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

**Supplementary Materials**

**Appendix 1: Methods**

**Protocol and reporting**

This review was conducted following the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adheres to the PRISMA reporting guidelines.1,2 The protocol was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019155475).

**Eligibility criteria**

We considered all randomized controlled trials and cluster randomized controlled trials of different policies and procedures regarding umbilical cord management in preterm infants (< 34 weeks' gestational age or with low birth weight (< 2500 g). Studies were included if they reported a mean gestational age of < 34 weeks or if more than 80% of the infants were < 34 weeks’ gestation. Unpublished studies (e.g. conference abstracts, trial protocols) were excluded.

Studies comparing the following cord management interventions were included in this review:

* **Early cord clamping,** defined as application of a clamp to the umbilical cord less than 30 seconds of the birth of the infant, without cord milking.
* **Later (delayed) cord clamping,** defined as application of a clamp to the umbilical cord greater than or equal to 30 seconds after birth or based on physiologic parameters (such as when cord pulsation has ceased or breathing has been initiated), without cord milking.
* **Intact cord milking (also referred to as “stripping”),** defined as repeated compression of the cord from the placental side toward the infant at any time point within the first few minutes after birth with the connection to the placenta intact.
* **Cut cord milking (also referred to as “stripping”),** defined as drainage of the cord by compression from the cut end toward the infant after clamping and cutting a long segment of umbilical cord

The following comparisons were eligible for inclusion in the review:

1. Later (delayed) cord clamping compared to early cord clamping
2. Intact-cord milking compared to early cord clamping
3. Cut-cord milking compared to early cord clamping
4. Later (delayed) cord clamping compared to intact-cord milking
5. Later (delayed) cord clamping compared to cut-cord milking
6. Intact-cord milking compared to cut-cord milking
7. Delayed cord clamping < 60 seconds compared to delayed cord clamping ≥ 60 seconds
8. Delayed cord clamping based on time since birth compared to physiological approach to cord clamping

The review outcomes were selected in consultation with representatives from the World Health Organization (WHO) and International Liaison Committee on Resuscitation (ILCOR), and comprised of outcomes and measures that were seen as clinically relevant and therefore likely to change clinical practice. Primary infant outcomes were survival to discharge from hospital, survival without moderate or severe neurodevelopmental impairment in early childhood, and severe intraventricular hemorrhage (IVH). The primary maternal outcome was postpartum hemorrhage (PPH). Secondary infant outcomes include outcomes related to condition at birth, and respiratory, cardiovascular, central nervous system, gastrointestinal and hematological outcomes. Maternal outcomes include mortality and relevant morbidities or morbidity-related measures. All collected outcomes and their definitions have been summarized in Supplemental Table 1.

**Information sources and search strategy**

Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 7) in the Cochrane Library; MEDLINE via Ovid (1946 to 26 July 2019); PubMed (for the previous year); Embase via Ovid (1974 to 26 July 2019); and CINAHL via EBSCO host (1981 to 26 July 2019) were searched using Cochrane Neonatal’s standard search strategy for neonates and RCTs, in combination with cord management terms. The full search strategies are available in Appendix 2 (supplemental materials). We included all years and all languages as long as there was an English abstract. We searched clinical trial registries for ongoing or recently completed trials (26 July 2019). We searched The World Health Organization’s International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/) and the U.S. National Library of Medicine’s ClinicalTrials.gov (clinicaltrials.gov) via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry and the Australia New Zealand Clinical Trials Registry for any unique trials not found through the Cochrane CENTRAL search. We also reviewed the reference lists of all identified articles for relevant articles not located in the primary search. We searched for follow-up reports of included studies by searching for their trial registration number in MEDLINE. We also searched Cochrane Pregnancy and Childbirth’s Trials Register by contacting their Information Specialist (10 November 2017).

**Study selection and data extraction**

Two authors reviewed the results of the search and separately selected studies for inclusion in two steps using Covidence software.3 We included all randomized and cluster-randomized controlled trials fulfilling our eligibility criteria. Any disagreements were resolved by discussion and consultation with a third author, and the first reason for exclusion was specified. The selection process is illustrated in a PRISMA flow diagram (Figure 1).

Two review authors independently extracted data using a pre-specified data extraction form tailored to this review including administrative details, details on study design and setting, participants, interventions, outcomes and pre-specified subgroups. Any disagreements in data extraction were resolved by discussion, consulting a third author when necessary to reach consensus. We have not contacted authors for unpublished information and data, but where contact with authors is reported in the Rabe 2019 Cochrane review, we have included these data.4

**Risk of bias and certainty of evidence assessment**

Two review authors independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane ‘Risk of bias’ tool.5 We rated studies that were not prospectively registered as high risk of selective outcome reporting if they started recruiting after ICMJE requirements for prospective registration were introduced in 2006.6 Two review authors independently assessed the certainty of evidence for all primary, and key secondary outcomes presented in Table 1 using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.7 We presented separate summary of findings tables for neonatal outcomes, outcomes in later infancy/early childhood and maternal outcomes, using GradePro.8

**Data analysis**

Two review authors used Cochrane statistical software for data entry and analysis.9 We replaced any standard error of the mean (SEM) by the corresponding SD. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis.

For dichotomous outcomes, we estimated risk ratios (RR) and risk differences (RD) and corresponding 95% CI with the Mantel-Haenzel method. For continuous outcomes, we calculated the mean difference or the standardized mean difference and 95% CI with the inverse variance method. We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials’ populations and methods were judged sufficiently similar. Heterogeneity among trials was assessed by inspecting the forest plots and quantifying the impact of heterogeneity using the I² statistic. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected (I2 > 40%), we used random-effects meta-analysis. We visually inspected funnel plots to assess for publication bias if there were sufficient numbers of studies (>10).

Pre-specified subgroup analyses were conducted for the following groups: mode of delivery (cesarean, vaginal), gestational age (< 30 weeks', ≥ 30 to < 34 weeks', mixed or not reported), respiratory support with intact cord (yes/no), different timing of delaying clamping (< 1 minute; 1-2 minutes; > 2 minutes, or based on physiological parameters), timing of administration of uterotonic agents (before delivery, after deliver, mixed or not reported), placement of newborn relative to placenta (at or below, above, unclear/not reported), timing of randomization (before delivery, after delivery), delay prior to cord milking (yes/no) for studies examining cord milking. We also conducted pre-specified subgroup analyses based on the following participant characteristics: Twins (monochorionic or dichorionic) or other multiples, newborns with congenital anomalies or other conditions noted at or prior to birth (including: congenital diaphragmatic hernia; cardiac anomalies, anemia; Rh disease), infant status at birth, sex. We were planning on also including a subgroup analysis on infants small-for-gestational age, but none of the included studies reported data for this subgroup.

**Appendix 2: Search Methods**

These are the final search strategies. Additional terms were tested but did not yield unique relevant results.

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomized trials.1 The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

**OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present:**

1. exp Umbilical Cord/

2. (cord or cords or umbilicus or umbilical or navel-string).mp.

3. 1 or 2

4. exp Constriction/

5. exp Ligation/

6. (clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict\*).mp.

7. ((cord or cords) adj3 management).mp.

8. (DCC or ICC or ECC or LCC).ti,ab.

9. exp Placental Circulation/

10. ((placental or placenta or placentofetal or placentofoetal) adj2 (transfusion\* or circulation)).mp.

11. 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp infant, newborn/

13. (newborn\* or new born or new borns or newly born or baby\* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat\*).ti,ab.

14. 12 or 13

15. randomized controlled trial.pt.

16. controlled clinical trial.pt.

17. randomized.ab.

18. placebo.ab.

19. drug therapy.fs.

20. randomly.ab.

21. trial.ab.

22. groups.ab.

23. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. exp animals/ not humans.sh.

25. 23 not 24

26. 3 and 11 and 14 and 25

**MEDLINE via PubMed:**

((((("Umbilical Cord"[Mesh] OR cord[TW] OR cords[TW] OR umbilicus[TW] OR umbilical[TW] OR navel-string[TW])) AND ("Constriction"[Mesh] OR "Ligation"[Mesh] OR clamp[TW] OR clamping[TW] OR clamped[TW] OR milking[TW] OR milked[TW] OR stripping[TW] OR stripped[TW] OR ligation[TW] OR ligature[TW] OR constrict\*[TW] OR ((cord[TW] OR cords[TW]) AND management[TW]) OR DCC[TIAB] OR ICC[TIAB] OR ECC[TIAB] OR LCC[TIAB] OR "Placental Circulation"[Mesh] OR ((placental[TW] OR placenta[TW] OR placentofetal[TW] OR placentofoetal[TW]) AND (transfusion\*[TW] OR circulation[TW])))) AND (infant, newborn[MeSH] OR newborn\*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby\*[TIAB] OR babies[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR “low birth weight”[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infant[TIAB] OR infants[TIAB] OR infantile[TIAB] OR infancy[TIAB] OR neonat\*[TIAB])) AND (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])) NOT (animals[mh] NOT humans[mh]))) Filters: Publication date from 2018/06/01

**CINAHL via EBSCOhost:**

cord or cords or umbilicus or umbilical or navel-string

AND

clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict\* OR ((cord or cords) AND management) OR ((placental or placenta or placentofetal or placentofoetal) AND (transfusion\* or circulation))

AND

infant or infants or infantile or infancy or newborn\* or "new born" or "new borns" or "newly born" or neonat\* or baby\* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW

AND

randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial

**Embase via Ovid:**

1. exp umbilical cord/

2. (cord or cords or umbilicus or umbilical or navel-string).mp.

3. 1 or 2

4. exp ligation/

5. (clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict\*).mp.

6. exp umbilical cord clamp/

7. ((cord or cords) adj3 management).mp.

8. (DCC or ICC or ECC or LCC).ti,ab.

9. exp placenta circulation/

10. ((placental or placenta or placentofetal or placentofoetal) adj2 (transfusion\* or circulation)).mp.

11. 4 or 5 or 6 or 7 or 8 or 9 or 10

12. exp prematurity/

13. exp infant/

14. (newborn\* or new born or new borns or newly born or baby\* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat\*).ti,ab.

15. 12 or 13 or 14

16. (human not animal).mp.

17. (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp.

18. 3 and 11 and 15 and 16 and 17

**Cochrane CENTRAL via CRS Web:**

1. MESH DESCRIPTOR Umbilical Cord EXPLODE ALL AND CENTRAL:TARGET

2. cord or cords or umbilicus or umbilical or navel-string AND CENTRAL:TARGET

3. #2 OR #1

4. MESH DESCRIPTOR Constriction EXPLODE ALL AND CENTRAL:TARGET

5. MESH DESCRIPTOR Ligation EXPLODE ALL AND CENTRAL:TARGET

6. clamp or clamping or clamped or milking or milked or stripping or stripped or ligation or ligature or constrict\* AND CENTRAL:TARGET

7. ((cord or cords) ADJ3 management) AND CENTRAL:TARGET

8. (DCC or ICC or ECC or LCC):TI AND CENTRAL:TARGET

9. (DCC or ICC or ECC or LCC):AB AND CENTRAL:TARGET

10. MESH DESCRIPTOR Placental Circulation EXPLODE ALL AND CENTRAL:TARGET

11. ((placental or placenta or placentofetal or placentofoetal) ADJ2 (transfusion\* or circulation)) AND CENTRAL:TARGET

12. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

13. MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET

14. infant or infants or infantile or infancy or newborn\* or "new born" or "new borns" or "newly born" or neonat\* or baby\* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET

15. #14 OR #13 AND CENTRAL:TARGET

16. #15 AND #12 AND #3

**References: Appendices 1 and 2**

* 1. Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017).* Cochrane; 2017.
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  5. Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017). Cochrane; 2017.
  6. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004;351:1250–1251.
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  9. Cochrane Collaboration. Review manager (RevMan) [computer program]. Version 5.3; 2014.

