Effects of cord milking in late preterm infants and full-term infants: a systematic review and meta-analysis

Abstract

Background: Umbilical cord milking (UCM) consists of performing several milkings of the cord from the placenta to the neonate. The objective was to evaluate the effects of UCM on newborns ≥34 weeks gestation.

Methods: Searches were conducted in MEDLINE, EMBASE, CINAHL, the Cochrane Database of Clinical Trials, and the clinicaltrails.gov database for randomized clinical trials (RCT), with no time or language restrictions, and for articles that compared UCM with other strategies. The main results were initial haemoglobin and haemoglobin after 6 weeks. The data were collected by two reviewers and the quality of the studies was assessed using the Cochrane Manual methodology.

Results: The sample included 1,845 newborns in 10 RCTs. The use of UCM in ≥34 weeks gestation newborns was not related to initial haemoglobin levels (Pooled Weighted Mean Difference: (PWMD=0.40g/L [-0.16 to 0.95]), or after 6 weeks (PWMD=0.07g/L [-0.29 to 0.27]). A reduction in haemoglobin levels was also observed at 6 weeks when the control group had undergone late clamping (PWDM=0.16g/L [-0.26 to -0.06]).

Conclusions: UCM produced no differences in haematological variables for newborns with ≥ 34 weeks of gestation relative to controls. However, a slight decrease in haemoglobin levels is observed at 6 weeks when the control group is made up of newborns with late clamping.

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Keywords: delayed cord clamping, umbilical cord clamping, preterm infants, full-term infants and meta-analysis**.**

1 INTRODUCTION

After birth, blood flow between the newborn and the placenta may continue for several minutes, until the umbilical cord is cut or clamped [1,2]. This placental transfusion is part of the physiologic transition from foetal to neonatal circulation [3].

For full-term births, umbilical blood flow usually completes in two minutes, but it may continue for up to five minutes. This gives the newborn 80 to 100 ml of additional blood which can imply from one-third to a quarter of the neonatal blood volume at birth [1,2] .

Increased blood intake from placental transfusion leads to higher levels of neonatal haemoglobin [4–8], additional iron reserves, and fewer cases of childhood anaemia [9–11].

For these reasons, Clinical Practice Guidelines (GPC) [12,13] and various scientific societies [14–16] recommend delaying umbilical cord clamping—known as delayed cord clamping (DCC)—whenever possible, due to its positive impact on neonatal health. However, this technique may not possible in some circumstances for a variety of reasons such as immediate neonatal resuscitation or maternal hemodynamic instability. As an alternative to DCC in these cases, the use of umbilical cord milking (UCM) has been proposed. This technique involves performing several milkings of the umbilical cord from the placenta to the neonate [17].

A meta-analysis on the use of UCM was published in 2015, including seven randomised controlled trials (RCTs) [18]. Two studies included in this meta-analysis included full-term newborns and late preterm infants (>34^6 weeks gestation); the rest of the studies included only premature infants. The authors concluded that by performing UCM in premature newborns, haemoglobin and haematocrit levels were higher than by performing another type of clamping. They also found a reduced risk of oxygen need and intraventricular haemorrhage when UCM

was performed. However, due to the small number of studies on full-term newborns, the researchers were unable to reach any conclusions about this group.

In addition, a review of UCM use in full-term newborns and late preterm infants was published in 2019 that included eleven studies [19]. This review did not perform a meta-analysis and both RCT and observational studies were included. The authors concluded that most studies showed benefits to haematological variables for both umbilical cord milking and late cord clamping, as compared to immediate cord clamping (ICC).

Despite the benefits shown for full-term newborns, the use of UCM remains an unstandardized practice that requires further evaluation. It is important to determine the benefits and risks by gestational age for DCC and ICC— the most relevant variables.

As such, the main objective of this systematic review and meta-analysis was to evaluate the effects of UCM on full-term newborns and late preterm infants (≥34 weeks of gestation). As a secondary objective, the effects of stratified UCM were evaluated by weeks of gestation (≥34/34-37/≥37 weeks) and type of control (ICC/DCC).

2 METHODS

This systematic review with meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) [20] statement.

2.1. Data sources and searches

The search strategy was: (stripping OR milking OR squeezing) AND (umbilicus OR umbilical cord OR cord). A systematic search was performed in the main databases: Cochrane Library

70 Plus, EMBASE, Scopus, Pubmed, and ClinicalTrials.gov. The specific database search strategy
71 is described in detail in Appendix 1.

72 The inclusion criteria were: (I) type of study: RCT; (II) population, including studies on ≥ 34
73 gestational age (GA) newborns; and (III) type of intervention, where studies that investigated
74 UCM against a control intervention (ICC or DCC) were included. The exclusion criteria were
75 RCTs that included both full-term and premature newborns without the possibility of isolating
76 information from each group.

77 RCTs were selected without time or language restrictions. Two reviewers (IOE and JRA)
78 independently evaluated the articles obtained from a bibliographic search that was conducted
79 using titles and summaries in a first stage. They then evaluated the selected full texts. Any
80 disagreement was resolved upon reaching a consensus. If this was not possible, a third reviewer
81 (AHM) evaluated the articles.

82 The main result of our study was haemoglobin measured within 24 hours of birth and
83 haemoglobin measured at six weeks. The secondary results were: birth adaptation variables
84 (Apgar score at 1 and at 5 minutes); other haematological variables (first haematocrit, need for
85 transfusion before hospital discharge, hyperbilirubinemia requiring light therapy, ferritin levels
86 at six weeks, and serum bilirubin at 48 hours). The mean blood pressure was also included
87 within 6 hours from birth, and the clinical observation of jaundice. Short-term morbidities were
88 studied such as hypotension in the first 24 hours requiring inotropic volume or support, heart
89 rate and breathing rate at 30 minutes and 48 hours after birth, and mortality before hospital
90 discharge.

91

92 **2.2. Data extraction and quality assessment**

The three reviewers (IOE, AAA and AHM) conducted data collection and quality assessment independently. For continuous results, means and standard deviations (SD) were collected whenever possible. When the means and SDs were not available and originally appeared as median and range, or interquartile range, contact was sought with the authors and results were requested. When this was not possible, the results were converted to mean and SD [21]. For the categorical outcomes, the records of the study events were collected.

The risk of bias in each included study was assessed using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions [22]. Seven domains related to the risk of bias were evaluated in each included trial because there is evidence that these problems are associated with biased estimates of the treatment effect: [1] random sequence generation; [2] concealment of assignment [3]; blinding of participants and staff [4]; blinding of results assessment [5]; incomplete results data [6]; selective reports; and [7] other bias. The authors' judgments on the reviews were classified as "low risk", "high risk", or "uncertain risk" of bias.

