# Umbilical cord milking in preterm infants: a systematic review and meta-analysis

Haribalakrishna Balasubramanian,[1] Anitha Ananthan,[2] Vaibhav Jain,[1] Shripada C Rao,[3] Nandkishor Kabra[1]

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[1]Department of Neonatology, Surya Hospitals, Mumbai, Maharashtra, India
[2]Department of Neonatology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India
[3]Department of Neonatology, Perth Children's Hospital, Nedlands, Western Australia, Australia

**Correspondence to**
Dr Anitha Ananthan, Neonatology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India; ani.gem81@gmail.com

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## ABSTRACT

**Objective** To conduct a systematic review and meta-analysis of the efficacy and safety of umbilical cord milking in preterm infants.

**Design** Randomised controlled trials comparing umbilical cord milking with delayed cord clamping/immediate cord clamping in preterm infants were identified by searching databases, clinical trial registries and reference list of relevant studies in November 2019. Fixed effects model was used to pool the data on various clinically relevant outcomes.

**Main outcome measures** Mortality and morbidities in preterm neonates.

**Results** Nineteen studies (2014 preterm infants) were included. Five studies (n=922) compared cord milking with delayed cord clamping, whereas 14 studies (n=1092) compared milking with immediate cord clamping. Cord milking, as opposed to delayed cord clamping, significantly increased the risk of intraventricular haemorrhage (grade III or more) (risk ratio (RR): 1.95 (95% CI 1.01 to 3.76), p=0.05). When compared with immediate cord clamping, cord milking reduced the need for packed RBC transfusions (RR:0.56 (95% CI 0.43 to 0.73), p<0.001). There was limited information on long-term neurodevelopmental outcomes. The grade of evidence was moderate or low for the various outcomes analysed.

**Conclusion** Umbilical cord milking, when compared with delayed cord clamping, significantly increased the risk of severe intraventricular haemorrhage in preterm infants, especially at lower gestational ages. Cord milking, when compared with immediate cord clamping, reduced the need for packed RBC transfusions but did not improve clinical outcomes. Hence, cord milking cannot be considered as placental transfusion strategy in preterm infants based on the currently available evidence.

## What is already known on this topic?

- Umbilical cord milking from the placental side towards the newborn is an alternative to placental transfusion from delayed cord clamping.
- Cord milking has shown to be feasible in infants requiring resuscitation at birth.
- Umbilical cord milking has shown to improve haemoglobin levels and short-term clinical outcomes in preterm infants.

## What this study adds?

- Placental transfusion through cord milking, as compared to delayed cord clamping, significantly increased the risk of severe intraventricular haemorrhage in preterm infants <34 weeks of gestation.
- When compared to immediate cord clamping, cord milking significantly reduced the need for packed RBC transfusions but did not result in improved clinical outcomes.

When the umbilical cord is clamped immediately after birth (ie, immediate cord clamping, ICC), a significant amount of the fetal blood remains in the placenta leading to relatively lower red blood cell (RBC) volume in the newborn infant. Delayed cord clamping (DCC) and umbilical cord milking (UCM) are two main placental transfusion strategies in the delivery room to increase the RBC volume of neonates. DCC involves delaying the clamping of the cord for 30–180 s after birth or until the cessation of cord pulsations. On the other hand, UCM consists of gently grasping the umbilical cord and squeezing it from the placental end towards the infant. While UCM is usually performed before clamping the umbilical cord (intact UCM), milking after clamping and cutting of the umbilical cord (cut UCM) has also been reported.[1]

Systematic reviews[2 3] have reported that DCC, when compared with ICC reduces the incidence of mortality, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and need for blood transfusions in preterm infants. Hence, many professional organisations have endorsed DCC as a standard delivery room practice for vigorous preterm infants.[4 5] However, DCC could be difficult to implement in critically ill and apneic preterm infants in the delivery room needing resuscitation. Hence, UCM has been investigated as a potential alternative to DCC because resuscitative measures can proceed shortly after delivery.