**Appendix 3: All included studies organized by comparison**

The index study for each comparison is denoted with an asterisk (\*). All published papers linked to the index study are listed.

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

1. Aladangady 2006

Aladangady N, McHugh S, Aitchison TC, Wardrop CAJ, Holland BM. Infant's blood volume in a controlled trial of placental transfusion at preterm delivery. *Pediatrics* 2006;117:93-8.

1. Armanian 2017

\*Armanian AM, Ghasemi Tehrani H, Ansari M, Ghasemi S. Is "delayed umbilical cord clamping" beneficial for premature newborns? *International Journal of Pediatrics* 2017;5:4909-18.

Armanian M. Is "delayed umbilical cord clamping" beneficial for premature newborns? en.search.irct.ir/view/22000 (first received 14 February 2015).

1. Backes 2016

Backes C, Copeland K, Iams JP, Giannone PJ, Bauer JA. Impact of delayed umbilical cord clamping at the limits of viability. In: *International Conference of Transitional Care*; 2013 19th April; Birmingham, UK. 2013.

\* Backes CH, Huang H, Iams JD, Bauer JA, Giannone PJ. Timing of umbilical cord clamping among infants born at 22 through 27 weeks' gestation. *Journal of Perinatology* 2016;36(1):35-40.

Backes CH, Huang H, Luce WA, Schanbacher BL, Backes KA, Ehrenberg H, et al. Postnatal progenitor cells pools and delayed umbilical cord clamping at the limits of viability. In: *Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting*; 2011 April 30-May 3; Denver, Colorado, USA. 2011:441

Huang H, Eastman N, Schanbacher B, Backes C, Giannone P, Bauer JA. [2887.675] Delayed cord clamping improves gross motor skills in extremely premature infants at age 6-9 months corrected age. In: *Pediatric Academic Societies Annual Meeting*; 2016 April 30 - May 3; Baltimore, USA. 2016.

Huang H, Eastman N, Schanbacher B, Backes C, Giannone P, Bauer JA. [3821.208] Impact of delayed cord clamping on circulating progenitor cells in extremely premature infants. In: *Pediatric Academic Societies Annual Meeting*; 2016 April 30 - May 3; Baltimore, USA. 2016.

1. Baenziger 2007

Baenziger O, Stolkin F, Keel, M, von Siebenthal K, Fauchere JC, Kundu SD, et al. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. *Pediatrics* 2007;119:455-9.

1. CORD Pilot 2018

Armstrong-Buisseret L, Powers K, Dorling J, Bradshaw L, Johnson S, Mitchell E. Randomised trial of cord clamping and initial stabilisation at very preterm birth: neurodevelopmental outcomes at age two years (corrected for gestation at birth). *NIHR Monograph* 2019;Monograph still to be published as well as paper.

Ayers S, Sawyer A, Chhoa C, Duley L. Clinicians’ and women’s experiences of two consent pathways in a trial of timing of clamping at very preterm birth: A qualitative study. BJOG: an international journal of obstetrics and gynaecology 2016;123(Suppl 2):151.

Bradshaw LE, Pushpa-Rajah A, Dorling J, Mitchell EJ, Duley L; for the Cord Pilot Trial Collaborative Group. Cord pilot trial: update to randomised trial protocol. Trials 2015;16:407.

Dorling J, Armstrong-Buisseret L, Powers K, Bradshaw L, Johnson S, Mitchell E, et al. Randomised trial of delayed cord clamping and initial stabilisation at very preterm birth. Neurodevelopmental outcome at age 2 years CGA. In: Abstract presented at 7th Congress of the European Academy of Paediatric Societies. Paris, 2018.

Duley L, Abbott J, Dorling J, Field D, Gyte G, Oddie S, et al. Timing of cord clamping and care at the bedside for very preterm birth: a randomised trial. *BJOG*: an international journal of obstetrics and gynaecology 2013;120(Suppl s1):159.

Duley L, Dorling J, Pushpa-Rajah A, Oddie S, Yoxall B, Schoonakker B, et al. Umbilical cord clamping after at least 2 minutes (and neonatal resuscitation with cord intact) versus clamping within 20 seconds: The Cord Pilot Trial, a controlled randomised trial of very preterm births. BJOG: an international journal of obstetrics and gynaecology 2016;123(Suppl 2):60.

\* Duley L, Dorling J, Pushpa-Rajah A, Oddie SJ, Yoxall CW, Schoonakker B, et al. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2018;103(1):F6-F14.

Duley L, Pushpa-Rajah A. Immediate versus deferred cord clamping for very preterm birth: a pilot randomised trial. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2014;99(Suppl 1):A76-A77, Abstract no: PC.117.

Pushpa-Rajah A, Bradshaw L, Dorling J, Gyte G, Mitchell EJ, Thornton J, et al. Cord pilot trial - immediate versus deferred cord clamping for very preterm birth (before 32 weeks gestation): study protocol for a randomized controlled trial. Trials 2014;15(1):258.

1. Das 2018

\* Das B, Sundaram V, Kumar P, Mordi WT, Dhaliwal LK, Das R. Effect of placental transfusion on iron stores in moderately preterm neonates of 30-33 weeks gestation. *Indian Journal of Pediatrics* 2018;85(3):172-8.

Das B, Sundaram V, Kumar P. [3842.16] Effect of placental transfusion on serum ferritin levels in moderately preterm neonates. In: *Pediatric Academic Societies Annual Meeting*; 2015 April 25-28; San Diego, California. 2015. [CRSREF: 2801055]

Das B. Placental transfusion in delivery room in preterm neonates 30 to 33 6/7 weeks: an open label randomized controlled trial. http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=7688&EncHid=&userName (first received 18 February 2014).\

1. Dipak 2017

Kumar Dipak N, Nanavati RN, Kabra NK, Srinivasan A, Ananthan A. Effect of delayed cord clamping on hematocrit, and thermal and hemodynamic stability in preterm neonates: A randomized controlled trial. *Indian Pediatrics* 2017;54(2):112-5.

1. Dong 2016

Dong XY, Sun XF, Li MM, Yu ZB, Han SP. [Influence of delayed cord clamping on preterm infants with a gestational age of <32 weeks]. Zhongguo Dang Dai Er Ke Za Zhi = *Chinese Journal of Contemporary Pediatrics* 2016;18(7):635-8.

1. Finn 2019

Finn D, Ryan DH, Pavel A, O'Toole JM, Livingstone V, Boylan GB, Kenny LC, Dempsey EM.. 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. *The Journal of Pediatrics* 2019 May;208:121-126.

1. Gokmen 2011

Gokmen Z, Ozkiraz S, Tarcan A, Kozanoglu I, Ozcimen EE, Ozbek N. Effects of delayed umbilical cord clamping on peripheral blood hematopoietic stem cells in premature neonates. *Journal of Perinatal Medicine* 2011;39:323-9.

1. Hofmeyr 1988

\* Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clamping. *South African Medical Journal* 1988;73:104-6.

Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular hemorrhage and umbilical cord clamping. In: Proceedings of the *10th European Congress of Perinatal Medicine*; 1986; Leipzig, Germany. 1986:309.

1. Hofmeyr 1993

\* Hofmeyr GJ, Gobetz L, Bex PJM, Van Der Griendt M, Nikodem CV, Skapinker R, et al. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping: a randomized trial. *Online Journal of Current Clinical Trials* 1993 Doc No 110: [2002 words; 26 paragraphs].

Hofmeyr GJ, Gobetz L, Bex PJM, Van Der Griendt M, Nikodem VC, Skapinker R, et al. Periventricular/intraventricular haemorrhage following early and delayed umbilical cord clamping. Letter to: *Cochrane Pregnancy and Childbirth Group*, Oxford 1991.

1. Kazemi 2017

Kazemi MV, Akbarianrad Z, Zahedpasha Y, Haghshenas Mojaveri M, Mehraein R. Effects of delayed cord clamping on intraventricular hemorrhage in preterm infants. *Iranian Journal of Pediatrics* 2017;27(5):e6570.

1. Kinmond 1993

\* Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CAJ. Umbilical cord clamping and preterm infants: a randomised trial. *BMJ* 1993;306:172-5.

Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CAJ. Umbilical cord clamping and preterm infants: a randomized trial. *International Journal of Gynaecology and Obstetrics* 1993;42(3):328.

Kinmond S, Hudson IRB, Aitchison T, Holland BM, Turner TL, Jones JG, et al. Placento-fetal transfusion in preterm infants. In: *Proceedings of the Neonatal Society*; 1990 March; London, UK. 1990.

1. Kugelman 2007

Kugelman A, Borenstein-Levin L, Kessel A, Riskin A, Toubi E, Bader D. Immunologic and infectious consequences of immediate versus delayed umbilical cord clamping in premature infants: A prospective, randomized, controlled study. *Journal of Perinatal Medicine* 2009;37(3):281-7.

Kugelman A, Borenstein-Levin L, Riskin A, Chistyakov I, Ohel G, Gonen R, et al. Early versus delayed umbilical cord clamping in premature infants: a prospective, randomized, controlled study. In: Conference Proceedings, *Pediatric Academic Societies Annual Meeting*, Toronto, Canada. 2007 May 5-8.

\* Kugelman A, Borenstein-Levin L, Riskin A, Christyakov I, Ohel G, Gonen R, et al. Immediate versus delayed umbilical cord clamping in premature neonates born < 35 weeks: a prospective, randomized, controlled study. *American Journal of Perinatology* 2007;24:307-15.

1. McDonnell 1997

McDonnell M, Henderson Smart DJ. Delayed umbilical cord clamping in preterm infants: a feasibility study. *Journal of Paediatrics and Child Health* 1997;33(4):308-10.

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Mercer JS, Vohr BR, Erickson-Owens DA, Padbury JF, Oh W. Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping. Journal of Perinatology 2010;30(1):11-6.

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Oh W, Carlo WA, Fanaroff AA, McDonald S, Donovan EF, Poole K, et al. Delayed cord clamping in extremely low birth weight infants - a pilot randomised controlled trial. *Pediatric Research* 2002;51(4 Suppl):365-6.

\* Oh W, Fanaroff AA, Carlo WA, Donovan EF, McDonald SA, Poole WK, et al. Effects of delayed cord clamping in very-low-birth-weight infants. *Journal of Perinatology* 2011;31:S68-S71.

1. Rabe 2000

Rabe H, Hentschel R, Brune T, Hulskamp G, Jorch G. A randomised study of delayed cord clamping: the starting point in treatment of anaemia of prematurity. *Prenatal and Neonatal Medicine* 1996;1 Suppl 1:174.

Rabe H, Wacker A, Hulskamp G, Hornig-Franz I, Jorch G. Late cord clamping benefits extrauterine adaptation [abstract]. *Pediatric Research* 1998;44(3):454.

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1. Rana 2018

Agarwal K. Delayed versus early umbilical cord clamping in preterm infants of less than 34 weeks of gestation. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=5900 (first received 4 April 2013).

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\* 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):655–661.

1. Ruangkit 2018

Ruangkit C, Bumrungphuet S, Panburana P, Khositseth A, and Nuntnarumit P. A Randomized Controlled Trial of Immediate Versus Delayed Umbilical Cord Clamping in Multiple-Birth Infants Born Preterm. *Neonatology* 2019;115(2):156.

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Song SY, Kim Y, Kang BH, Yoo HJ, Lee M. Safety of umbilical cord milking in very preterm neonates: a randomized controlled study. *Obstetrics & Gynecology Science* 2017;60(6):527-34.

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

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

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Finn D, Ryan DH, Pavel A, O'Toole JM, Livingstone V, Boylan GB, Kenny LC, Dempsey EM.. 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. *The Journal of Pediatrics* 2019 May;208:121-126.