2.3- Data synthesis

For the categorical results, relative risk (RR) was used, along with 95% of confidence interval (95% CI). The Fixed Effects models by Mantel-Haenszel and the random effect models by Der Simonian-Lairden were used depending on the absence or presence of heterogeneity, respectively. Heterogeneity between the studies was estimated by statistical tests I^2 and Cochran's Q-tests. I^2 <25%, 25–50 and >50% values typically correspond to small, medium, and large heterogeneity, respectively [23,24].

For the quantitative results, the pooled weighted mean difference (PWMD) with 95% CI were used. Publication bias was also evaluated using the Egger test [25]. Statistical significance was defined at 0.05 level.

All calculations were performed with the StatsDirect statistical software, version 2.7.9 (StatsDirect Ltd., Cheshire, England).

3 RESULTS

3.1. Study selection

A total of 1,492 studies were extracted from the literature search. After the duplicate items were removed, the 504 remaining documents were screened by title and summary. After applying the inclusion/exclusion criteria, 10 articles were selected for qualitative and quantitative analysis (meta-analysis) (Figure 1).

3.2. Study characteristics

The sample included 1,845 newborns with GA between 34^{6} and $41^{6/7}$ weeks. The selected studies were conducted in the US [26], India [27–32], Egypt [33,34], and Italy [35].

The sample size of the studies ranged from 24 to 300 newborns. UCM was compared with DCC in six RCTs [28,29,31–34], and ICC in four RCTs [26,27,30,35]. One RCT [28] included DCC as control and DCC with milking the cut cord (DCM). In this case, to carry out the metanalysis, we only included data on the UCM and DCC groups, and excluded data on the DCM group.

The description of the UCM technique varied between the studies, including the number of times the cord was milked towards the newborn (3 to 5 times), as well as studies describing milking speed as 10 cm within 1 second.

The number of neonates in each study, the description of the UCM method used, how the cord was handled in the control group, and the exclusion criteria are shown in Table 1.

3.3. Study and data quality

The risk of bias for the seven domains in each study is shown in Supplementary Figure 1. Six of the ten studies were assessed as low risk for randomised sequence generation; in one study, it was unclear; and three of them were assessed as high risk because the details on the methods used for randomisation were not described. All studies reported that blinding of the involved healthcare professionals was not possible due to the nature of the intervention (Supplementary Table 1).

3.4 Main outcome and meta-analysis

3.4.1. Primary outcomes

3.4.1.1. Haemoglobin at 24 hours of birth

When grouping 5 newborn studies ≥34 GA [26–28,30,34], no significant differences in initial haemoglobin values between the intervention and the control groups were observed (figure 2a and figure 2b). In another study [27], newborns between 34-37 GA proved to have increased

haemoglobin levels in the intervention group (PWMD 1.60 g/L [0.96-2.23]) relative to the the control group (Table 2 and Supplementary Table 2). In three studies that had ICC as the control group [26,27,30], it was observed that UCM was not related to an increase in haemoglobin relative to the control group. No significant differences were found when comparing the intervention group versus DCC (Table 2 and Supplementary Table 2).

3.4.1.2. Haemoglobin at 6 weeks

Six studies [27–29,31,33,34] evaluated haemoglobin levels at six weeks after birth in neonates with GA ≥34, and no significant differences were found between the intervention and the control group. However, in four studies on 885 ≥37 GA newborns [28,29,33,34], a significant decrease in haemoglobin levels at six weeks from birth was observed in the intervention group as compared to the control group (PWDM-0.16 g/L [-0.26 to -0.06]) (Figure 2c and figure 2d. Table 2 and Supplementary Table 2).

In the sub-analysis by control group, when comparing the intervention group with the ICC group, only one study [27] showed an increase in haemoglobin levels at six weeks (PWDM 1.10 g/L [0.73 to 1.47]). However, in five studies evaluating UCM versus DCC [28,29,31,33,34], haemoglobin levels at six weeks of birth were lower in the intervention group, as compared to the control group (PWDM-0.16 g/L [-0.26 to-0.06]) (Table 2 and Supplementary Table 2).

3.4.2. Secondary outcomes

3.4.2.1. Phototherapy

No significant differences in light therapy were observed between the intervention and control groups in four studies [26–28,33] (figure 2e and figure 2f. Table 2 and Supplementary Table 3).

3.4.2.2. Mean blood pressure

In three studies [26,27,29], mean blood pressure of the UCM group was significantly higher than in the control group (PWMD-2.87 mmHg [0.76 to 4.98]) (Table 2 and Supplementary Table 2).

3.4.2.3. APGAR scores at 1 minute

Only two studies [26,32] evaluated APGAR scores at 1 minute and found that this was higher in the intervention group than in the control group (PWMD-0.49 mmHg [0.04 to 0.94]) (Table 2 and Supplementary Table 2).

3.4.2.4. Other variables

No intergroup differences were found for the clinical observation of jaundice, haematocrit, serum bilirubin at 48 hours, Apgar scores at 5 minutes, ferritin at 6 weeks, and heart and respiratory rate at 30 minutes and 48 hours after birth (Table 2, Supplementary Table 2 and Supplementary Table 3).

3.4.6. Publication bias

No publication bias was observed in the study of any variable, although there were many outcomes with few studies, so it was not possible to evaluate the bias for all of them (Table 2).

4 DISCUSSION

The results of our meta-analysis showed that performing UCM in full-term and late preterm newborns (≥34 GA) was not globally related to the initial haemoglobin levels nor levels at six weeks. Neither was it related to the need for light therapy, haematocrit levels, nor the other studied variables, except for small, non-clinically relevant increases in Apgar at 1 minute and blood pressure scores with respect to the control groups.

As for the initial haemoglobin levels, no differences were found globally, by the type of control, nor in the ≥37 GA newborns group. The late preterm infants (34-37 GA) group sub-analysis was the only one associated with higher initial haemoglobin levels, although the data belonged to a single study. In addition, in this study, ICC defined the control group, so higher initial levels of haemoglobin could indeed be attributed to the type of control rather than to gestational age.

Another studied outcome was haemoglobin levels at 6 weeks. No differences were found either globally or in the late preterm infant group. However, lower haemoglobin levels were observed in the UCM group, as compared to the control group in those > 37 GA and when the control group was defined by DCC. By contrast, when the control group was defined by ICC, the outcomes showed higher values in the UCM group. These results could be explained by the technical superiority of DCC as compared to UCM and the superiority of UCM with respect to ICC. However, studies on this topic are scarce and their low number of study subjects prevents conclusive results.

Findings suggest that in cases when it is not possible to perform DCC, UCM may be an alternative method to consider. The placenta contains approximately 15 to 20 ml of blood per

kilogram of body weight, regardless of the birth weight [36] which, if UCM is performed, results in an increase in systemic blood volume, and therefore increased foetal haemoglobin, that could reduce the risk of anaemia among newborns [37,38].