Systematic reviews comparing UCM with immediate/delayed cord clamping have reported that UCM lowered the incidence of IVH, mortality and the need for oxygen at 36 weeks postmenstrual age, among preterm infants.[6 7] However, results from a recent large trial suggested an increased risk of severe IVH with cord milking when compared with DCC, especially in extremely preterm infants.[8]

Majority of the trials on cord milking were not powered to assess mortality and other important



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morbidities. The impact of this intervention on long-term neurodevelopment of preterm infants is also unclear. There is a need to synthesise available evidence to inform clinical practice and the design of future clinical trials. Hence, we conducted this systematic review to evaluate the efficacy and safety of UCM in preterm infants.

## METHODS

Guidelines from the Cochrane Neonatal Review Group, Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were used for conducting and reporting this systematic review.[9]

### Eligibility criteria

Randomised controlled trials (RCTs) comparing UCM with DCC/ICC were included in the review.

### Types of participants

Studies done in preterm infants born at a gestational age (GA) <37 weeks were included.

### Intervention

I-UCM or C-UCM at birth.

### Comparison

DCC or ICC.

The following analyses were planned: (1) intact UCM (I-UCM) vs DCC; (2) I-UCM vs ICC; (3) cut UCM (C-UCM) vs ICC/DCC.

### Outcomes

(1) All-cause mortality, (2) IVH (all grades), (3) severe IVH (grade III or more), (4) patent ductus arteriosus (PDA) needing treatment, (5) NEC (stage not reported), (6) definite NEC (stage II or more on modified Bell staging), (7) retinopathy of prematurity (ROP) all stages, (8) ROP needing intervention, (9) periventricular leukomalacia, (10) bronchopulmonary dysplasia (BPD), (11) need for packed RBCs during NICU stay, (12) need for phototherapy, (13) duration of hospital stay and (14) neurodevelopmental outcomes at 24 months.

### Search strategy

The databases MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and clinical trial registries were searched in November 2019. 'Google Scholar' was searched for articles that might not have been cited in the standard medical databases. The reference lists of eligible studies and review articles were searched to identify additional studies. Reviewers HB, AA, VJ and SCR conducted the literature search independently. All the authors of the included studies were contacted through emails to obtain additional data and clarification of methods. The search criteria for this systematic review have been included in the supplement file.

### Study selection

The studies were assessed for eligibility by reviewers HB, AA, VJ and SCR independently using the predefined eligibility criteria and data were extracted using a data collection form designed for this review. Care was taken to ensure that multiple publications of the same study were excluded to avoid data duplication. Discrepancies during the data extraction process were resolved by group discussion.

### Assessment of risk of bias

Risk of bias (ROB) was assessed using the Cochrane 'Risk of Bias Assessment Tool'.[10] Authors HB and AA independently assessed the ROB in all domains including random number generation, allocation concealment, blinding of intervention and outcome assessors, completeness of follow-up, selectivity of reporting and other potential sources of bias. For each domain, the ROB was assessed as low, high or unclear risk based on the Cochrane Collaboration guidelines.

### Assessment of quality of evidence

The key information concerning the quality of evidence, based on the (1) sample size for clinically important outcomes, (2) magnitude and precision of the treatment effect of the intervention, (3) ROB, (4) directness of evidence, (5) consistency of results (statistical heterogeneity), has been presented as per GRADE guidelines (Grades of Recommendation, Assessment, Development and Evaluation).[11]

### Data synthesis

Meta-analysis was conducted using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre). Fixed effects model (FEM) was used. Random effects model (REM) analysis was conducted to recheck the results if there was significant statistical heterogeneity on FEM. Effect size was expressed as risk ratio (RR) and 95% CIs. Statistical heterogeneity was assessed by the $I^2$ statistic and was interpreted as per the Cochrane handbook guidelines.[12] Publication bias could not be assessed since the meta analyses for the outcomes included less than 10 studies.[13] We used the method described by Wan *et al* to estimate mean and SD for the continuous outcomes that were primarily reported as median and range/IQR in the individual studies.[14]