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**Supplementary Table 1: Study characteristics**

Supplementary Table 1a. Study characteristics - Comparison 1: Delayed (later) cord clamping versus early cord clamping

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **ILCOR Preterm cord management**  Comparison 1: Delayed (later) cord clamping versus early cord clamping | | | | | | |
| Study | Study Characteristics | Inclusion Criteria | Exclusion Criteria | Intervention DCC vs ECC | | Notes |
| Intervention | Control |
| *Example* | *i.e.: RCT*  *Single or multicenter*  *Country(s)* | *Gestational Age or*  *Birth weight*  *Mode of delivery (vaginal/C-section) etc* | *Congenital anomalies, Multiple gestation etc* | *Later (delayed) cord clamping*  *X seconds*  *(# infants)* | *Early cord clamping*  *immediate*  *(# infants)* |  |
| Aladangady 2006 | Same protocol for a multicenter RCT\*  (Data from this publication from Scotland, UK) | Mother-infant pairs at 24 weeks to 32 6/7 weeks' gestation  Singletons  Both vaginal birth and CS | Known major malformation, hemolytic disease, intrauterine transfusion. | Later (delayed) cord clamping  30-90 seconds  (23 infants) | Early cord clamping:  immediately  (23 infants) | \*Shares protocol with Baenziger 2007. Report from Scotland |
| Armanian 2017 | Parallel RCT  Single center  Iran | Mixed gestational age ( ≤ 34 weeks) (and admitted to the tertiary referral NICU)  Both vaginal birth and CS | Infants born with a gestational age ≤ 34 weeks and NOT admitted to the tertiary referral NICU; twin pregnancies, attending not compliant with protocol, birth asphyxia, major congenital abnormalities | Later (delayed) cord clamping:  30-45 seconds  (32 infants but 2 lost to follow-up; 30 infants providing data) | Early cord clamping:  5-10 sec  (31 infants but 1 lost to follow-up; 30 infants providing data) |  |
| Backes 2016 | Parallel RCT  Single center  Ohio, USA | Mothers 22.5-27.6 weeks gestation  Singletons  Both vaginal birth and CS | Women whose pregnancies were complicated by placental abruption, placenta previa, multiple gestations, chromosomal abnormalities (including trisomy 21), known major congenital malformations, attending obstetrician refusal to participate or intent to withhold care | Later (delayed) cord clamping:  30-45 seconds  (18 infants) | Early cord clamping: 5 -10 seconds  (22 infants) |  |
| Baenziger 2007 | Parallel RCT  Multicenter\*  Zurich, Switzerland | Mother-infant pairs at 24 weeks to 32 weeks' gestation  Singletons  Both vaginal birth and CS | Known major malformation, hemolytic disease, intrauterine transfusion, multiple births; children with perinatal asphyxia | Later (delayed) cord clamping:  60-90 seconds  (15 infants) | Early cord clamping: immediately after birth (< 20 seconds)  (24 infants) | Shares protocol with Aladangady 2006 |
| CORD Pilot 2018 | Parallel RCT  Multicenter  Eight UK tertiary maternity units with a neonatal intensive care unit | Women expected to have a live birth before 32 weeks GA.  Both vaginal birth and CS | Monochorionic twins; triplets or higher-order multiple pregnancy and known major congenital malformation | Later (delayed) cord clamping:  after at least 2 minutes  (137 infants  (132 women))  (Cord clamping was before 2 minutes for 55 infants) | Early cord clamping: within 20 seconds  (139 infants (129 women)) | (n = 261 women randomized, 254 women included in analysis at discharge as birth >36 weeks) |
| Das 2018 | Parallel RCT  Single center  Northern India | Mothers 30 0/7 to 33 6/7 weeks’ gestation  Both vaginal birth and CS Singletons | Multiple pregnancies, suspected or proven major congenital malformation in the foetus, and antenatally diagnosed hydrops foetalis | Later (delayed) cord clamping:  60 seconds  (233 infants; (60 received cut cord milking)) | Early cord clamping: within 10 seconds  (infants = 228 (5 received DCC)) |  |
| Dipak 2017 | RCT  Single center  Mumbai, India | Mothers at 27 to 31 6/7 weeks' gestation.  Singleton pregnancies  Both vaginal birth and CS | Births ≥32 weeks' gestation; multiple births, Rh-ve status, placenta previa or abruption-placenta, and those having foetus with major congenital anomalies, hydrops, foetal growth restriction with abnormal Doppler waveforms, or evidence of foetal distress | Later (delayed) cord clamping:  1\* DCC: 60 seconds  (26 infants);    2\*. DCC + IM ergometrine to mother  (25 infants)  51 infants in total | Early cord clamping: within 10 seconds  (27 infants) | DCC  \*We pooled the data from these two groups for this review  Number randomized to this group: 51 infants |
| Dong 2016 | RCT  (type of center not described)  China | Vaginal birth  Singleton | Neonates that require immediate resuscitation; placenta previa; placenta abruption | Later (delayed) cord clamping: 45 seconds (46 infants) | Early cord clamping: within 10 seconds  (44 infants) |  |
| Finn 2019 | 3-arm prospective RCT  Single center  Cork, Ireland | Preterm infants born at <32 weeks of gestation  Mode of delivery not reported | Major congenital anomaly, bleeding from placenta previa, placental abruption or accreta, twin-to-twin transfusion syndrome, hydrops, and cord prolapse | Later (delayed) cord clamping: 60 seconds  (14 infants) | Early cord clamping: within 20 seconds  (12 infants) | This is a 3-arm trial (milking, DCC and control) |
| Gokmen 2011 | Parallel RCT  Single center  Turkey | All women admitted between 24 and 31.6 weeks’ gestation with preterm labour.  For multiple-birth pregnancies, there was a single assignment for all fetuses.  Both vaginal birth and CS | Vaginal bleeding due to placental abruption or placental tear; suspected major foetal anomalies; severe IUGR (IUGR, -3rd percentile); suspected twin-twin transfusion syndrome or discordant twin growth; maternal drug abuse. | Later (delayed) cord clamping: 30-45 seconds  (21 infants) | Early cord clamping: immediate cord clamping  (21 infants) |  |
| Hofmeyr 1988 | Parallel RCT  South Africa | Mother-infant pairs, judged to be < 35 weeks' gestation and in advanced labour.  Singleton pregnancies  Mode of delivery not reported | Multiple pregnancies | Later (delayed) cord clamping: 60 seconds  (24 infants) | Early cord clamping: immediate cord clamping  (14 infants) |  |
| Hofmeyr 1993 | Parallel RCT  Single center  South Africa | Mother-infant pairs, with the woman expected to give birth to an infant weighing < 2000 g  Both vaginal birth and CS | Not reported | Later (delayed) cord clamping: 60-120 seconds  (40 infants) | Early cord clamping: immediate cord clamping  (46 infants) |  |
| Kazemi 2017 | Parallel RCT  Single center  Babol, Northern Iran | Preterm infants with gestational age of less than 32 weeks, weighing less than 1500 grams at birth  C-section | Maternal use of medications affecting the coagulation system, birth asphyxia, need for resuscitation at the time of delayed clamping, birth trauma, need for advanced resuscitation, infants from multiple gestation or breech presentation as the cause of C-section, and mother’s systemic diseases such as preeclampsia, hypertension, and uncontrolled diabetes | Later (delayed) cord clamping: 30-45 seconds  (35 infants) | Early cord clamping: immediate cord clamping (< 10 seconds)  (35 infants) |  |
| Kinmond 1993 | Parallel RCT  Single center  Glasgow, Scotland, UK | Mother-infant pairs, 27 to 33 weeks' gestation  Multiples included (unpublished data)  Vaginal birth | Hemolytic disease, major congenital malformations | Later (delayed) cord clamping: 30 seconds  (17 infants) | Early cord clamping: cord clamped at clinicians’ discretion (<20 seconds)  (19 infants) |  |
| Kugelman 2007 | Parallel RCT  Single center  Haiha, Israel | Mother-infant pairs, at >24 weeks and <35 weeks' gestation  Multiple pregnancies included.  Both vaginal birth and CS | Women with vaginal bleeding due to placenta previa or abruption or placental tear; foetus expected of having major anomaly; severe IUGR (< 3%); maternal gestational diabetes treated with insulin; suspected twin-to-twin transfusion or discordant twins (cautious definition of estimated weight difference by foetal ultrasound of <20% even without monozygosity) and maternal drug abuse | Later (delayed) cord clamping: 30-45 seconds  (30 infants) | Early cord clamping: cord clamped immediately (<10 seconds)  (35 infants) |  |
| McDonnell 1997 | Parallel RCT  Single center  Sydney, Australia | Infants at 26 to 33 weeks' gestation  Vaginal or CS  Single or multiple pregnancies | Severe foetal distress, IUGR with abnormal umbilical Doppler waveforms, foetal hydrops, foetal malformations, Rhesus incompatibility | Later (delayed) cord clamping: 30 seconds  (23 infants\*) | Early cord clamping: cord clamped immediately  (23 infants\*) | \* not reported in publication, rather through direct communication with study author |
| Mercer 2003 | Parallel RCT  Single center  Rhode Island, USA | Gestational age between 24 and 31 6/7 weeks  Singleton pregnancy  Both vaginal birth and CS | Obstetrician or parents refused consent, Multiple gestations, intend to withhold or withdraw care, or if the women had diagnoses of placenta previa or abruption, bleeding, or a foetus with a major anomaly. | Later (delayed) cord clamping: 30-45 seconds  (16 infants) | Early cord clamping: cord clamped 5-10 seconds  (16 infants) |  |
| Mercer 2006 | Parallel RCT  Single center  Rhode Island, USA | Mother-infant pairs between 24 and 31.6 <33 weeks' gestation  Vaginal or cesarean births  Singletons | Obstetrician's refusal to participate, major congenital anomalies, multiple gestations, intend to withhold care, severe maternal illnesses, placenta abruption or previa, or rapid delivery after admission | Later (delayed) cord clamping: 30-45 seconds  (36 infants) | Early cord clamping: cord clamped 5-10 seconds  (36 infants) |  |
| Oh 2011 | Parallel RCT  USA.  Multicenter  3 centers: 1) Birmingham, Alabama, Birmingham, 2) Cleveland, Ohio. 3) Providence, Rhode Island. | Infants 24+0 to 27+6 weeks' gestation  Singletons  Both vaginal birth and CS | None specified\* | Later (delayed) cord clamping: 30-45 seconds  (16 infants) | Early cord clamping: cord clamped <10 seconds  (17 infants) | \*Registration record (NCT01222364) states that the exclusion criteria are: prenatally diagnosed major congenital abnormalities, intent to withhold or withdraw care, and significant bleeding due to placenta previa or abruption |
| Rabe 2000 | Parallel RCT  Single center  Germany | Infants < 33 weeks' gestation  Both vaginal birth and CS | Multiple pregnancies, Rhesus incompatibility, foetal hydrops, congenital malformation, Apgar < 3 at 0 minutes | Later (delayed) cord clamping: 45 seconds  (20 infants) | Early cord clamping: cord clamped at 20 seconds  (20 infants) |  |
| Rana 2018 | Parallel RCT  Single center  India | Pregnant women whose pregnancies had reached less than 34 weeks’ gestation and were in the late first stage of labour  Both vaginal birth and CS | Any known congenital malformations, serious maternal illnesses (severe preeclampsia or eclampsia, uncompensated heart disease, any abnormal bleeding before cord clamping), twins or triplets, and babies requiring immediate resuscitation at birth | Later (delayed) cord clamping: 120 seconds  (50 infants) | Early cord clamping: cord clamped ≤30 seconds  (50 infants) |  |
| Ruangkit 2018 | Parallel RCT  Single center  Bangkok, Thailand | 28-36 weeks GA  Multiples  Both vaginal birth and CS\* |  | Later (delayed) cord clamping: 30-60 seconds  (51 infants) | Early cord clamping: cord clamped <3-5 seconds  (50 infants) | \*95% cesarean, only 4 out of 101 vaginal |
| Tarnow-Mordi 2017 | Parallel RCT;  Multi center  25 centers in 7 countries:  Australia; New Zealand; Canada; France; Northern Ireland; Pakistan and USA. Led by University of Sydney, Australia | Women expected to give birth before 30 weeks' gestation  Multiples were included with randomization by infant  Both vaginal birth and CS | Exclusion criteria included foetal hemolytic disease, hydrops foetalis, twin–twin transfusion, genetic syndromes, and potentially lethal malformations | Later (delayed) cord clamping: >60 seconds  (818 infants)\* | Early cord clamping: cord clamped <10 seconds  (816 infants)\*\* | \*DCC 818 infants with data on 748 (and on 784 for death) \*\*DCC 816 infants with data on 749 (and on 782 for death) |

