medium deferral of cord clamping.
4. Long deferral of cord clamping for.
5. Intact cord milking immediately after birth.

Figure 1: Network diagrams *Reprinted from The Lancet, Seidler AL, Libesman S, Hunter KE, Barba A, Aberoumand M et al. pages 2223-2234 Copyright 2023 with permission from Elsevier.*

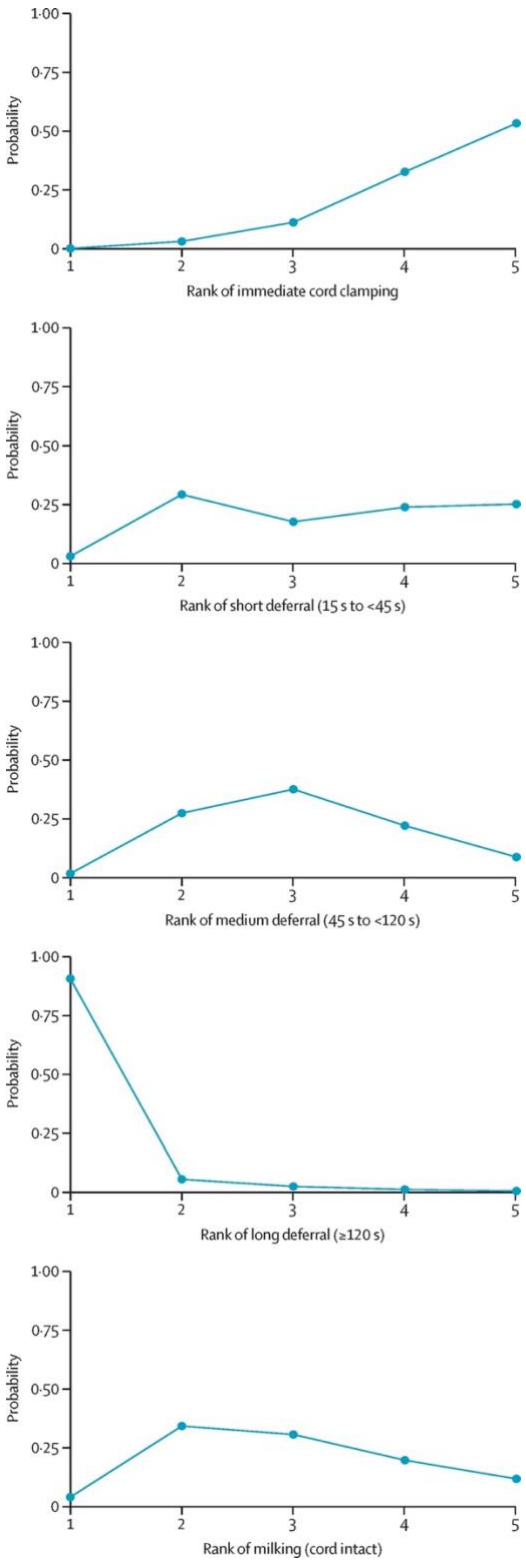


Each circular node represents an intervention. The diameter of the circular node captures the total number of infants in an intervention. The width of the line linking the nodes captures the number of trials making a direct comparison between two interventions. (A) Death before discharge (primary outcome). (B) Any intraventricular hemorrhage. (C) Receipt of blood transfusion. {Seidler 2023 2223}

*For the critical outcome of **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 s) reduced death** before discharge (OR 0.31; 95%CrI 0.11-0.80, number needed to treat to benefit (NNTB) = 18, 95% CrI 4-143). **moderate certainty evidence**
- Compared to immediate clamping, 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 evidence**) and short deferral (OR 0.82; 95%CrI 0.41-1.73, **very low certainty evidence**).
- Compared to immediate clamping, **Intact cord milking** crossed the line of no effect (OR 0·75; 95%CrI 0·41-1·43, **very low certainty evidence**).

Figure 2: Ranking probabilities of different interventions for death before discharge: *Reprinted from The Lancet, Seidler AL, Libesman S, Hunter KE, Barba A, Aberoumand M et al. pages 2223-2234 Copyright 2023 with permission from Elsevier.*



Each rankogram depicts the probability of an intervention being ranked as the first, second, third, fourth, or fifth 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 that the probability that immediate clamping is ranked the best (first) intervention is low, and that the probability that it is ranked the worst (fifth) intervention is high.

- Long deferral had a 91% probability of being the highest ranked treatment to prevent *death before discharge*.
- Immediate clamping had <1% probability of being the best treatment to prevent *death before discharge*, and a 53% probability of being the worst treatment.
- Medium length deferral and intact cord milking had a high probability of being second or third best (Figure 2).

*For the important outcome of **any intraventricular hemorrhage,*** 27 trials including 4,283 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) crossed the line of no effect (OR 0·77; 95%CrI 0·34-1.64, **very low certainty evidence**).
- Compared to immediate clamping, medium and short deferral crossed the line of no effect: medium deferral (OR 0.98; 95%CrI 0.69-1.51, **very low certainty evidence**).
- Compared to immediate clamping, intact cord milking crossed the line of no effect (OR 0.99; 95%CrI 0.67-1.50, **very low certainty evidence**).

*For the important outcome of **receiving red cell transfusions***, 29 trials including 4,746 infants were available. Direct comparisons were available for all but one intervention pair (long versus medium deferral).

- Compared to immediate clamping, all **short and medium deferral and intact-cord milking reduced the receipt of red cell transfusions** by about 50%.

For **short** deferral the OR was 0·44 (95%CrI 0·17-0·90, **moderate certainty evidence**), for medium deferral OR was 0·45 (95%CrI 0·23-0·75, **moderate certainty evidence**) and for intact-cord milking OR was 0·56 (95%CrI 0·31-0·97, **low certainty evidence**).

- For **long deferral**, evidence was inconclusive due to insufficient evidence (OR 0.55; 95%CrI 0.12-2.43, **very low certainty evidence**).