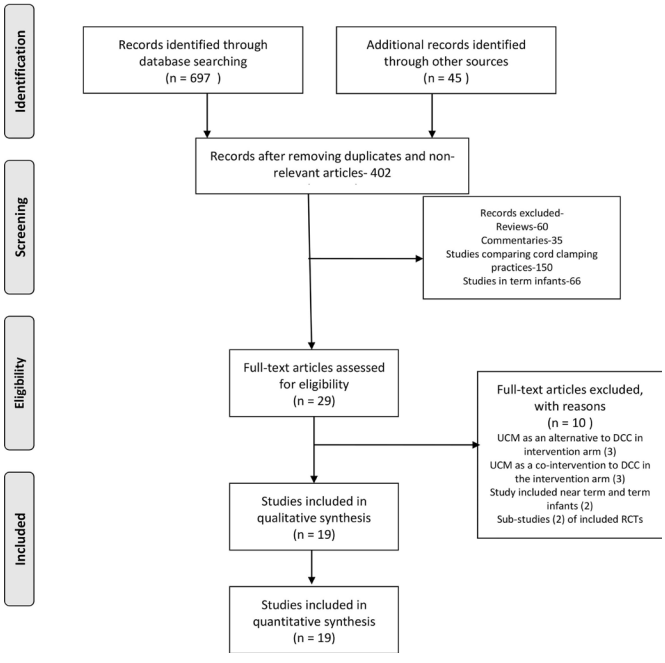


**Figure 1** Flow diagram of study selection process. DCC, delayed cord clamping; UCM, umbilical cord milking.



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**Table 1** Characteristics of the included studies