Supplementary Table 1b. Study characteristics - Comparison 2: Intact-cord milking versus early cord clamping

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **ILCOR Preterm cord management**  Comparison 2: Intact-cord milking versus early cord clamping | | | | | | |
| Study | Study Characteristics | Inclusion Criteria | Exclusion Criteria | Intervention | | Notes |
| Intervention | Control |
| *Example* | *i.e.: RCT*  *Single or multicenter*  *Country(s)* | *Gestational Age or*  *Birth weight*  *Mode of delivery (vaginal/C-section) etc* | *Congenital anomalies, Multiple gestation etc* | *Intact-cord milking*  *(# infants)* | *Early cord clamping*  *(# infants)* |  |
| Alan 2014 | Single Center RCT  Ankara, Turkey | Very low birth weight infants. Gestational age ≤ 32 weeks and estimated birth weight ≤1500g  Both vaginal birth and CS | Suspected twin-to-twin transfusion syndrome or discordant twins; major congenital anomalies or chromosomal anomalies; vaginal bleeding due to placenta previa or abruption or placental tear; hemolytic disease of the foetus and newborn like Rhesus sensitization; IUGR; maternal gestational diabetes treated with insulin; hydrops foetalis; and refused parental consent | Intact-cord milking  X3  24 infants \* | Early cord clamping  24 infants \*\* | \*ICM 24 babies randomized but 2 were excluded because inappropriate milking – leaving N = 22. A further 3 babies were excluded in days 2-7 for death or major bleeding.  \*\*24 babies randomized but 2 excluded because: 1) tracheal bleeding during resuscitation in a preterm infant with 23 weeks of gestation, 2) 24 weeks' gestation infant who did not respond to resuscitation) leaving N = 22. A further 3 babies were excluded on days 2-7 for death or major bleeding. |
| El-Naggar 2018 | RCT  Single center | Preterm infants born between 24 and 30+6 weeks’ gestation | monochorionic twins, major congenital anomalies, placental abruption, fetal anemia and  intention to withhold resuscitation | Intact-cord milking  X3  37 infants | Early cord clamping  36 infants |  |
| Elimian 2014 | Parallel RCT  Single center  Oklahoma, USA | Single pregnancies between 24 weeks 0 days and 34 weeks 0 days of gestation  Both vaginal birth and CS | Pregnant women carrying foetuses with known major foetal structural or chromosomal abnormalities, multiple gestations, diabetes, IUGR, or non-reassuring foetal heart tracings | Intact-cord milking  X3  99 infants | Early cord clamping  101 infants |  |
| Finn 2019 | 3-arm prospective RCT  Single center  Cork, Ireland | Preterm infants born at <32 weeks of gestation  Mode of delivery not reported | Major congenital anomaly, bleeding from placenta previa, placental abruption or accreta, twin-to-twin transfusion syndrome, hydrops, and cord prolapse | Intact-cord milking  X3  19 infants | Early cord clamping  12 infants | This is a 3 arm trial (milking, DCC and control) |
| Hosono 2008 | Parallel RCT  Single center  Tokyo, Japan | < 29 weeks gestation or 24-28 weeks gestation  Both vaginal birth and CS | Multiple births, major congenital anomalies or chromosomal anomalies, hydrops foetalis | Intact-cord milking  X2-3  20 infants | Early cord clamping  20 infants |  |
| Katheria 2014 | RCT  Single center  San Diego, USA | Gestational age of 23 0/7 to 31 6/7  Both vaginal birth and CS  Singletons and multiples | Pregnant women who on admission were considered to have imminent delivery were not approached  Monochorionic multiples, incarcerated mothers, placenta previa, concern for abruptions, Rh sensitization, hydrops, congenital anomalies, or refusal to perform the intervention by the obstetrician | Intact-cord milking  X3  30 infants | Early cord clamping  30 infants |  |
| Kilicdag 2016 | Parallel RCT  Single center  Turkey | Preterm births ≤32 weeks gestation  Mode of delivery: CS  Singletons and multiples | Congenital anomalies, placenta abruption, IUGR, twin–twin transfusion syndrome, discordant twin growth, vaginal births and Rh hemolytic disease | Intact-cord milking  29 infants | Early cord clamping  25 infants |  |
| Leal 2018 | 2-arm prospective RCT  Single Center  Spain | Pregnant women between 24+0 and 36+6 weeks of gestation  Both vaginal birth and CS  Singletons and multiples | umbilical cord abnormalities (true and false knots, short cord, nuchal cords), major congenital anomalies or chromosomal anomalies, hydrops foetalis, twin-to-twin transfusion syndrome, clinical suspicion or diagnosis of placental abruption, and infants whose parents refused to consent | Intact-cord milking  X4  69 infants | Early cord clamping  69 infants |  |
| Li 2018 | RCT  Single center  Chengdu, China | Neonates who were delivered vaginally between 28 0/7 and 36 6/7 weeks’ and complicated by PPROM in utero  Singletons | Congenital anomalies, Rh hemolytic disease, intrauterine growth restriction, multiple births (twins,  triplets), placental abruption, or other pregnancy complications | Intact-cord milking x4  48 infants | Early cord clamping  54 infants |  |
| March 2013 | Parallel RCT  Single center  East Virginia, USA | Women giving birth between 24-28 weeks’ gestation | Antenatally diagnosed major foetal congenital anomaly; known Rh sensitization; hydrops foetalis; known recent maternal exposure to parvovirus; elevated peak systolic velocity of the foetal middle cerebral artery or clinical suspicion of placental abruption at delivery due to excessive maternal bleeding or uterine hypertonicity | Intact-cord milking x3  36 infants | Early cord clamping  39 infants |  |
| Mercer 2016 | Parallel RCT  Single center  USA | Women with a singleton pregnancy estimated at 24-31.6 weeks' gestation  Vaginal or cesarean | Multiple gestation, prenatally diagnosed major congenital anomalies, severe or multiple maternal illnesses, and mothers who were at risk for loss to follow-up. | Intact-cord milking x1 + DCC – 30-45 secs  or intact-cord milking x2-3  103 infants | Early cord clamping  105 infants |  |
| Silahli 2019 | Parallel RCT  Single center  Konya, Turkey | Pregnant women who delivered ≤ 32 weeks of gestation | Twin-to-twin transfusion syndrome, foetal and maternal bleeding, dysmorphic features and conotruncal heart disease. | Intact-cord milking x3  38 infants | Early cord clamping  37 infants |  |
| Song 2017 | Parallel RCT  Single center  Daejeon, South Korea | Pregnant women expected to deliver between 24 0/7 and 32 6/7 completed weeks of gestation  Both vaginal birth and CS  Singletons | Multiple gestations, rhesus sensitization, foetal hydrops, or major foetal anomalies.  Women without antenatal written consent | Intact-cord milking x4  34 infants | Early cord clamping  32 infants |  |

Supplementary Table 1c. Study characteristics - Comparison 3: Cut-cord milking versus early cord clamping

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **ILCOR Preterm cord management**  Comparison 3: Cut-cord milking versus early cord clamping | | | | | | |
| Study | Study Characteristics | Inclusion Criteria | Exclusion Criteria | Intervention | | Notes |
| Intervention | Control |
| Ram Mohan 2018 | Parallel RCT  Single center  Bangalore, India | Preterm newborn < 37 weeks' GA requiring resuscitation | Multiple gestation, Antenatally detected major congenital anomalies, Delivery to Rh negative mothers, cord prolapse, Hydrops, Umbilical cord abnormalities like true knot | Cut-cord milking  (30 infants) | Early cord clamping  (30 infants) |  |

Supplementary Table 1d. Study characteristics - Comparison 4: Delayed (later) cord clamping versus intact-cord milking

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **ILCOR Preterm cord management**  Comparison 4: Delayed (later) cord clamping versus intact-cord milking | | | | | | |
| Study | Study Characteristics | Inclusion Criteria | Exclusion Criteria | Intervention | | Notes |
| Intervention 1 | Intervention 2 |
| *Example* | *i.e.: RCT*  *Single or multicenter*  *Country(s)* | *Gestational Age or*  *Birth weight*  *Mode of delivery (vaginal/C-section) etc* | *Congenital anomalies, Multiple gestation etc* | *Later (delayed) cord clamping*  *X seconds*  *(# infants)* | *Intact-cord milking*  *X seconds*  *(# infants)* |  |
| Finn 2019 | 3-arm prospective RCT  Single center  Cork, Ireland | Preterm infants born at <32 weeks of gestation  Mode of delivery not reported | Major congenital anomaly, bleeding from placenta previa, placental abruption or accreta, twin-to-twin transfusion syndrome, hydrops, and cord prolapse | Later (delayed) cord clamping  60 seconds  (14 infants*)* | Intact-cord milking  20 cm over 2 seconds, 3 times  (19 infants) | This is a 3-arm trial (milking, DCC and control) |
| Katheria 2015 | Parallel RCT  Multi center  California, USA. 2 tertiary centers | Gestational age 23+0 to 31+6  Infants < 32 weeks gestation  Both vaginal birth and CS | Monochorionic multiples; incarcerated mothers; placenta previa; concern for abruptions; Rh sensitization; hydrops, congenital anomalies; or the obstetrician declining to perform the intervention (i.e. unaware of the study protocol) | Later (delayed) cord clamping  45 seconds  (99 infants) | Intact-cord milking  Cord pinched as close to the placenta as possible and milked toward the infant over a 2-second duration. Cord then released, allowed to refill with blood for a brief 1- to 2-secs pause between each milking motion  (98 infants) |  |
| Katheria 2019 | Parallel RCT  Multi center  9 sites (6 in the United States and 1 site each in Ireland, Germany, and Canada | Preterm infants (born at 23-31 weeks’ gestation)  Both vaginal birth and CS | Major congenital anomalies, severe placental abruption, transplacental incision, umbilical cord prolapse, hydrops, bleeding accreta, monochorionic multiple births, foetal or maternal risk for severe compromise  at delivery, and family unlikely to return for 24-month neurodevelopmental testing.  Additional exclusion criteria listed in protocol (supplement 1), e.g. Maternal HIV, Hepatitis B and C | Later (delayed) cord clamping  at least 60 seconds  (238 infants) | Intact-cord milking  20 cm of the umbilical cord was milked 4 times  (236 infants) |  |
| Kreuger 2015 | Parallel prospective RCT  Single center  Alabama, USA | Estimated gestational ages between 22 0/7 and 31 6/7 weeks  Singletons  Both vaginal birth and CS | Foetus had known anomalies or suspected placental abruption | Later (delayed) cord clamping  30 seconds  32 infants | Intact-cord milking  In addition to 30 seconds delay; stripped 4 times, 4- 5 seconds between stripping  35 infants |  |
| Pratesi Simone 2018 | Feasibility RCT  Single center  Italy | Pregnant women admitted to the obstetrical unit and at risk of delivering between 23 0/7 and 29 6/7 weeks’ gestation | major congenital malformations and disorders, hydrops fetalis, placental or cord problems, or twin pregnancy. | Later (delayed) cord clamping  180 seconds  20 infants | Intact-cord milking  20 infants | Respiratory support provided during DCC |
| Rabe 2011 | Parallel RCT  Single center  Brighton, UK | Preterm neonates between 24+0/7 and 32+6/7 completed weeks of gestation  Both vaginal birth and CS | Multiple pregnancies (twins and more), foetal hydrops, Rhesus sensitization, or known major congenital abnormalities | Later (delayed) cord clamping  30 seconds  31 infants | Intact-cord milking  Cord clamped after 4th milking (30 seconds)  27 infants |  |
| Shirk 2019 | RCT  Single center  Cincinnati, Ohio, USA  Mode of delivery not reported | Singleton preterm infants who were born 23 weeks 0 days to 34 weeks 6 days gestation  Singletons | Known congenital anomalies; precipitous delivery preventing completion of the protocol; placental abruption around the time of or as indication for delivery; uterine rupture; non-reassuring foetal heart tracing (FHT) immediately prior/leading to delivery; multiple gestation; Parvo B19; infants known to be at risk of anemia due to isoimmunization (mother has red blood cell antibodies) | Later (delayed) cord clamping  At 30 seconds  100 infants | Intact-cord milking  Cord milked 4 times, before clamping, below placenta level  104 infants |  |