Similarly, this increase in blood volume contributes to the physiological mechanisms that help the newborn transition from placental to neonatal circulation, which may help stabilise blood pressure and cardiovascular changes. This could explain the increase in mean blood pressure observed in the intervention group relative to the control group [39–41]. However, it is important to note that a mean difference of 2.87 mmHg may not have a clinically significant impact on the haemodynamic state of the newborn.

In our study, an increase in APGAR score at 1 minute was found in the intervention group, as compared to the control group, although this difference was likely not clinically relevant. As such, new trials are required to confirm this benefit since only two studies evaluated this variable. New studies that set cut-off points, such as Apgar scores <7, are required to help establish whether the differences have a clinically relevant impact on newborn health. Nevertheless, no differences were found between the Apgar scores at five minutes, and this is widely understood to be a more valuable assessment criterion of newborn wellbeing than one-minute Apgar. The need for phototherapy, neonatal jaundice, bilirubin levels, heart rate, and respiratory rate showed no differences among the study groups.

Several trials have been conducted demonstrating the advantages of DCC for the haematological status of full-term newborns, but there have been few trials that analyse the benefits of performing UCM. In our review, no superiority of the UCM technique over DCC is found. However, despite this, the authors of an Italian study on caesarean-born, term neonates suggested that if DCC cannot be performed, UCM may be considered as an alternative procedure to increase haemoglobin levels in the postnatal period and iron reserves in the

following weeks [42]. Some scientific societies, including the Royal College of Obstetricians and Gynaecologist (RCOG) [43] also see UCM as an alternative to late clamping in premature newborns, however they warn that further research is needed on its benefits and associated risks before the technique should be carried out systematically.

4.1 Strengths and limitations

The main strength of this systematic review and meta-analysis is that, to our knowledge, this is the first meta-analysis that only includes studies on full-term newborns and late preterm infants. In addition, the effect of UCM by subpopulations according to gestational age and type of controls, as well as the study of publication bias, have been analysed.

There are several limitations of our systematic review. The inclusion and exclusion criteria were of high variance, so there is heterogeneity in the study population. However, it was also observed that the measured variables varied widely between the different studies. Another limitation is the lack of standardisation of UCM practice among the studies, although the method was described in detail in most trials. Finally, based on the results of this review of ten studies, UCM may have beneficial effects. However, further research is needed before its widespread use can be recommended. As the current guidelines [12–16] recommend DCC, future studies should consider DCC as a control intervention, in addition to using more uniform inclusion and exclusion criteria and well-defined outcome measures for more reliable synthesis of the data.

4.2 Conclusions

The main conclusion drawn from our systematic review is that performing UCM does not appear to lead to significant differences in haematologic variables in late preterm infants and full-term newborns with respect to controls (ICC/DCC). However, small differences have been observed when stratifying by GA meta-analysis and type of control. UCM does not appear to present an increased risk of associated complications for the variables studies and could be considered as an alternative to DCC on those occasions when delayed cord clamping cannot be carried out. However, due to the low frequency with which some of these complications appear, and the low number of participants among the published studies, further research is needed to confirm the safety of this practice and its recommended use.

Disclosure of interest.

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REFERENCES

1. Boere I, Roest AAW, Wallace E, et al. Umbilical blood flow patterns directly after birth before Delayed cord clamping. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(2):F121-F125. doi:10.1136/archdischild-2014-307144

2. Farrar D, Airey R, Law GR, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: Weighing babies with cord intact. *BJOG An Int J Obstet Gynaecol*. 2011;118(1):70-75. doi:10.1111/j.1471-0528.2010.02781.x

3. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. *J Perinatol*. 2017;37(2):105-111. doi:10.1038/jp.2016.151

4. Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. *Obstet Gynecol*. 2017;129(1):e5-e10. doi:10.1097/AOG.0000000000001860

5. Fogarty M, Osborn DA, Askie L, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2018;218(1):1-18. doi:10.1016/j.ajog.2017.10.231

6. Mercer JS. Current best evidence: A review of the literature on umbilical cord clamping. *J Midwifery Women's Heal*. 2001;46(6):402-414. doi:10.1016/S1526-9523(01)00196-9

7. Airey RJ, Farrar D, Duley L. Alternative positions for the baby at birth before clamping the umbilical cord. *Cochrane database Syst Rev*. 2010;(10):CD007555. doi:10.1002/14651858.CD007555.pub2

8. Vatansever B, Demirel G, Ciler Eren E, et al. Is early cord clamping, delayed cord clamping or cord milking best? *J Matern Fetal Neonatal Med*. 2018;31(7):877-880. doi:10.1080/14767058.2017.1300647

9. Chaparro CM, Neufeld LM, Tena Alavez G, Eguia-Líz Cedillo R, Dewey KG. Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial. *Lancet*. 2006;367(9527):1997-2004. doi:10.1016/S0140-6736(06)68889-2

10. Raju TNK. Timing of umbilical cord clamping after birth for optimizing placental transfusion. *Curr Opin Pediatr*. 2013;25(2):180-187. doi:10.1097/MOP.0b013e32835d2a9e

11. Chaparro CM. Timing of umbilical cord clamping: Effect on iron endowment of the newborn and later iron status. *Nutr Rev*. 2011;69(SUPPL. 1). doi:10.1111/j.1753-4887.2011.00430.x

12. Grupo de trabajo de la Guía de Práctica Clínica sobre Atención al Parto Normal. *Guía de Práctica Clínica Sobre La Atención Al Parto Normal*. http://www.guiasalud.es/GPC/GPC_472_Parto_Normal_Osteba_compl.pdf.

13. National Institute for Health and Care Excellence. Intrapartum care for healthy women and babies. 2014. https://www.nice.org.uk/guidance/cg190/resources/intrapartum-care-for-healthy-women-and-babies-pdf-35109866447557.

14. WHO recommendations Intrapartum care for a positive childbirth experience. *World Heal Organ*. 2018. https://apps.who.int/iris/bitstream/handle/10665/260178/9789241550215-eng.pdf.

15. American College of Nurse Midwives. Delayed Umbilical Cord Clamping. http://www.midwife.org/ACNM/files/ACNMLibraryData/UPLOADFILENAME/000000000290/Delayed-Umbilical-Cord-Clamping-May-2014.pdf. Accessed January 24, 2019.