| Study ID | Patient population | Mean/median GA (weeks) mean birth weight (g) | Intervention vs Control sample size | Baseline characteristics | Primary outcome |
|---|---|---|---|---|---|
| *UCM vs DCC* | | | | | |
| Rabe *et al*[17] | 24–32 $^{6/7}$ weeks | 29.5±2.7 vs 29.2±2.3 weeks<br>1235±468 vs 1263±428 g | I-UCM vs DCC<br>58 (27 vs 31) | CS: 78% vs 58%<br>Resuscitation:<br>Intubation: 55% vs 52%<br>APGAR at 5 min: 8 vs 9 | Hematocrit and haemoglobin at 1 hour after birth (I-UCM vs DCC): 0.52 vs 0.51, p=0.65 and 17.5 g/L vs 17.3 g/L, p=0.71 |
| Rabe *et al*[45] | | Follow-up of Rabe 2011 at 2 years and 3.5 years | I-UCM vs DCC<br>39 (22 vs 17) at 2 years<br>29 (18 vs 11) at 3.5 years | | 2--year Bayley III scores (I-UCM vs DCC): cognitive: 119±17.5 vs 111±25.7, p=0.08; language: 108±18.3 vs 95±21.5, p=0.05; motor: 105±14.8 vs 102±18.8, p=0.39<br>3.5 years: Bayley III scores: cognitive: 127±19.8 vs 120±26.6, p=0.62; language: 115±18.1 vs 106±22.8, p=0.11; motor: 114±23.0 vs 108±20.9, p=0.3 |
| Katheria *et al*[16] | 23–31 $^{6/7}$ weeks | 28±2 vs 28±2 weeks<br>1255±413 vs 1132±392 g | I-UCM vs DCC<br>154 (CS delivered)<br>(75 vs 79) | CS rate 100%.<br>Resuscitation details:<br>IPPV : 57% vs 56%<br>Intubation: 28% vs 33%<br>APGAR at 1, 5 min: 5,7 | SVC flow with in first 12 hours (I-UCM vs DCC): 93 vs 81 mL/kg/min, p<0.05 |
| Katheria *et al*[46] | | Follow-up study of Katheria 2015 at 22–26 months of age | I-UCM vs DCC<br>135 (70 vs 65) | | At 22–26 months (I-UCM vs DCC): Bayley III scores: cognitive: 100±13 vs 95±12, p=0.031; language: 93±15 vs 87±13, p=0.013; motor: 99±12 vs 97±12, p=0.349 |
| Shirk *et al*[18] | 23–34 weeks | 32.1 (29.5 to 34) vs 32.0 (29.2 to 34) weeks<br>1620±587 vs 1579±576 g | I-UCM vs DCC<br>204 (100 vs 104) | CS: 54% vs 49%<br>APGAR at 1,5 min: 7,8 vs 7,9 | First hematocrit after birth (I-UCM vs DCC)=51.8% vs 49.9%, p=0.07 |
| Finn *et al*[15] | <32 weeks | 28.4 (25.7 to 29.6) vs 28 (26.4 to 29.6) weeks<br>930 (700 to 1545) vs 925 (630 to 1490) g | I-UCM vs DCC<br>32 (18 vs 14) | APGAR at 1 min; 5 vs 6 | Cerebral EEG activity (burst ratio) at 6 hours (I-UCM vs DCC): 83% vs 68%, p=0.27. Regional cerebral oxygenation at 6 hours (I-UCM vs DCC)=83% vs 85%, p=0.94 |
| Katheria *et al*[8] | 23–31 weeks | 28.4±2.4 vs 28.4±2.5 weeks | I-UCM vs DCC<br>474 (236 vs 238) | CS:76% vs 67% | Death or severe IVH (I-UCM vs DCC):=29/236 (12%) vs 20/238 (8%), p=0.16<br>Severe IVH (I-UCM vs DCC): =20/236 (8%) vs 8/238 (3%), p=0.02 |
| *UCM vs ICC* | | | | | |
| Hosono *et al*[22] | 24–28 weeks | 27.0±1.5 vs 26.6±1.2 weeks<br>836±223 vs 846±171 g | I-UCM vs ICC<br>40 (20 vs 20) | 1 min APGAR score higher in milking group<br>CS-70% vs 70% | Probability of not needing transfusion (I-UCM vs ICC): p=0.03<br>Total number of RBC transfusions (I-UCM vs ICC): 1.7 vs 4.0, p=0.02 |
| March *et al*[29] | 24–28 weeks | 27.0 (25.5 to 28.1) vs 26.3 (25.1 to 27.1) weeks<br>: 755 (687.5 to 980) vs 770 (650 to 940) g | I-UCM vs ICC<br>75 (36 vs 39) | CS-55.6% vs 66.7%<br>Intubation rate :100% in both groups<br>APGAR at 1, 5 min: 4, 6 vs 4, 7 | Need of packed RBC transfusion in first 28 days of life (I-UCM vs ICC): 83.3% vs 97.4%, p=0.05 |
| Alan *et al*[19] | ≤32 weeks and ≤1500 g | 28.4±1.8 vs 28.0±1.9 weeks<br>1103±236 vs 1101 ±262 g | I-UCM vs ICC<br>44 (22 vs 22) | CS-86.4% vs 81.8%<br>APGAR at 1, 5 min: 7, 8 vs 7, 8 | No. of packed RBC transfusions in the first 35 days of age (median) (I-UCM vs ICC): 2 vs 2, p=0.84 |
| Josephsen *et al*[23] | 24–27 $^{6/7}$ weeks | 26.5±1.4 vs 26.1±0.9 weeks<br>914±208 vs 809±178 g | I-UCM vs ICC<br>25 (13 vs 12) | Not specified | Initial infant haemoglobin (I-UCM vs ICC): 139 g/L vs 134 g/L, p=0.62 |
| Katheria 2014[24] | 23–31 $^{6/7}$ weeks | 28±2 vs 28±3 weeks<br>1170±356 vs 1131 ±396 g | I-UCM vs ICC<br>60 (30 vs 30) | CS-60% vs 44%<br>APGAR at 1, 5 min: 5,.7 vs 6, 7 | SVC flow at <6 hours, 12–24 hours and 24–36 hours (I-UCM vs ICC): significant difference at <6 hours and at 24–36 hours, p<0.05 |
| Kumar *et al*[26] | 32–36 $^{6/7}$ weeks | 34.7±1.3 vs 34.5±1.5 weeks<br>2397±268 vs 2354±274 g | C-UCM vs ICC<br>200 (100 vs 100) | CS-44% vs 39%<br>APGAR at 1 min: 7 vs 7 | Haemoglobin and serum ferritin at 6 weeks of life (C-UCM vs ICC): 121±15 vs 104±12 g/L, p<0.01 and 428.9±217 vs 237.5±118, p<0.01 |
| Kilicdag *et al*[25] | <32 weeks | 30.2±1.9 vs 31.0±1.4 weeks<br>1495±409 vs 1661±351 g | I-UCM vs ICC<br>54 (29 vs 25) | 100% CS delivery<br>APGAR at 1,5 min: 6, 8 vs 6,8 | Absolute neutrophil count on first day of life (I-UCM vs ICC): 5566 cells/µL vs 8120 cells/µL, p=0.032 |
| Song *et al*[32] | 24–32 $^{6/7}$ weeks | 30.1±2.5 vs 29.0±2.6 weeks<br>1256±271 vs 1256±288 g | I-UCM vs ICC<br>66 (34 vs 32) | CS-70.6% vs 78.1%<br>APGAR 1,5 min: 5,8 vs 5, 7<br>Intubation rate: 55.9% vs 46.9% | Initial haemoglobin (I-UCM vs ICC): 158±16 vs 147±21 g/L, p=0.018 |