Supplementary Table 2a: Evidence Profile Table: Comparison 1: later (delayed) cord clamping vs early cord clamping neonatal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Later (delayed) cord clamping** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Survival to discharge from hospital | | | | | | | | | | | | |
| 16 | randomized trials | not serious a | not serious | not serious | serious b | none | 1383/1490 (92.8%) | 1364/1498 (91.1%) | **RR 1.02** (1.00 to 1.04) | **18 more per 1,000** (from 0 fewer to 36 more) | ⨁⨁⨁◯ MODERATE |  |
| Severe intraventricular hemorrhage (IVH): ultrasound diagnosis grades III, IV | | | | | | | | | | | | |
| 14 | randomized trials | serious c | not serious | not serious | serious d | none | 50/1488 (3.4%) | 51/1484 (3.4%) | **RR 0.98** (0.67 to 1.42) | **1 fewer per 1,000** (from 11 fewer to 14 more) | ⨁⨁◯◯ LOW |  |
| Chronic lung disease (CLD): oxygen at 36 weeks' PMA | | | | | | | | | | | | |
| 10 | randomized trials | not serious a | not serious | not serious | not serious | none | 470/1228 (38.3%) | 444/1199 (37.0%) | **RR 1.03** (0.94 to 1.13) | **11 more per 1,000** (from 22 fewer to 48 more) | ⨁⨁⨁⨁ HIGH |  |
| Necrotizing enterocolitis (≥ Bell's Stage II or any grade; requiring surgery) | | | | | | | | | | | | |
| 14 | randomized trials | not serious a | not serious | not serious | serious e | none | 65/1386 (4.7%) | 78/1359 (5.7%) | **RR 0.83** (0.61 to 1.13) | **10 fewer per 1,000** (from 22 fewer to 7 more) | ⨁⨁⨁◯ MODERATE |  |
| Peak hemoglobin (Hb) concentrations within the first 24 h after birth | | | | | | | | | | | | |
| 4 | randomized trials | not serious a | serious f | not serious | not serious | none | 96 | 100 | - | MD 1.24 higher (0.01 higher to 2.47 higher) | ⨁⨁⨁◯ MODERATE |  |
| Peak hematocrit (Hct) within the first 24 h after birth | | | | | | | | | | | | |
| 14 | randomized trials | not serious a | not serious | not serious | not serious | none | 554 | 546 | - | MD 2.63 higher (1.85 higher to 3.42 higher) | ⨁⨁⨁⨁ HIGH |  |
| Peak hemoglobin (Hb) concentrations within 7 days after birth | | | | | | | | | | | | |
| 0 | randomized trials |  |  |  |  |  |  |  | - | - | Not pooled |  |
| Peak hematocrit (Hct) within 7 days after birth | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious g | not serious | not serious | none | 779 | 771 | - | MD 2.7 higher (1.88 higher to 3.52 higher) | ⨁⨁⨁⨁ HIGH |  |
| Hyperbilirubinemia (treated by phototherapy) | | | | | | | | | | | | |
| 6 | randomized trials | not serious a | not serious | not serious | not serious | none | 373/457 (81.6%) | 371/451 (82.3%) | **RR 0.99** (0.95 to 1.03) | **8 fewer per 1,000** (from 41 fewer to 25 more) | ⨁⨁⨁⨁ HIGH |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. Some concerns due to lack of participant & personnel blinding. No downgrade since outcome unlikely to be influenced by this. This is a borderline decision.

b. Confidence interval includes null-effect, or clinically important outcome of 36 more survivals per 1000. Downgrade by 1. This is a borderline decision.

c. Largest study (>50% weight) unblinded for outcome assessment. IVH grading can be subjective, downgrade by 1

d. Confidence interval includes clinically important increase and clinically important decrease. Downgrade by 1.

e. Confidence interval includes clinically important decrease and no effect. Downgrade by 1.

f. Substantial heterogeneity. Direction of effect the same across all studies. Downgrade by 1.

g. Unable to assess inconsistency (only one study). No downgrade.

Supplementary Table 2b: Evidence Profile Table: Comparison 1: later (delayed) cord clamping vs early cord clamping infant/early childhood outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Later (delayed) cord clamping** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Moderate to severe neurodevelopmental impairment in early childhood** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Cerebral palsy in early childhood** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Significant mental developmental delay in early childhood** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Legal blindness in early childhood (< 20/200 visual acuity)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Hearing deficit in early childhood (aided or < 60 dB on audiometric testing)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Supplementary table 2c: Evidence Profile Table: Comparison 1: later (delayed) cord clamping vs early cord clamping maternal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Later (delayed) cord clamping** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Postpartum hemorrhage (clinically estimated blood loss of ≥ 500 mL) | | | | | | | | | | | | |
| 3 | randomized trials | serious c | serious d | not serious | serious b | none | 64/742 (8.6%) | 60/735 (8.2%) | **RR 0.9339** (0.5399 to 1.6155) | **5 fewer per 1,000** (from 38 fewer to 50 more) | ⨁◯◯◯ VERY LOW |  |
| Maternal death or severe morbidity | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Severe postpartum hemorrhage (PPH) (blood loss ≥ 1000 mL) | | | | | | | | | | | | |
| 1 | randomized trials | serious c | not serious e | not serious | very serious f | none | 11/130 (8.5%) | 13/124 (10.5%) | **RR 0.81** (0.38 to 1.73) | **20 fewer per 1,000** (from 65 fewer to 77 more) | ⨁◯◯◯ VERY LOW |  |
| Use of therapeutic uterotonic agents | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious e | not serious | not serious | none | 717/784 (91.5%) | 712/782 (91.0%) | **RR 1.00** (0.97 to 1.04) | **0 fewer per 1,000** (from 27 fewer to 36 more) | ⨁⨁⨁⨁ HIGH |  |
| Blood transfusion (maternal) | | | | | | | | | | | | |
| 2 | randomized trials | not serious a | not serious | not serious | very serious f | none | 15/363 (4.1%) | 8/352 (2.3%) | **RR 1.82** (0.78 to 4.23) | **19 more per 1,000** (from 5 fewer to 73 more) | ⨁⨁◯◯ LOW |  |
| Manual removal of the placenta | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious e | not serious | very serious f | none | 5/48 (10.4%) | 6/57 (10.5%) | **RR 0.99** (0.32 to 3.04) | **1 fewer per 1,000** (from 72 fewer to 215 more) | ⨁⨁◯◯ LOW |  |
| Additional treatment for PPH (uterine tamponade, embolization) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Postpartum infection | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious e | not serious | very serious g | none | 34/130 (26.2%) | 29/124 (23.4%) | **RR 1.12** (0.73 to 1.72) | **28 more per 1,000** (from 63 fewer to 168 more) | ⨁⨁◯◯ LOW |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. Some concerns due to lack of participant & personnel blinding. No downgrade since outcome unlikely to be influenced by this. This is a borderline decision.

b. Confidence interval includes clinically important increase and clinically important decrease. Downgrade by 1.

c. All studies unblinded for intervention and outcome assessment. Subjective outcome, may have been influenced by lack of blinding. Downgrade by 1.

d. Moderate heterogeneity. Downgrade by 1.

e. Unable to assess inconsistency (only one study). No downgrade.

f. Very large CI and low event rates. Downgrade by 2.

g. Only one study, large confidence interval, low event rates. Downgrade by 2. (Borderline decision whether to downgrade by 1 or 2)

Supplementary Table 3a: Evidence Profile Table: Comparison 2: Intact-cord milking compared vs early cord clamping neonatal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Intact-cord milking compared** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Survival to discharge from hospital | | | | | | | | | | | | |
| 10 | randomized trials | not serious a | not serious b | not serious | serious c | none | 438/467 (93.8%) | 440/478 (92.1%) | **RR 1.02** (0.98 to 1.06) | **18 more per 1,000** (from 18 fewer to 55 more) | ⨁⨁⨁◯ MODERATE |  |
| Severe intraventricular hemorrhage (IVH): ultrasound diagnosis grades III, IV | | | | | | | | | | | | |
| 10 | randomized trials | not serious d | not serious | not serious | very serious e | none | 23/444 (5.2%) | 32/445 (7.2%) | **RR 0.72**  (0.44 to 1.19) | **20 fewer per 1,000** (from 40 fewer to 14 more) | ⨁⨁◯◯ LOW |  |
| Chronic lung disease (CLD): oxygen at 36 weeks' PMA | | | | | | | | | | | | |
| 7 | randomized trials | not serious | serious f | not serious | serious g | none | 73/341 (21.4%) | 68/344 (19.8%) | **RR 1.02** (0.63 to 1.65) | **4 more per 1,000** (from 73 fewer to 128 more) | ⨁⨁◯◯ LOW |  |
| Necrotizing enterocolitis (≥ Bell's Stage II or any grade; requiring surgery) | | | | | | | | | | | | |
| 9 | randomized trials | not serious a | not serious | not serious | serious j | none | 36/423 (8.5%) | 47/420 (11.2%) | **RR 0.80** (0.55 to 1.18) | **22 fewer per 1,000** (from 50 fewer to 20 more) | ⨁⨁⨁◯ MODERATE |  |
| Peak hemoglobin (Hb) concentrations within the first 24 h after birth | | | | | | | | | | | | |
| 10 | randomized trials | not serious k | serious l | not serious | not serious | none | 459 | 455 | - | MD 1.18 higher (0.65 higher to 1.71 higher) | ⨁⨁⨁◯ MODERATE |  |
| Peak hematocrit (Hct) within the first 24 h after birth | | | | | | | | | | | | |
| 7 | randomized trials | not serious k | serious l | not serious | not serious | none | 383 | 391 | - | MD 3.04 higher (1.28 higher to 4.8 higher) | ⨁⨁⨁◯ MODERATE |  |
| Peak hemoglobin (Hb) concentrations within 7 days after birth | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious h | serious i | serious m | none | 29 | 25 | - | MD 0.6 higher (0.57 lower to 1.77 higher) | ⨁⨁◯◯ LOW |  |
| Peak hematocrit (Hct) within 7 days after birth | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious h | serious i | serious m | none | 29 | 25 | - | MD 1 higher (2.32 lower to 4.32 higher) | ⨁⨁◯◯ LOW |  |
| Hyperbilirubinemia (treated by phototherapy) | | | | | | | | | | | | |
| 5 | randomized trials | not serious a | not serious | not serious | not serious | none | 175/238 (73.5%) | 170/242 (70.2%) | **RR 1.04** (0.94 to 1.16) | **28 more per 1,000** (from 42 fewer to 112 more) | ⨁⨁⨁⨁ HIGH |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. No downgrade despite concerns due to blinding of intervention and selective outcome reporting bias. Blinding less likely to affect this outcome. Selective outcome reporting bias less likely to affect this estimate since this is a null-result. This is a borderline decision.