16. Committee on Obstetric Practice. Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. *Obstet Gynecol*. 2017;129(1):e5-e10. doi:10.1097/AOG.0000000000001860

17. Katheria AC. Umbilical Cord Milking: A Review. *Front Pediatr*. 2018;6:335. doi:10.3389/fped.2018.00335

18. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: a systematic review and meta-analysis. *JAMA Pediatr*. 2015;169(1):18-25. doi:10.1001/jamapediatrics.2014.1906

19. Basile S, Pinelli S, Micelli E, Caretto M, Benedetti Panici P. Milking of the Umbilical Cord in Term and Late Preterm Infants. *Biomed Res Int*. 2019;2019. doi:10.1155/2019/9185059

20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Ann Intern Med*. 2009;151(4):W. doi:10.7326/0003-4819-151-4-200908180-00136

21. Higgins JPT DJ (editors). Chapter 7: Selecting studies and collecting data. In: *Higgins JPT, Green S (Editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). The Cochrane Collaboration, 2011.* from www.cochrane-handbook.org.

22. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928-d5928. doi:10.1136/bmj.d5928

23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-

353 analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

354 24. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*.
355 2002;21(11):1539-1558. doi:10.1002/sim.1186

356 25. Egger M, Smith GD. Bias in location and selection of studies. *BMJ*.
357 1998;316(7124):61-66. doi:10.1136/bmj.316.7124.61

358 26. Erickson-Owens DA, Mercer JS, Oh W. Umbilical cord milking in term infants
359 delivered by cesarean section: A randomized controlled trial. *J Perinatol*.
360 2012;32(8):580-584. doi:10.1038/jp.2011.159

361 27. Upadhyay A, Gothwal S, Parihar R, et al. Effect of umbilical cord milking in term and
362 near term infants: randomized control trial. *Am J Obstet Gynecol*. 2013;208(2):120.e1-
363 6. doi:10.1016/j.ajog.2012.10.884

364 28. Yadav AK, Upadhyay A, Gothwal S, Dubey K, Mandal U, Yadav CP. Comparison of
365 three types of intervention to enhance placental redistribution in term newborns:
366 Randomized control trial. *J Perinatol*. 2015;35(9):720-724. doi:10.1038/jp.2015.65

367 29. Jaiswal P, Upadhyay A, Gothwal S, Chaudhary H, Tandon A. Comparison of
368 Umbilical Cord Milking and Delayed Cord Clamping on Cerebral Blood Flow in Term
369 Neonates. *Indian J Pediatr*. 2015;82(10):890-895. doi:10.1007/s12098-015-1734-2

370 30. Bora R, Akhtar SS, Venkatasubramaniam A, Wolfson J, Rao R. Effect of 40-cm
371 segment umbilical cord milking on hemoglobin and serum ferritin at 6 months of age
372 in full-term infants of anemic and non-anemic mothers. *J Perinatol*. 2015;35(10):832-
373 836. doi:10.1038/jp.2015.92

374 31. Agarwal S, Jaiswal V, Singh D, Jaiswal P, Garg A, Upadhyay A. Randomised control
375 trial showed that delayed cord clamping and milking resulted in no significant

differences in iron stores and physical growth parameters at one year of age. *Acta Paediatr Int J Paediatr*. 2016;105(11):e526-e530. doi:10.1111/apa.13559

32. Girish M, Jain V, Dhokane R, Gondhali SB, Vaidya A, Aghai ZH. Umbilical cord milking for neonates who are depressed at birth: a randomized trial of feasibility. *J Perinatol*. 2018;38(9):1190-1196. doi:10.1038/s41372-018-0161-4

33. Hazem F El Shahawy. Milking Versus Delayed Cord Clamping in Full Term Neonates - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02454101?cond=Milking+Versus+Delayed+Cord+Clamping+in+Full+Term+Neonates&draw=2&rank=1. Accessed November 1, 2019.

34. Alzaree F, Elbohoty A, Abdellatif M. Early versus delayed umbilical cord clamping on physiologic anemia of the term newborn infant. *Open Access Maced J Med Sci*. 2018;6(8):1399-1404. doi:10.3889/oamjms.2018.286

35. Zanardo V, Guerrini P, Severino L, Simbi A, Parotto M, Straface G. A Randomized Controlled Trial of Intact Cord Milking versus Immediate Cord Clamping in Term Infants Born by Elective Cesarean Section. *Am J Perinatol*. October 2019. doi:10.1055/s-0039-1697673

36. Brune T, Garritsen H, Witteler R, et al. Autologous Placental Blood Transfusion for the Therapy of Anaemic Neonates. *Neonatology*. 2002;81(4):236-243. doi:10.1159/000056754

37. Linderkamp O. Placental transfusion: Determinants and effects. *Clin Perinatol*. 1982;9(3):559-592. doi:10.1016/s0095-5108(18)31013-3

38. Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive

guidelines for red blood cell transfusion in preterm infants. *Pediatrics*. 2005;115(6):1685-1691. doi:10.1542/peds.2004-1884

39. Duley L, Dorling J, Gyte G. When should the umbilical cord be clamped? *BMJ*. 2015;351. doi:10.1136/bmj.h4206

40. Gunther M. The transfer of blood between baby and placenta in the minutes after birth. *Obstet Gynecol Surv*. 1957;12(6):840-843. doi:10.1016/S0140-6736(57)92302-4

41. Mercer JS, Skovgaard RL. Neonatal transitional physiology: a new paradigm. *J Perinat Neonatal Nurs*. 2002;15(4):56-75. http://www.ncbi.nlm.nih.gov/pubmed/11911621. Accessed November 3, 2019.

42. Perrone B, Ghirardello S, "Italian Survey on Placental Transfusion Group." Placental Transfusion Strategies in Italy: A Nationwide Survey of Tertiary-Care Delivery Wards. *Am J Perinatol*. 2017;34(7):722-728. doi:10.1055/s-0036-1597995

43. Royal College of Obstetricians and Gynaecologists. *Clamping of the Umbilical Cord and Placental Transfusion*.; 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/sip-14.pdf. Accessed April 10, 2019.