Continued



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**Table 1** Continued

| Study ID | Patient population | Mean/median GA (weeks) mean birth weight (g) | Intervention vs Control sample size | Baseline characteristics | Primary outcome |
|---|---|---|---|---|---|
| Alavi *et al*[20] | 28–34 weeks | 31.25±1.56 vs 31.35±1.86 weeks<br>2089±260 vs 2145±320 g | C-UCM vs ICC<br>80 (40 vs 40) | CS-20% vs 17.5%<br>Resuscitation:<br>IPPV: 12.5% vs 17.5% | Haemoglobin (g/L) and haematocrit at birth (C-UCM vs ICC): 170.9±8.7 vs 152.4±13.2, p=0.0001 and 51.16±1.57 vs 45.59±4.86, p=0.0001 |
| El-Naggar *et al*[21] | 24–31 weeks | 27.6±1.8 vs 27.2±2 weeks<br>1061±383 vs 1019±282 g | I-UCM vs ICC<br>73 (37 vs 36) | CS-56.8% vs 66.7%<br>APGAR at 1, 5 min: 5, 7 vs 5, 7<br>IPPV: 84% vs 72%<br>Intubation: 65% vs 58% | SVC flow at 4–6 hours after birth (I-UCM vs ICC): 88.9 mL/kg/min vs 107.3 mL/kg/min, p=0.13 |
| Lago Leal *et al*[27] | 24–36 $^{6/7}$ weeks | Mean/Median GA not specified<br>1816±637 vs 2042±636 g | I-UCM vs ICC<br>138 (69 vs 69) | CS rate: not specified<br>Resuscitation: not specified | Requirement of phototherapy (I-UCM vs ICC): 39/69 vs 24/69; RR, 95% CI 1.62 (1.12 to 2.38), p=0.01 |
| Li *et al*[28] | 28–37 weeks | 33.0 (28.5 to 36.4) vs 33.9 (29.3 to 36.2) weeks<br>1940±477 vs 1893±510 g | I-UCM vs ICC<br>102 (48 vs 54) | CS: 0% in both groups | Incidence of certain or probable infection in neonates with PPROM (I-UCM vs ICC): 40/48 (83.3%) vs 48/54 (88.9%), p=0.87 |
| Ram Mohan *et al*[30] | <33 weeks | 33.0 (27–36) vs 33.0 (29–36) weeks<br>1400 (945–3750) vs 1516 (760–2370) g | C-UCM vs ICC<br>60 (30 vs 30) | APGAR at 1, 5 min: 7,8 vs 6, 8<br>IPPV: 96.6% vs 86.6%<br>Intubation: 10% vs 16.6% | Haemoglobin at 6 weeks of life (C-UCM vs ICC): 100.7±15.4 vs 89±26.3 g/L,p=0.003<br>Serum ferritin at 6 weeks of life (C-UCM vs ICC): 244.85±187.33 vs 148.54±162 ng/ml, p=0.04 |
| Silahli *et al*[31] | <32 weeks | Mean/Median GA not specified<br>1408±387 vs 1454±394 g | I-UCM vs ICC<br>75 (38 vs 37) | CS: 97% vs 78% | Thymic index in the first 24 hours of life (I-UCM vs ICC): 2.4 $cm^3$ vs 2.8 $cm^3$, p=0.077 |

CS, caesarean section; C-UCM, cut umbilical cord milking; EEG, Electroencephalogram; GA, gestational age; ICC, immediate cord clamping; IPPV, intermittent positive pressure ventilation; I-UCM, intact umbilical cord milking; IVH, Intraventricular haemorrhage; PPROM, Preterm premature rupture of the membranes; RBC, Red blood cell; SVC, Superior vena cava.