b. Some inconsistency, but not sufficient to downgrade. I-square = 24%.

c. Effect ranges from clinically important reduction to clinically important increase of survival.

d. No downgrade despite concerns due to blinding of intervention and selective outcome reporting bias. Blinding less likely to affect this outcome. Biggest & majority of studies were blinded for outcome assessment. Selective outcome reporting bias less likely to affect this estimate since this is a null-result. This is a borderline decision.

e. Effect ranges from clinically important reduction to clinically important increase. Downgrade by 2.

f. Moderate heterogeneity downgrade by 1

g. Effect ranges from clinically important reduction to clinically important increase. Downgrade by 1.

h. Unable to assess inconsistency (only one study). No downgrade.

i. Only one, single-center study impairs generalizability. Downgrade by 1

j. Wide confidence interval and relatively low event rates. Downgrade by 1.

k. No downgrade despite concerns due to blinding of intervention and selective outcome reporting bias. Blinding less likely to affect this outcome. This is a borderline decision.

l. Substantial heterogeneity, all but one effect estimates point in the same direction. Downgrade by 1.

m. Only one small study, wide CI. Downgrade by 1

Supplementary Table 3b: Evidence Profile Table: Comparison 2: Intact-cord milking compared vs early cord clamping infant/early childhood outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Intact-cord milking compared** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Moderate to severe neurodevelopmental impairment in early childhood | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | serious c | very serious d | none | 3/13 (23.1%) | 4/13 (30.8%) | **RR 0.75** (0.21 to 2.71) | **77 fewer per 1,000** (from 243 fewer to 526 more) | ⨁◯◯◯ VERY LOW |  |
| Cerebral palsy in early childhood | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | serious c | very serious d | none | 11/82 (13.4%) | 4/79 (5.1%) | **RR 2.65** (0.88 to 7.97) | **84 more per 1,000** (from 6 fewer to 353 more) | ⨁◯◯◯ VERY LOW |  |
| Significant mental developmental delay in early childhood | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Legal blindness in early childhood (< 20/200 visual acuity) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Hearing deficit in early childhood (aided or < 60 dB on audiometric testing) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. No downgrade despite concerns due to blinding of intervention and selective outcome reporting bias. Blinding less likely to affect this outcome. Selective outcome reporting bias less likely to affect this estimate since this is a null-result. This is a borderline decision.

b. Unable to assess inconsistency (only one study). No downgrade.

c. Only one, single-center study impairs generalizability. Downgrade by 1

d. Only one small study, low event numbers, very wide CI. Downgrade by 2

Supplementary Table 3c: Evidence Profile Table: Comparison 2: Intact-cord milking compared vs early cord clamping maternal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Intact-cord milking compared** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Postpartum hemorrhage (clinically estimated blood loss of ≥ 500 mL) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Maternal death or severe morbidity | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Severe postpartum hemorrhage (PPH) (blood loss ≥ 1000 mL) | | | | | | | | | | | | |
| 2 | randomized trials | serious c | not serious | not serious | very serious d | none | 1/133 (0.8%) | 0/133 (0.0%) | **RR 2.83** (0.12 to 67.01) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW |  |
| Use of therapeutic uterotonic agents | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Blood transfusion (maternal) | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious | serious b | very serious d | none | 1/34 (2.9%) | 0/32 (0.0%) | **RR 2.83** (0.12 to 67.01) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW |  |
| Manual removal of the placenta | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Additional treatment for PPH (uterine tamponade, embolization) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| Postpartum infection | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. No downgrade despite concerns due to blinding of intervention and selective outcome reporting bias. Blinding less likely to affect this outcome. Selective outcome reporting bias less likely to affect this estimate since this is a null-result. This is a borderline decision.

b. Only one, single-center study impairs generalizability. Downgrade by 1

c. All studies unblinded for intervention and outcome assessment. Subjective outcome, may have been influenced by lack of blinding. Downgrade by 1.

d. Very wide CI, only one event. Downgrade by 2.

Supplementary Table 4a: Evidence Profile Table: Comparison 3: cut-cord milking vs early cord clamping neonatal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Cut-cord milking compared** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Survival to discharge from hospital | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | serious c | very serious d | none | 30/30 (100.0%) | 30/30 (100.0%) | **RR 1.00** (0.94 to 1.07) | **0 fewer per 1,000** (from 60 fewer to 70 more) | ⨁◯◯◯ VERY LOW |  |
| Severe intraventricular hemorrhage (IVH): ultrasound diagnosis grades III, IV | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | serious c | very serious e | none | 0/30 (0.0%) | 1/30 (3.3%) | **RR 0.33** (0.01 to 7.87) | **22 fewer per 1,000** (from 33 fewer to 229 more) | ⨁◯◯◯ VERY LOW |  |
| Chronic lung disease (CLD): oxygen at 36 weeks' PMA | | | | | | | | | | | | |
| 1 | randomized trials | not serious | serious | not serious | very serious f | none | 1/30 (3.3%) | 1/30 (3.3%) | **RR 1.00** (0.07 to 15.26) | **0 fewer per 1,000** (from 31 fewer to 475 more) | ⨁◯◯◯ VERY LOW |  |
| Necrotizing enterocolitis (≥ Bell's Stage II or any grade; requiring surgery) | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | serious c | very serious f | none | 1/30 (3.3%) | 2/30 (6.7%) | **RR 0.50** (0.05 to 5.22) | **33 fewer per 1,000** (from 63 fewer to 281 more) | ⨁◯◯◯ VERY LOW |  |
| Peak hemoglobin (Hb) concentrations within the first 24 h after birth | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0 | 0 | - | see comment | - |  |
| Peak hematocrit (Hct) within the first 24 h after birth | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | serious c | serious g | none | 30 | 30 | - | MD 3.34 higher (0.6 higher to 6.08 higher) | ⨁⨁◯◯ LOW |  |
| Peak hemoglobin (Hb) concentrations within 7 days after birth | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0 | 0 | - | see comment | - |  |
| Peak hematocrit (Hct) within 7 days after birth | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0 | 0 | - | see comment | - |  |
| Hyperbilirubinemia (treated by phototherapy) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations

a. Some concerns due to lack of blinding. No downgrade, since this outcome unlikely to be influenced by lack of blinding. This is a borderline decision.

b. Only one study, so not possible to assess inconsistency. No downgrade.

c. Only one, single-center study with 60 participants. Impairs generalizability. Downgrade by 1.

d. No death in either one of the intervention groups. Effect could range from clinically meaningful reduction to clinically meaningful increase in survival.

e. Effect could range from very large reduction to very large increase in outcome. Only one event. Downgrade by 2.

f. Effect could range from very large reduction to very large increase in outcome. Low event number. Downgrade by 2.

g. Low participant number, wide CI. Downgrade by 1.

Supplementary Table 4b: Evidence Profile Table: Comparison 3: cut-cord milking vs early cord clamping infant/early childhood outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Cut-cord milking compared** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Moderate to severe neurodevelopmental impairment in early childhood** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Cerebral palsy in early childhood** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Significant mental developmental delay in early childhood** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Legal blindness in early childhood (< 20/200 visual acuity)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Hearing deficit in early childhood (aided or < 60 dB on audiometric testing)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Supplementary Table 4c: Evidence Profile Table: Comparison 3: cut-cord milking vs early cord clamping maternal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Cut-cord milking compared** | **early cord clamping** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Postpartum hemorrhage (clinically estimated blood loss of ≥ 500 mL)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Maternal death or severe morbidity** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Severe postpartum hemorrhage (PPH) (blood loss ≥ 1000 mL)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Use of therapeutic uterotonic agents** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Blood transfusion (maternal)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Manual removal of the placenta** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Additional treatment for PPH (uterine tamponade, embolization)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Postpartum infection** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Supplementary Table 5a: Evidence Profile Table: Comparison 4: Later (delayed) cord clamping compared to intact-cord milking neonatal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Later (delayed) cord clamping** | **intact-cord milking** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Survival to discharge from hospital | | | | | | | | | | | | |
| 5 | randomized trials | not serious a | not serious | not serious | serious b | none | 468/504 (92.9%) | 467/496 (94.2%) | **RR 0.99** (0.95 to 1.02) | **9 fewer per 1,000** (from 47 fewer to 19 more) | ⨁⨁⨁◯ MODERATE |  |
| Severe intraventricular hemorrhage (IVH): ultrasound diagnosis grades III, IV | | | | | | | | | | | | |
| 4 | randomized trials | not serious c | not serious | not serious | serious d | none | 14/382 (3.7%) | 24/379 (6.3%) | **RR 0.60** (0.32 to 1.12) | **25 fewer per 1,000** (from 43 fewer to 8 more) | ⨁⨁⨁◯ MODERATE |  |
| Chronic lung disease (CLD): oxygen at 36 weeks' PMA | | | | | | | | | | | | |
| 4 | randomized trials | not serious a | not serious | not serious | serious | none | 60/366 (16.4%) | 66/368 (17.9%) | **RR 0.91** (0.67 to 1.25) | **16 fewer per 1,000** (from 59 fewer to 45 more) | ⨁⨁⨁◯ MODERATE |  |
| Necrotizing enterocolitis (≥ Bell's Stage II or any grade; requiring surgery) | | | | | | | | | | | | |
| 5 | randomized trials | not serious a | not serious | not serious | serious d | none | 23/466 (4.9%) | 14/456 (3.1%) | **RR 1.57** (0.83 to 2.97) | **18 more per 1,000** (from 5 fewer to 60 more) | ⨁⨁⨁◯ MODERATE |  |
| Peak hemoglobin (Hb) concentrations within the first 24 h after birth | | | | | | | | | | | | |
| 6 | randomized trials | not serious a | serious e | not serious | not serious | none | 466 | 475 | - | MD 0.02 lower (0.56 lower to 0.53 higher) | ⨁⨁⨁◯ MODERATE |  |
| Peak hematocrit (Hct) within the first 24 h after birth | | | | | | | | | | | | |
| 5 | randomized trials | not serious a | serious f | not serious | not serious | none | 419 | 422 | - | MD 0.18 lower (1.9 lower to 1.54 higher) | ⨁⨁⨁◯ MODERATE |  |
| Peak hemoglobin (Hb) concentrations within 7 days after birth | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0 | 0 | - | see comment | - |  |
| Peak hematocrit (Hct) within 7 days after birth | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0 | 0 | - | see comment | - |  |
| Hyperbilirubinemia (treated by phototherapy) | | | | | | | | | | | | |
| 2 | randomized trials | not serious a | serious g | not serious | not serious | none | 102/118 (86.4%) | 100/118 (84.7%) | **RR 1.05** (0.90 to 1.24) | **42 more per 1,000** (from 85 fewer to 203 more) | ⨁⨁⨁◯ MODERATE |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

#### Explanations

a. Risk of bias no downgrade, even though there were some concerns due to lack of blinding in most studies, since this outcome unlikely to be influenced by lack of blinding. This is a borderline decision.

b. Effect ranges from clinically important increase to clinically important decrease. Downgrade by 1.

c. Risk of bias no downgrade, even though there were some concerns due to lack of intervention delivery blinding in most studies, since this outcome unlikely to be influenced by lack of blinding of intervention delivery. Outcome assessment blinded in all but one small study. This is a borderline decision.

d. Wide CI, relatively low event rate. Downgrade by 1.

e. Moderate heterogeneity (I^2 = 52%). Downgrade by 1.

f. Moderate heterogeneity (I^2 = 51%). Downgrade by 1.

g. Moderate heterogeneity (I^2 = 43%). Downgrade by 1.