Figure 1: PRISMA flow diagram of the literature review process

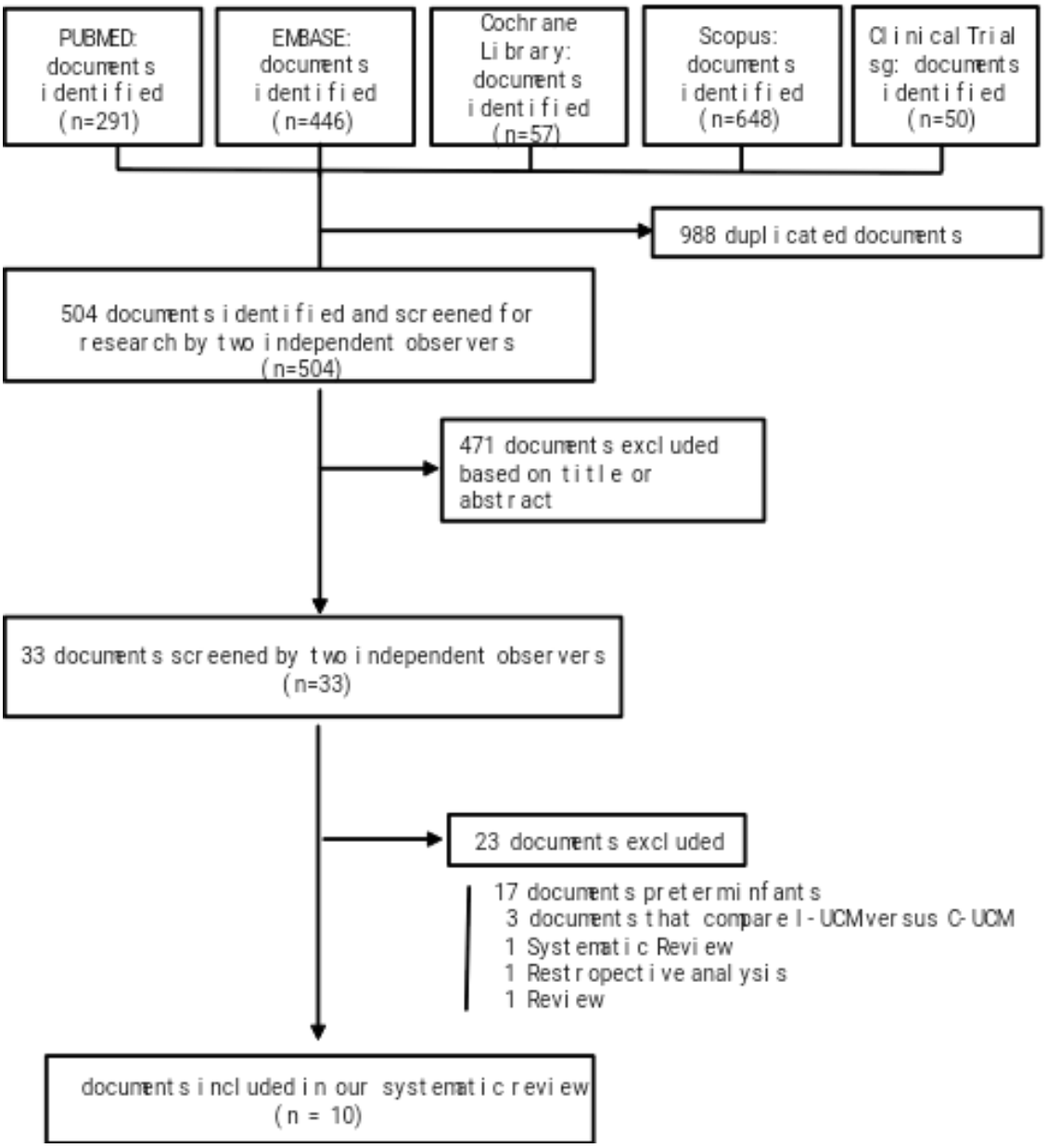

Figure 2: Forest Plot Main outcome and meta-analysis (2a-2f)

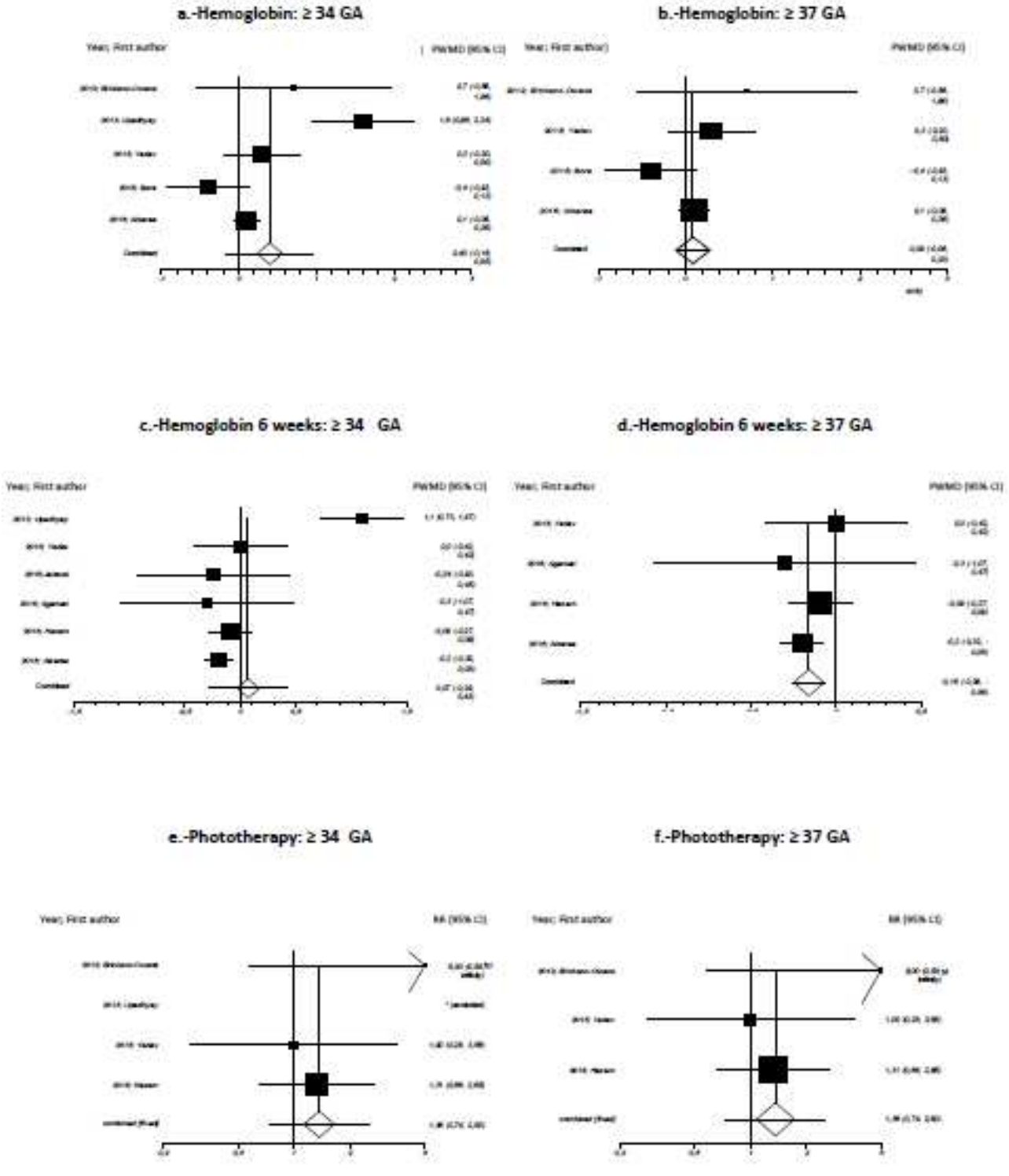

Table 1. Characteristics of the included studies.