### Sensitivity analysis

Sensitivity analysis was performed after excluding RCTs with high ROB in the domain of allocation concealment and those where the mean GA of the included infants was greater than 32 weeks.

## RESULTS

Nineteen RCTs [5 RCTs (n=922) comparing UCM with DCC,[8 15–18] 14 RCTs (n=1092) comparing UCM with ICC[19–32]] were included in this systematic review. Milking was performed on an intact cord (I-UCM) in 16 RCTs, while cut UCM was performed in 3 studies.[20 26 30] Eighteen studies were available as full articles and one was a conference abstract.[23] The flow diagram of study selection process is given in figure 1. Authors of three studies[8 17 27] provided additional information on important clinical outcomes.

All the five studies comparing UCM with DCC included infants less than 34 weeks of gestation; however, three studies comparing UCM with ICC[26–28] included preterm infants>34 weeks. Three RCTs included only extremely preterm infants (<28 weeks).[22 23 29] The characteristics of the included studies are given in table 1. The cord milking technique followed in the included studies is described in online supplementary table 1. The details of ROB are given in table 2 and the overall evidence according to GRADE guidelines is summarised in online supplementary table 2. The results of sensitivity analyses are given in online supplementary table 3 and the neonatal outcomes with cut UCM are depicted in online supplementary table 4.

We also identified fourteen ongoing studies (six comparing UCM with DCC, eight comparing UCM with ICC) from clinical trial registries (online supplementary table 5).

### Outcomes

#### All-cause mortality

Meta-analysis found no significant effect on mortality with UCM when compared with DCC (RR 0.93 (95% CI 0.55 to 1.55), p=0.77, $I^2$=0%, 4 studies[8 16–18] (n=890)) (figure 2) .There was no significant difference in mortality between the I-UCM and ICC groups (RR 0.85 (95% CI 0.49 to 1.46), p=0.56, $I^2$=27%, 10 studies[19 21–24 27–29 31 32] (n=698)) (figure 3). Cut UCM did not have a significant effect on mortality when compared with ICC (RR 1.00 (95% CI 0.35 to 2.90), p=1.00, $I^2$=34%, 2 studies[26 30] (n=260)) (online supplementary table 4).

#### IVH (grade 3 or more)

Meta-analysis estimated a significant increase in the risk of severe IVH in the UCM group when compared with DCC (RR 1.95 (95% CI 1.01 to 3.76), p=0.05, $I^2$=0%, 4 studies[8 15–17] (n=718)) (figure 2). Number needed to treat with UCM that could result in IVH >grade 3 in one additional infant (NNTH) was 29 (95% CI 500 to 15). When compared with ICC, intact cord milking was not associated with an increased risk of IVH (grade 3 or more) (RR 0.69 (95% CI 0.38 to 1.24), p=0.22, $I^2$=0%, 8 studies[19 21 22 24 27–29 32] (n=598)) (figure 3). Only one study on cut UCM reported on this outcome[30] and found no difference (online supplementary table 4).

#### Other morbidities

For the other prespecified outcomes—IVH (all grades), NEC, PDA, BPD, ROP and duration of hospital stay, there were no statistically significant differences between the UCM and DCC/ICC groups (figures 2 and 3, and online supplementary figure 1, 2 and table 4).



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**Table 2** Risk of bias of the included studies