Supplementary Table 5b: Evidence Profile Table: Comparison 4: Later (delayed) cord clamping compared to intact-cord milking infant/early childhood outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Later (delayed) cord clamping** | **intact-cord milking** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Moderate to severe neurodevelopmental impairment in early childhood | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious b | not serious | very serious c | none | 0/65 (0.0%) | 2/70 (2.9%) | **RR 0.22** (0.01 to 4.40) | **22 fewer per 1,000** (from 28 fewer to 97 more) | ⨁⨁◯◯ LOW |  |
| Cerebral palsy in early childhood | | | | | | | | | | | | |
| 2 | randomized trials | not serious a | not serious | not serious | very serious d | none | 0/96 (0.0%) | 1/97 (1.0%) | **RR 0.36** (0.01 to 8.65) | **7 fewer per 1,000** (from 10 fewer to 79 more) | ⨁⨁◯◯ LOW |  |
| Significant mental developmental delay in early childhood | | | | | | | | | | | | |
| 1 | randomized trials | not serious a | not serious | serious e | very serious f | none | 5/17 (29.4%) | 0/22 (0.0%) | **RR 14.06** (0.83 to 237.84) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW |  |
| Legal blindness in early childhood (< 20/200 visual acuity) | | | | | | | | | | | | |
| 1 |  |  |  |  |  |  | 0/31 (0.0%) | 0/27 (0.0%) | not estimable |  | - |  |
| Hearing deficit in early childhood (aided or < 60 dB on audiometric testing) | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

#### Explanations

a. Risk of bias no downgrade, even though there were some concerns due to lack of blinding in most studies, since this outcome unlikely to be influenced by lack of blinding. This is a borderline decision.

b. Unable to assess inconsistency (only one study). No downgrade.

c. Very wide CI, only two events. Downgrade by 2.

d. Very wide CI, only one event. Downgrade by 2.

e. Only one single-center study, impairs generalizability. Downgrade by 1.

f. Very wide CI, very low event rate. Downgrade by 2.

Supplementary Table 5c: Evidence Profile Table: Comparison 4: Later (delayed) cord clamping compared to intact-cord milking maternal outcomes

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Later (delayed) cord clamping** | **intact-cord milking** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Postpartum hemorrhage (clinically estimated blood loss of ≥ 500 mL)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Maternal death or severe morbidity** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Severe postpartum hemorrhage (PPH) (blood loss ≥ 1000 mL)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Use of therapeutic uterotonic agents** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Blood transfusion (maternal)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Manual removal of the placenta** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Additional treatment for PPH (uterine tamponade, embolization)** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |
| **Postpartum infection** | | | | | | | | | | | | |
| 0 |  |  |  |  |  |  | 0/0 | 0/0 | not pooled | see comment | - |  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

Supplementary Table 6. Post-hoc sensitivity analysis: Survival versus mortality

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Comparison | Survival  RR [95% CI] | Mortality RR, CI | Mortality\*  RR, CI | Survival RD, CI | Mortality RD, CI | Mortality\*  RD, CI |
| 1: Later (delayed) cord clamping compared to early cord clamping | 1.02 [0.993, 1.04] | 0.80 [0.63, 1.02] | 0.80 [0.63, 1.02] | 0.02 [-0.001, 0.04] | -0.02 [-0.04, 0.001] | -0.02 [-0.04; 0.001] |
| 2: Intact-cord milking compared to early cord clamping | 1.02 [0.98, 1.06] | 0.77 [0.49, 1.23] | 0.77 [0.49; 1.23] | 0.02 [-0.01, 0.05] | -0.02 [-0.05, 0.01] | -0.02 [-0.05, 0.01] |
| 3: Cut-cord milking compared to early cord clamping | 1.00 [0.94, 1.07] | Not estimable | Not estimable | 0.00 [-0.06, 0.06] | 0.00 [-0.06, 0.06] | 0.00 [-0.06, 0.06] |
| 4: Later (delayed) cord clamping compared to intact-cord milking | 0.99 [0.95, 1.02] | 1.21 [0.76, 1.94] | 1.21 [0.76, 1.94] | -0.01 [-0.04, 0.02] | 0.01 [-0.02, 0.04] | 0.01 [-0.02, 0.04] |

\*Continuity correction of 0.5 for studies with zero cell frequencies

Supplementary Table 7a: Comparison 1: Delayed (later) cord clamping compared to early cord clamping: Secondary Outcomes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Number of studies | Number of infants (or mothers as applicable) | Relative Risk (RR)(95%CI) | Risk Difference (RD)(95%CI) | Mean Difference (MD)(95%CI) | Statistical heterogeneity (I2)\* |
| Apgar score at 5 minutes of age | 7 | 2357 infants |  |  | MD -0.00, 95% CI  -0.07 to 0.07 | I2 = 0% No heterogeneity |
| Positive pressure ventilation (PPV) for resuscitation | 2 | 161 infants | RR 0.93, 95% CI 0.49 to 1.74 | RD -0.01, 95% CI -0.14 to 0.11 |  | I2 = 0% No heterogeneity |
| Intubation for resuscitation | 4 | 440 infants | RR 0.93, 95% CI 0.79 to 1.10 | RD -0.04, 95% CI -0.12 to 0.05 |  | I2 = 0% No heterogeneity |
| Chest compression/cardiac massage for resuscitation | 3 | 407 infants | RR 0.69, 95% CI 0.30 to 1.61 | RD -0.02, 95% CI -0.06 to 0.02 |  | I2 = 0% No heterogeneity |
| Respiratory distress syndrome (RDS) | 4 | 201 infants | RR 1.23, 95% CI 0.94 to 1.61 | RD 0.06, 95% CI -0.02 to 0.15 |  | I2 = 5% No heterogeneity |
| Respiratory support | 7 | 515 infants | RR 1.07, 95% CI 0.89 to 1.29 | RD 0.03, 95% CI -0.05 to 0.11 |  | I2 = 0% No heterogeneity |
| Duration of respiratory support | 5 | 417 infants |  |  | MD 0.00, 95% CI  -1.23 to 1.24 | I2 = 0% No heterogeneity |
| Surfactant treatment | 8 | 650 infants | RR 0.92, 95% CI 0.78 to 1.07 | RD -0.04, 95% CI -0.11 to 0.03 |  | I2 = 0% No heterogeneity |
| Home oxygen | 2 | 101 infants | RR 0.47, 95% CI 0.06 to 3.72 (random effects) | RD -0.16, 95% CI -0.55 to 0.22 (random effects) |  | I2 = 69% moderate heterogeneity |
| Treatment for patent ductus arteriosus (medical and/or surgical) | 10 | 2053 infants | RR 0.96, 95% CI 0.84 to 1.09 | RD -0.01, 95% CI -0.05 to 0.03 |  | I2 = 0% No heterogeneity |
| Inotropic support for hypotension during the first 24 hours of life | 6 | 351 infants | RR 0.36, 95% CI 0.17 to 0.74 | RD -0.09, 95% CI -0.15 to -0.03 |  | I2 = 0% No heterogeneity |
| Lowest mean arterial blood pressure in the first 12 hours of life | 7 | 374 infants |  |  | MD 1.79, 95% CI 0.53 to 3.05 | I2 = 0% No heterogeneity |
| Any intraventricular hemorrhage (IVH)(Grade 1 or greater) | 15 | 2937 infants | RR 0.93, 95% CI 0.79 to 1.09 | RD -0.01, 95% CI -0.04 to 0.01 |  | I2 = 16% No heterogeneity |
| Fully breastfed or mixed feeding at infant discharge | 1 | 248 infants | RR 0.98, 95% CI 0.79 to 1.22 | RD -0.01, 95% CI  -0.14 to 0.11 |  | NA |
| Blood transfusion (infant) | 12 | 2910 | RR 0.83, 95% CI 0.77 to 0.90 | RD -0.07, 95% CI -0.11 to -0.04 |  | I2 = 36% Low heterogeneity |
| Total number of blood transfusions | 6 | 242 infants |  |  | MD -0.63, 95% C  -1.08 to -0.17 | I2 = 35% Low heterogeneity |
| Late sepsis | 11 | 2266 infants | RR 0.97, 95% CI 0.84 to 1.12 | RD -0.01, 95% CI -0.04 to 0.03 |  | I2 = 23% No heterogeneity |
| Retinopathy of prematurity in infants examined (all stages) | 8 | 749 infants | RR 0.94, 95% CI 0.68 to 1.30 | RD -0.01, 95% CI -0.06 to 0.04 |  | I2 = 0% No heterogeneity |
| Treatment for retinopathy of prematurity (RoP) | 5 | 2244 infants | RR 0.77, 95% CI 0.53 to 1.12 | RD -0.01, 95% CI -0.03 to 0.01 |  | I2 = 0% No heterogeneity |
| Length of infant stay in neonatal intensive care unit (days) | 1 | 100 infants |  |  | MD -1.00, 95% CI -2.35 to 0.35 | NA |
| Mean temperature on admission to NICU (post-hoc) | 4 | 449 infants |  |  | MD -0.52, 95% CI -0.30 to 0.20  (random effects) | I2 = 83% High heterogeneity |
| Length of infant hospital stay (days) (post-hoc) | 7 | 643 infants |  |  | MD -0.48, 95% CI -1.02 to 0.06 | I2 = 28% Low heterogeneity |
| Prolonged third stage (> 30 minutes) | 1 | 105 women | RR 0.79, 95% CI 0.24 to 2.64 | RD -0.02, 95% CI -0.13 to 0.09 |  | NA |
| Length of maternal hospital stay | 1 | 254 women |  |  | MD 0.00, 95% CI  -0.74 to 0.74 | NA |

\*Heterogeneity: using the I² statistic, heterogeneity is graded as: less than 25% no heterogeneity; 25% to 49% low heterogeneity; 50% to 75% moderate heterogeneity; more than 75% substantial heterogeneity