Author	Year	N	Country	Gestational age	UCM No. of times	UCM Speed	Control Condition	Exclusion Criteria
Erickson-Owens	2012	24	Rhode Island (USA)	37-41$^{6/7}$wk	5	-	ICC	Maternal medical and obstetric complications, severe anaemia (⩽9.0 g dl^{-1} Hb), clotting disorders and suspected intrauterine growth restriction. Women who smoked in pregnancy or who were non-English speakers were excluded. After delivery, the infant was excluded if there was a confirmed diagnosis of intrauterine growth restriction or serious congenital anomalies.
Upadhyay	2013	200	North India	>34^{6}wk	3	10 cm within 1s	ICC	Short umbilical cord length (<25 cm), limp at birth, non-vigorous and born through meconium-stained liquor, delivery by caesarean section for fetal compromise, multiple births, delivery to Rh-negative mothers, major congenital anomalies, cord prolapse, hydrops fetalis, placenta previa, placental abruption, and cord abnormalities such as true knots.
Yadav	2015	300	Northern India	≥ 37wk	3	10 cm within 1s	DCC, DCM	Umbilical cord length <25 cm, non-vigorous babies with or without meconium-stained liquor, multiple births (twins, triplets), babies of Rh-negative mothers, babies of retrovirus positive mothers, babies born with any major congenital anomalies, cord prolapse and cord anomalies such as true knots.

Jaiswal	2015	200	India	>36 wk	3	10 cm within 1s	DCC	Length of umbilical cord <25cm, non-vigorous babies, multiple births (twins, triplets), babies of Rh negative and retrovirus positive mothers, antenatally diagnosed major congenital anomalies, cord prolapse, hydrops fetalis and cord anomalies like true knots.
Bora	2015	179	Northeast India	37-41[6] wk	3	-	ICC	Mothers with Rh negative blood group, haemolytic anaemia, those on medications, such as anticonvulsants, insulin, thyroxin and steroids, and those having obstetrical problems, such as preeclampsia, eclampsia and diabetes mellitus, prolonged rupture of membranes, confirmed or suspected infection and those with foetal malformations.
Agarwal	2016	161	Northern India	37-41wk	3	10 cm within 1s	DCC	Cases were excluded from the study if the time exceeded 30 seconds of the cord cut.
Hazem	2016	300	El Cairo (Egypt)	>37 wk	5	-	DCC	Known congenital anomalies of foetus, Rhesus sensitisation, foetal hydrops, medical disorder (preeclampsia - diabetes mellitus - hypertension - SLE), need for urgent resuscitation and multiple pregnancies.
Girish	2018	101	India	≥ 35wk	3	-	DCC	Congenital malformation of central nervous system, chromosomal abnormalities, major congenital malformations, and culture positive early onset sepsis.
Azaree	2018	250	El Cairo (Egypt)	≥ 37wk	5	-	DCC	Mothers with twins pregnancy, preterm delivery (< 37 weeks, patient should be sure of date and date confirmed by ultrasound, e.g. biparietal diameter and femur length), prolonged rupture of membranes (> 18 hours), fever, or foul smelling liquor, antepartum haemorrhage, pregnancy-induced hypertension or diabetes mellitus and history of maternal liver or kidney disease or any other systemic illness.

Zanardo	2019	130	AbanoTerme, (Italy)	39-40$^{0}/^{7}$	3	-	ICC	Diagnosis of intrauterine growth restriction or serious congenital anomalies or NICU admission, Rh, or major ABO isoimmunisation indexed by a positive direct antiglobulin test, and drugs administered to the infants. Neonates were also excluded if an umbilical artery blood sample for blood gas analysis and contemporary Hct levels was not or incorrectly obtained.

Abbreviations: ICC, immediate cord clamping; DCC, delayed cord clamping; UCM, umbilical cord milking.; DCM, DCC with milking the cut cord.

Table 2. Comparison of Umbilical Cord Milking vs Control Intervention

Outcome	Gestational age	No of studies	No of participants	RR (95% CI)[b]	MD (95% CI)[b]	I^2 Value, %	Cochran's Q	Egger bias
Haemoglobin	≥34 weeks	5	853		0.40 (-0.16 to 0.95)*	**84.2% (57.3-91.5)****	**<0.001**	0.469
	≥37 weeks	4	653		0.09 (-0.06 to 0.23)	39.0% (0-78.9)	0.178	0.946
	34-37 weeks	1	200		**1.60 (0.96 to 2.23)**	NC	NC	NC
	Control ICC	3	403		0.62 (-0.81 to 2.05)*	NC	<0.001	0.716
	Control DCC	2	450		0.12 (-0.03 to 0.27)	NC	0.455	NC
Haemoglobin 6 weeks	≥34 weeks	6	1255		0.07(-0.29 to 0.43)*	**88.4% (76.1-92.9)****	**<0.001**	0.449
	≥37weeks	4	885		**-0.16 (-0.26 to -0.06)**	0.0% (0-67.9)	0.650	0.657
	34 -37weeks	2	370		0.46 (-0.85 to 1.77)*	NC	**<0.001**	NC
	Control ICC	1	170		**1.10 (0.73 to 1.47)**	NC	NC	NC
	Control DCC	5	1085		**-0.16 (-0.26 to -0.06)**	0.0% (0-64.1)	0.792	0.780
Phototherapy	≥34 weeks	4	712	1.36 (0.74-2.50)		0.0% (0-72.9)	0.619	0.534
	≥37weeks	3	512	1.36 (0.74-2.50)		0.0% (0-77.9)	0.619	NC
	34-37weeks	1	200	NC		NC	NC	NC
	Control ICC	2	224	5.00 (0.26-95.07)		NC	NC	NC
	Control DCC	2	488	1.24 (0.66-2.32)		NC	0.726	NC
Clinical observation of jaundice	≥34weeks	2	224	0.63 (0.07-5.26)*		NC	0.005	NC
Haematocrit	≥34 weeks	3	354		0.49 (-0.55 to 1.54)	23.7% (0-78.7)	0.270	NC
Mean blood pressure	≥34 weeks	3	424		**2.87 (0.76 to 4.98)**	0.0% (0-72.9)	0.608	NC
Serum Bilirubin	≥34 weeks	4	554		0.33 (-0.05 to 0.73)	0.0% (0-67.9)	0.478	0.737
Apgar scores 1 minute	≥34 weeks	2	125		**0.49 (0.04 to 0.94)**	NC	0.276	NC
Apgar scores 5 minutes	≥34 weeks	3	413		0.11 (-0.31 to 0.53)*	**87.8% (51.1-94.2)****	**0.003**	NC

Ferritin 6 weeks	≥34 weeks	3	327	-8.40 (-26.30 to 9.50)*	**97.3% (95.5-98.2)****	**<0.001**	NC
Heart rate 30 min	≥34 weeks	2	400	0.11 (-1.61 to 1.84)	NC	0.143	NC
Heart rate 48 h	≥34 weeks	2	400	1.17 (-0.66 to 3.01)	NC	0.862	NC
Respiratory rate 30 min	≥34 weeks	2	400	-0.17 (-1.66 to 1.32)	NC	0.513	NC
Respiratory rate 48 h	≥34 weeks	2	400	0.83 (-0.54 to 2.22)	NC	0.544	NC

NR: Not reported; NR: Not calculated; CI: Confidence Interval. *Random effects (DerSimonian-Laird).** I^2 >50% correspond to large heterogeneity.

Appendix 1. Search strategies

Database	Search Strategies	Hits
Pubmed	(stripping[All Fields] OR milking[All Fields] OR squeezing[All Fields]) AND (("umbilicus"[MeSH Terms] OR "umbilicus"[All Fields]) OR ("umbilical cord"[MeSH Terms] OR ("umbilical"[All Fields] AND "cord"[All Fields]) OR "umbilical cord"[All Fields]) OR ("cone-rod dystrophies"[MeSH Terms] OR ("cone-rod"[All Fields] AND "dystrophies"[All Fields]) OR "cone-rod dystrophies"[All Fields] OR "cord"[All Fields]))	291
Embase	('stripping'/exp OR stripping OR 'milking'/exp OR milking OR squeezing) AND ('umbilicus'/exp OR umbilicus OR 'umbilical cord'/exp OR 'umbilical cord' OR (('umbilical'/exp OR umbilical) AND cord) OR cord)	446
Scopus	(***stripping*** OR ***milking*** OR ***squeezing***) AND (***umbilicus*** OR ***umbilical*** AND ***cord*** OR ***cord***)	648
Clinicaltrials	(stripping OR milking OR squeezing) AND (umbilical cord OR cord)	50
Cochrane Library plus	(*stripping* OR *milking* OR *squeezing*) AND (*umbilicus* OR *umbilical* AND *cord* OR *cord*)	57

Supplementary table 1. Assessment of the risk of bias. Information sources comments by reviewers

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment	Incomplete outcomes data (attrition bias)	Selective reporting (reporting bias)	Other bias
	Unclear	**Unclear**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**
Erickson-Owens DA; 2012 Randomised controlled trial Oct 2008 – Jan 2009 N = 24 (12:12)	Randomisation card was opened how this card was performed is not reported)	(No information available on envelopes being sealed, opaque, numbered …)	Not blinded: Obstetrician, paediatrician and staff (It is only reported that they did not know about the intervention and that those who knew about it, did not report it)	Blinded: Nursery and lab staff. In addition, those variables measured as main outcome are Hb and haematocrit, whose measurement does not depend on blinding	Only 1 loss in cord milking Follow up: 36 – 48 hours		
	Low Risk	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**
Upadhyay A; 2013 Randomised controlled trial April 2010 – Sept 2011	Computer generated random numbers in blocks of 4. These numbers were divided	Serially numbered opaque sealed envelopes	It reports not being possible for researchers or clinicians.	The variables measured as main outcome are analytical, so its	14 losses in intervention group		

N = 200 (100:100)	into 2 groups based on whether the random number was odd or even.			measurement does not depend on blinding.	15 losses in control group Follow up: 6 weeks		
	Low Risk	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**
2015; Yadav Randomised controlled trial Jan 2014 – Dec 2014 N = 300 (100:100:100)	Generated random number list in sequentially using an online software	Numbered, opaque, sealed envelopes,	Not blinded: Primary investigator and neonatal team	Blinded: Study participants and lab investigators	UCM: 7 losses DCC 7 losses DCM: 5 losses Follow up: 6 weeks		
	Low Risk	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**
2015; Jaiswal Randomised controlled trial Aug 2012 – Aug 2013 N = 200 (100:100)	Computer generated random numbers in blocks of 8.	Serially numbered opaque sealed envelopes	Not blinded: Clinicians	Blinded: Lab investigator, NICU staff, and radiologist	Follow up: 24 – 48 hours		
2015; Bora	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**	**Low Risk**

Randomised controlled trial July 2012 – June 2013 N = 200 (50:50:50:50)	Computer generated random numbers	Opaque sealed envelopes	Not blinded: Clinicians	Blinded: Nursery, follow up providers, and lab staff.	Anaemia milk: 5 losses Anaemia non-milk: 6 losses No anaemia milk: 5 losses No anaemia, no milk: 5 losses Follow up: 6 months		
2016; Agarwal Randomised controlled trial Aug 2013 – Aug 2014 N = 200 (100:100)	**Low Risk** Trial follow-up ("*we used computer-generated random numbers in blocks of 8*")	**Low Risk** Sealed, numbered opaque envelopes	**Low Risk** Not blinded: Clinicians	**Low Risk** Blinded: Staff, researchers involved	**Low Risk** UCM: 17 losses DCC: 22 losses Follow-up: 1 year	**Low Risk**	**Low Risk**
2016; Hazem Randomised controlled trial Aug 2015 – March 2016 N = 300 (150:150)	**High Risk** No information	**High Risk** No information	**Low Risk** Masking: Single (Outcomes Assessor)	**Low Risk** Masking: Single (Outcomes Assessor)	**Low Risk** Started: 300 (UCM 150; DCC 150)	**Low Risk**	**Low Risk**

					Completed: 292 (UCM 145: DCC147) Reason Not Completed: Adverse Event (UCM 2; DCC 3) and Lost to Follow-up (UCM 3: DCC 4)		
	High Risk	**High Risk**	**Low Risk**	**Unclear***	**Low Risk**	**Low Risk**	**Low Risk**
Girish; 2018 Quasi-randomised controlled Jan 2015 – Oct 2016 N = 101 (50:51)	We choose to randomise neonates based on their months of birth. Infants born during even months (February, April, June, August, October, and December) were included in the UCM group, and those born during odd months (January, March, May, July, September, and	No information	Non-blinded	Non-blinded. (Analyst could have been blinded)	UCM: 12 losses Control: 8 losses		

	November) were assigned to the control group.						
	High Risk	**High Risk**	**Unclear**	**Unclear**	**Low Risk**	**Low Risk**	**Low Risk**
2018; Azaree Randomised controlled trial June 2017 – Dec 2017 N = 250 (125:125)	No information	No information	No information	No information	No losses		
	Low Risk	**Unclear**	**Unclear**	**Unclear**	**Low Risk**	**Low Risk**	**Low Risk**
2019; Zanardo Randomised controlled trial Oct 2018 – Jan 2019 N = 130 (65:65)	Just before surgery, a randomisation card was opened by the investigator, who informed the obstetrician of the group assignment: ICC or intact UCM, the intervention group.	(It is not reported whether the randomisation card was opaque, sealed, numbered…)	No information	No information	167 women were admitted for a term elective Caesarean section. Overall, 130 women and their foetuses were enrolled and randomised, and all women/infant pairs completed		

	the haematological study,

Supplementary Table 2. Quantitative variables subjected to study in full-term and late preterm infants