Supplementary Table 7b: Comparison 2: Intact-cord milking compared to early cord clamping: Secondary Outcomes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Number of studies | Number of infants (or mothers, as applicable) | Relative Risk (RR)(95%CI) | Risk Difference (RD) (95%CI) | Mean Difference (MD)(95%CI) | Statistical heterogeneity (I2)\* |
| Apgar score at 5 minutes of age | 5 | 308 infants |  |  | MD 0.26, 95% CI -0.03 to 0.56 | I2 = 0% No heterogeneity |
| Positive pressure ventilation (PPV) for resuscitation | 2 | 139 infants | RR 1.05, 95% CI 0.87 to 1.27 | RD 0.04, 95% CI -0.10 to 0.18 |  | I2 = 13% No heterogeneity |
| Intubation for resuscitation | 3 | 214 infants | RR 0.95, 95% CI 0.74 to 1.23  (random effects) | RD -0.03, 95% CI -0.17 to 0.11 (random effects) |  | I2 = 66% Moderate heterogeneity |
| Chest compressions for resuscitation | 2 | 148 infants | RR 1.05, 95% CI 0.42 to 2.62 | RD 0.69, 95% CI 0.30 to 1.61 |  | I2 = 0% No heterogeneity |
| Respiratory distress syndrome (RDS) | 5 | 492 infants | RR 0.97, 95% CI 0.83 to 1.12 | RD -0.02, 95% CI -0.10 to 0.06 |  | I2 = 0% No heterogeneity |
| Respiratory support | 6 | 373 infants | RR 0.96, 95% CI 0.87 to 1.07 | RD -0.03, 95% CI -0.10 to 0.05 |  | I2 = 24% No heterogeneity |
| Duration of respiratory support | 4 | 355 infants |  |  | MD -0.63, 95% CI -2.89 to 1.64 | I2 = 0% No heterogeneity |
| Surfactant treatment | 8 | 602 infants | RR 1.06, 95% CI 0.93 to 1.21 | RD 0.03, 95% CI -0.04 to 0.11 |  | I2 = 37%Low heterogeneity |
| Home oxygen | 1 | 199 infants | RR 0.89, 95% CI 0.38 to 2.10 | RD -0.01, 95% CI  -0.09 to 0.07 |  | NA |
| Treatment for patent ductus arteriosus (medical and/or surgical) | 4 | 377 infants | RR 0.94, 0.66 to 1.34 | RD -0.02, 95% CI -0.10 to 0.07 |  | I2 = 0% No heterogeneity |
| Inotropic support for hypotension during the first 24 hours of life | 5 | 439 infants | RR 0.61, 0.44 to 0.84 | RD -0.12, 95% CI -0.19 to -0.05 |  | I2 = 0%  Low heterogeneity |
| Lowest mean arterial blood pressure in the first 12 hours of life | 5 | 431 infants |  |  | MD 0.58, 95% CI  -0.79 to 1.94 | I2 = 0% Low heterogeneity |
| Any intraventricular hemorrhage (IVH)(Grade 1 or greater) | 10 | 934 infants | RR 0.85, 95% CI 0.67 to 1.08 | RD -0.04, 95% CI -0.09 to 0.02 |  | I2 = 14% No heterogeneity |
| Periventricular leukomalacia (PVL) (any grade (Grade 1 or greater) | 3 | 315 infants | RR 0.66, 95% CI 0.18 to 2.47 | RD -0.01, 95% CI -0.05 to 0.02 |  | I2 = 0% No heterogeneity |
| Peak hemoglobin (Hb) concentrations within 7 days after birth | 1 | 54 infants |  |  | MD 0.60, 95% CI  -0.57 to 1.77 | NA |
| Peak hematocrit (Hct) within 7 days after birth | 1 | 54 infants |  |  | MD 1.00, 95% CI  -2.32 to 4.32 | NA |
| Blood transfusion | 7 | 545 infants | RR 0.73, 95% CI 0.56 to 0.94  (random effects) | RD -0.17, 95% CI -0.30 to -0.04  (random effects) |  | I2 = 54% Moderate heterogeneity |
| Total number of blood transfusions | 4 | 209 infants |  |  | MD -0.49, 95% CI -1.13 to 0.15 | I2 = 37% Low heterogeneity |
| Late sepsis | 6 | 482 infants | RR 1.02, 95% CI 0.79 to 1.32 | RD 0.01, 95% CI -0.06 to 0.07 |  | I2 = 0% No heterogeneity |
| Retinopathy of prematurity in infants examined (all stages (stage 1 or greater) | 4 | 211 infants | RR 0.84, 95% CI 0.65 to 1.09 | RD -0.06, 95% CI -0.16 to 0.03 |  | I2 = 38% Low heterogeneity |
| Severe RoP (≥ stage 3) | 1 | 40 infants | RR 0.29, 0.07 to 1.21 | RD -0.25, 95% CI  -0.50 to -0.00 |  | NA |
| Treatment for retinopathy of prematurity (RoP) | 3 | 165 infants | RR 0.79, 95% CI 0.25 to 2.51 | RD -0.02, 95% CI -0.09 to 0.06 |  | I2 = 0% No heterogeneity |
| Length of infant stay in neonatal intensive care unit (days) | 2 | 337 infants |  |  | MD 2.57, -1.67 to 6.81 | I2 = 0% No heterogeneity |
| Mean temperature on admission to NICU (post-hoc) | 2 | 266 infants |  |  | MD 0.10, 95% CI  -0.08 to 0.28 | I2 = 0% No heterogeneity |
| Length of infant hospital stay (post-hoc) | 3 | 203 infants |  |  | MD -1.74, 95% CI  -9.39 to 5.92 | I2 = 0% No heterogeneity |
| Maternal death: there were no deaths in the only study which reported on maternal death | 1 | 66 women | Not estimable | RD 0.00, 95% CI  -0.06 to 0.06 |  | NA |

\*Heterogeneity: using the I² statistic, heterogeneity is graded as: less than 25% no heterogeneity; 25% to 49% low heterogeneity; 50% to 75% moderate heterogeneity; more than 75% substantial heterogeneity

Supplementary Table 7c: Comparison 3: Cut-cord milking compared to early cord clamping: Secondary Outcomes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Number of studies | Number of infants (or mothers, as applicable) | Relative Risk (RR)(95%CI) | Risk Difference (RD) (95%CI) | Mean Difference (MD)(95%CI) | Statistical heterogeneity (I2)\* |
| Apgar score at 5 minutes of age | 1 | 60 infants |  |  | MD 0.33, 95% CI  -1.45 to 2.11 | NA |
| Positive pressure ventilation (PPV) for resuscitation | 1 | 60 infants | RR 1.12, 95% CI 0.95 to 1.30 | RD 0.10, 95% CI  -0.04 to 0.24 |  | NA |
| Intubation for resuscitation | 1 | 60 infants | RR 0.60, 95% CI 0.16 to 2.29 | RD -0.07, 95% CI  -0.24 to 0.10 |  | NA |
| Chest compressions for resuscitation | 1 | 60 infants | RR 1.00, 95% CI 0.07 to 15.26 | RD 0.00, 95% CI  -0.09 to 0.09 |  | NA |
| Treatment for patent ductus arteriosus (medical and/or surgical) | 1 | 60 infants | RR 0.40, 95% CI 0.08 to 1.90 | RD -0.10, 95% CI  -0.26 to 0.06 |  | NA |
| Inotropic support for hypotension during the first 24 hours of life | 1 | 60 infants | RR 1.17, 95% CI 0.44 to 3.06 | RD 0.03, 95% CI  -0.17 to 0.24 |  | NA |
| Lowest mean arterial blood pressure in the first 12 hours of life | 1 | 60 infants |  |  | MD 5.06, 95% CI  -3.79 to 13.91 | NA |
| Periventricular leukomalacia (PVL) (any grade (Grade 1 or greater) | 1 | 60 infants | RR 3.00, 95% CI 0.13 to 70.83 | RD 0.03, 95% CI  -0.05 to 0.12 |  | NA |
| Blood transfusion | 1 | 60 infants | RR 0.50, 95% CI 0.14 to 1.82 | RD -0.10, 95% CI  -0.28 to 0.08 |  | NA |
| Late sepsis | 1 | 60 infants | RR 0.50, 95% CI 0.14 to 1.82 | RD -0.13, 95% CI  -0.28 to 0.01 |  | NA |
| Retinopathy of prematurity in infants examined (all stages) | 1 | 60 infants | RR 1.00, 95% CI 0.07 to 15.26 | RD 0.00, 95% CI  -0.09 to 0.09 |  | NA |

\*Heterogeneity: using the I² statistic, heterogeneity is graded as: less than 25% no heterogeneity; 25% to 49% low heterogeneity; 50% to 75% moderate heterogeneity; more than 75% substantial heterogeneity

Supplementary Table 7d: Comparison 4: Later (delayed) cord clamping compared to intact cord milking: Secondary Outcomes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Number of studies | Number of infants (or mothers, as applicable) | Relative Risk (RR)(95%CI) | Risk Difference (RD) (95%CI) | Mean Difference (MD)(95%CI) | Statistical heterogeneity (I2)\* |
| Apgar score at 5 minutes of age | 2 | 242 infants |  |  | MD 0.12, 95% CI  -0.86 to 1.09 (random effects) | I2 = 80% High heterogeneity |
| Positive pressure ventilation (PPV) for resuscitation | 1 | 154 infants | RR 0.93, 95% CI 0.77 to 1.13 | RD -0.05, 95% CI  -0.19 to 0.09 |  | NA |
| Intubation for resuscitation | 2 | 192 infants | RR 1.12, 95% CI 0.76 to 1.64 | RD 0.04, 95% CI -0.09 to 0.17 |  | I2 = 0% No heterogeneity |
| Chest compressions for resuscitation | 1 | 474 infants | RR 1.13, 95% CI 0.42 to 3.08 | RD 0.00, 95% CI -0.03 to 0.04 |  | NA |
| Temperature < 360 within one hour of birth | 1 | 204 infants | RR 1.14, 95% CI 0.53 to 2.42 | RD 0.01, 95% CI -0.07 to 0.10 |  | NA |
| Respiratory support (use of mechanical ventilation or continuous positive airway pressure (CPAP)) | 1 | 32 infants | RR 0.89, 95% CI 0.55 to 1.44 | RD -0.08, 95% CI -0.40 to 0.25 |  | NA |
| Duration of respiratory support (days of mechanical ventilation or continuous positive airway pressure (CPAP)) | 2 | 89 infants |  |  | MD -1.45, 95% CI  -11.58 to 8.68 (random effects) | I² = 51%  Moderate heterogeneity |
| Surfactant treatment | 2 | 90 infants | RR 1.04, 95% CI 0.71 to 1.53 | RD 0.02, 95% CI -0.18 to 0.22 |  | I2 = 0% No heterogeneity |
| Inotropic support for hypotension during the first 24 hours of life | 1 | 135 infants | RR 1.62, 95% CI 0.71 to 3.70 | RD 0.07 95% CI  -0.05 to 0.19 |  | NA |
| Lowest mean arterial blood pressure in the first 12 hours of life | 1 | 29 infants |  |  | MD -1.83, 95% CI -6.97 to 3.31 | NA |
| Any intraventricular hemorrhage (IVH)(Grade 1 or greater) | 5 | 1000 infants | RR 1.10, 95% CI 0.84 to 1.44 | RD 0.02, 95% CI -0.03 to 0.06 |  | I² = 29%  Low heterogeneity |
| Periventricular leukomalacia (PVL) (any grade (Grade 1 or greater) | 2 | 532 infants | RR 0.52, 95% CI 0.24 to 1.15 | RD -0.03, 95% CI -0.07 to 0.01 |  | NA |
| Blood transfusion | 4 | 448 infants | RR 1.05, 95% CI 0.77 to 1.44  (random effects) | RD 0.04, 95% CI -0.04 to 0.13  (random effects) |  | I² = 41%  Low heterogeneity |
| Total number of blood transfusions | 1 | 32 infants |  |  | MD -0.30, 95% CI  -1.70 to 1.10 | NA |
| Late sepsis | 4 | 699 infants | RR 0.78, 95% CI 0.46 to 1.31 | RD -0.02, 95% CI -0.06 to 0.02 |  | I2 = 0% No heterogeneity |
| Retinopathy of prematurity in infants examined (all stages (stage 1 or greater) | 3 | 157 infants | RR 0.81, 95% CI 0.30 to 2.17 | RD -0.02, 95% CI -0.11 to 0.07 |  | I2 = 0% No heterogeneity |
| Treatment for retinopathy of prematurity (RoP) | 2 | 628 infants | RR 1.89, 95% CI 0.93 to 3.84 | RD 0.03, 95% CI -0.00 to 0.07 |  | I2 = 0% No heterogeneity |
| Length of infant stay in neonatal intensive care unit (days) | 2 | 271 infants |  |  | MD 0.89, 95% CI  -4.59 to 6.38 | I2 = 0% No heterogeneity |
| Mean temperature on admission to NICU (post-hoc) | 1 | 154 infants |  |  | MD -0.10, 95% CI -0.26 to 0.06 | NA |
| Maternal death | 2 | 531 women | RR 0.33, 95% CI 0.01 to 8.07 | RD -0.00, 95% CI -0.02 to 0.01 |  | NA |

\*Heterogeneity: using the I² statistic, heterogeneity is graded as: less than 25% no heterogeneity; 25% to 49% low heterogeneity; 50% to 75% moderate heterogeneity; more than 75% substantial heterogeneity