Author	Haemoglobin		Haematocrit		Mean blood pressure		Ferritin 6 weeks		Serum Bilirubin		Haemoglobin 6 weeks	
	Milking	Control	Milking	Control	Milking	Control	Milking	Control	Milking	Control	Milking	Control
2012; Erickson-Owens	15.3 (1.8)	14.6 (1.3)	47.5 (6.1)	45.2 (4.1)	57 (9)	51 (10)	NR	NR	12.4 (2.1)	11.8 (3.8)	NR	NR
2013; Upadhyay	15.1 (2.5)	13.5 (2.1)	NR	NR	51.6 (11.3)	48.4 (10.7)	355.9 (182.6)	177.5 (135.8)	7.4 (3.1)	6.6 (2.3)	11.9 (1.5)	10.8 (0.9)
2015; Yadav	16.5 (1.8)	16.2 (1.8)	49.9 (5.4)	48.8 (5.5)	NR	NR	190.73 (94.35)	257.86(94.88)	7.2 (2.4)	7.2 (2.4)	10.8 (1.4)	10.8 (1.5)
2015; Jaiswal	NR	NR	NR	NR	64.39 (10.85)	62.40 (11.84)	NR	NR	NR	NR	11.03 (2.37)	11.27 (2.62)
2015; Bora	14.4 (1.8)	14.8 (1.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2016; Agarwal	NR	NR	NR	NR	NR	NR	134 (89.8)	142.7 (87)	NR	NR	11 (2.4)	11.3 (2.6)
2016; Hazem	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	11.86 (0.71)	11.95 (0.88)
2018; Girish	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2018; Azaree	15.9 (0.6)	15.8 (0.7)	NR	NR	NR	NR	NR	NR	NR	NR	10.4 (0.5)	10.6 (0.5)
2019; Zanardo	NR	NR	44.5(4.8)	44.9(4.2)	NR	NR	NR	NR	7.4(2.1)	7.1(1.8)	NR	NR
Egger's Bias(p-value)	0.469		NC		NC		NC		0.737		0.449	
I^2 95% CI	**84.2% (57.3-91.5)**		23.7% (0-78.7)		0.0% (0-72.9)		**97.3% (95.5-98.2)**		0.0% (0-67.9)		**88.4% (76.1-92.9)**	
Cochran's Q(p-value)	**<0.001**		0.270		0.608		**<0.001**		0.478		**<0.001**	
PWMD IC 95%	0.40 (-0.16 to 0.95)[b]		0.49 (-0.55 to 1.54)[a]		**2.87 (0.76 to 4.98)[a]**		-8.40 (-26.30 to 9.50)[b]		0.33 (-0.05 to 0.73)[a]		0.07(-0.29 to 0.43)[b]	

NR: Non reported; NR: Not calculated; CI: Confidence Interval. [a]Mantel-Haenszel fixed effect. [b]Random effects Model (DerSimonian-Laird)

Author	Apgar scores 1 minute		Apgar scores 5 minutes		HR at 30 min		HR at48 h		RR at 30 min		RR at 48h	
	Milking	**Control**	**Milking**	**Control**	**Milking**	**Control**	**Milking**	**Control**	**Milking**	**Control**	**Milking**	**Control**
2012; Erickson-Owens	8 (0.61)	7.75(0.91)	8.75 (0.30)	8.75 (0.30)	NR	NR	NR	NR	NR	NR	NR	NR
2013; Upadhyay	NR	NR	NR	NR	139.0 (10.0)	137.5 (8.2)	135.3 (15.0)	134.4 (10.6)	43.3 (6.2)	43.9 (7.9)	41.9 (6.1)	41.4 (6.6)
2015; Yadav	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2015; Jaiswal	NR	NR	NR	NR	143.28 (8.00)	144.37 (8.98)	127.43 (7.66)	126.16 (7.71)	47.56 (10.98)	47.16 (3.85)	33.74 (10.72)	32.36 (3.82)
2015; Bora	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2016; Agarwal	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2016; Hazem	NR	NR	8.73 (0.58)	8.26 (0.66)	NR	NR	NR	NR	NR	NR	NR	NR
2018; Girish	5 (1.78)	4.25 (1.55)	7 (1.33)	7.25 (1.11)	NR	NR	NR	NR	NR	NR	NR	NR
2018; Azaree	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2019; Zanardo	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
EggerBias (p-value)	NC		NC		NC		NC		NC		NC	
I^2 95% CI	NC		**87.8% (51.1-94.2)**		NC		NC		NC		NC	
Q Cochran (p-value)	0.276		**0.003**		0.143		0.862		0.513		0.544	
PWMD IC 95%	**0.49 (0.04 to 0.94)**		0.11 (-0.31 to 0.53)*		0.11 (-1.61 to 1.84)		1.17 (-0.66 to 3.01)		-0.17 (-1.66 to 1.32)		0.83 (-0.54 to 2.22)	

HR, heart rate per minute; RR, respiratory rate per minute.PWMD: Pooled weighted mean difference; NR: Non reported; Not calculated; [a]Mantel-Haenszel fixed effect.[b]Random effects Model (DerSimonian-Laird).

Supplementary Table 3. Categorical variables subjected to study in full-term and late preterm infants

Author	Transfusion		Phototherapy		Oxygen at birth		Clinicalobservation of jaundice		Hipot. Drugs		Hipot. Expanders		Mortality	
	Milking	Control	Milking	Control	Milking	Control	Milking	Control	Milking	Control	Milking	Control	Milking	Control
2012;Erickson-Owens	0/12	0/12	2/12	0/12	5/12	8/12	12/12	10/12	NR	NR	NR	NR	NR	NR
2013; Upadhyay	NR	NR	0/100	0/100	NR	NR	14/100	8/100	NR	NR	NR	NR	NR	NR
2015; Yadav	NR	NR	4/100	4/100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2015; Jaiswal	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2015;Bora	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2016; Agarwal	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2016; Hazem	NR	NR	16/145	12/143	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2018; Girish	NR	NR	NR	NR	NR	NR	NR	NR	6/50	5/51	4/50	3/51	4/50	3/51
2018; Azaree	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
2019; Zanardo	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
EggerBias (p-value)	NC		0.534		NC		NC		NC		NC		NC	
I^2 95% CI	NC		0.0% (0-72.9)		NC		NC		NC		NC		NC	
Q Cochran (p-value)	NC		0.619		NC		0.005		NC		NC		NC	
RR 95% CI	NC		1.36 (0.74-2.50)		**NC**		0.63 (0.07-5.26)*		NC		NC		NC	

Supplementary figure 1: Risk of Bias Assessment