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| *UCM vs DCC* | | | | | | | |
| Rabe *et al*[17] | Low | Low | High | Low | Low | Low | Low |
| Katheria *et al*[16] | Low | Low | Low | Low | Low | High* | High† |
| Shirk *et al*[18] | Low | Low | High | High | High‡ | Low | Low |
| Finn *et al*[15] | Low | Low | High | Low | Low | Low | High§ |
| Katheria *et al*[8] | Low | Low | Low | Low | Low | Low | High¶ |
| *UCM vs ICC* | | | | | | | |
| Hosono *et al*[22] | Unclear | Low | High | Low | Low | Low | Low |
| March *et al*[29] | Low | Low | High | Low | High** | Low | High¶ |
| Alan *et al*[19] | Unclear | Low | High | Low | Low | Low | Low |
| Josephsen *et al*[23] | Unclear | Unclear | Unclear | Unclear | Low | Unclear | Unclear |
| Katheria *et al*[24] | Unclear | Low | High | Low | Low | Low | Low |
| Kumar *et al*[26] | Low | Low | High | High | Low | Low | Low |
| Kilicdag *et al*[25] | Unclear | Low | Unclear | Unclear | Low | Low | Unclear†† |
| Song *et al*[32] | Low | Unclear | Unclear | Low | Low | Low | Low |
| Alavi *et al*[20] | High‡‡ | High | Unclear | Unclear | Low | Low | Unclear†† |
| El-Naggar *et al*[21] | Low | Low | Low | Low | Low | Low | High† |
| Lago Leal 2018[27] | Unclear | Low | Low | Low | Low | Low | Low |
| Li *et al*[28] | Unclear | Unclear | Unclear | Low | Low | Low | Low |
| Ram Mohan *et al*[30] | Low | Low | High | High | Low | Low | Low |
| Silahli *et al*[31] | Low | Low | High | Low | Low | Low | Low |

*Outcomes reported only for 154 caesarean delivered neonates, no outcomes reported for 43 vaginally delivered infants.
†Crossover rate of >10% in DCC arm.
‡27% infants excluded after randomisation.
§Underpowered for the primary outcome.
¶Study discontinued after second interim analysis, incomplete sample size).
**Pregnancies continuing beyond 28 weeks were excluded after randomisation.
††Sample size calculation not mentioned.
‡‡First 40 patients were milked, next 40 patients received ICC.

### Need for packed RBC transfusion

Transfusion requirements were similar between UCM and DCC groups (online supplementary figure 1). Meta-analysis estimated a significant reduction in the incidence of RBC transfusion in the I-UCM group when compared with ICC (RR 0.56 (95% CI 0.43 to 0.73), p<0.00001, $I^2$=73%, 4 studies)[19 22 24 28] (figure 3). The results were found to be significant even on REM. Number needed to treat with I-UCM to prevent a packed RBC transfusion in one additional infant (NNTB) was 4 (95% CI 2.6 to 6.3).

### Need for phototherapy

There was no difference in the phototherapy requirement between the UCM and DCC groups (online supplementary figure 1). However, our analysis showed a significant increase in the need of phototherapy in I-UCM group when compared with ICC (RR 1.17 (95% CI 1.04 to 1.31), p=0.01, $I^2$=85%, 4 studies).[21 27–29] The results were not found to be significant by REM (RR 1.13 (95% CI 0.90 to 1.41), p=0.29) (online supplementary figure 2).

Cut UCM when compared with ICC, significantly increased the need for phototherapy (RR 4.00 (95% CI 2.57 to 6.24), p<0.001, $I^2$=0%, 2 studies) (online supplementary table 4).

### Long-term neurodevelopmental outcomes

Neurodevelopmental follow-up at 24 months of age was reported only in two studies (n=174)[16 17] comparing UCM with DCC. Meta-analysis of the Bayley III neurodevelopmental scores revealed no difference in the motor scores but significantly improved cognitive and language scores in the UCM group (online supplementary figure 3). None of the studies comparing UCM with ICC reported long-term neurodevelopmental outcomes.

### Quality of evidence

The quality of evidence for the UCM vs DCC comparison was deemed moderate for the outcomes of all-cause mortality, IVH (all grades), severe IVH, definite NEC, PDA requiring treatment, BPD, ROP requiring intervention, need for packed RBC transfusions and the need for phototherapy. The evidence was graded low for the outcomes of NEC (stage not specified), ROP (all stages) and duration of hospital stay. For the intact UCM vs ICC comparison, the quality of evidence was rated moderate to low for the various outcomes analysed. The evidence for cut UCM was rated very low for all the outcomes studied (online supplementary table 2).

### Sensitivity analyses

The results were similar to the main meta-analysis even after excluding studies where the mean GA was >32 weeks and those that had high ROB in the domain of allocation concealment (online supplementary table 3).

## DISCUSSION

Our systematic review found that cord milking, when compared with DCC significantly increased the risk of severe IVH (grade



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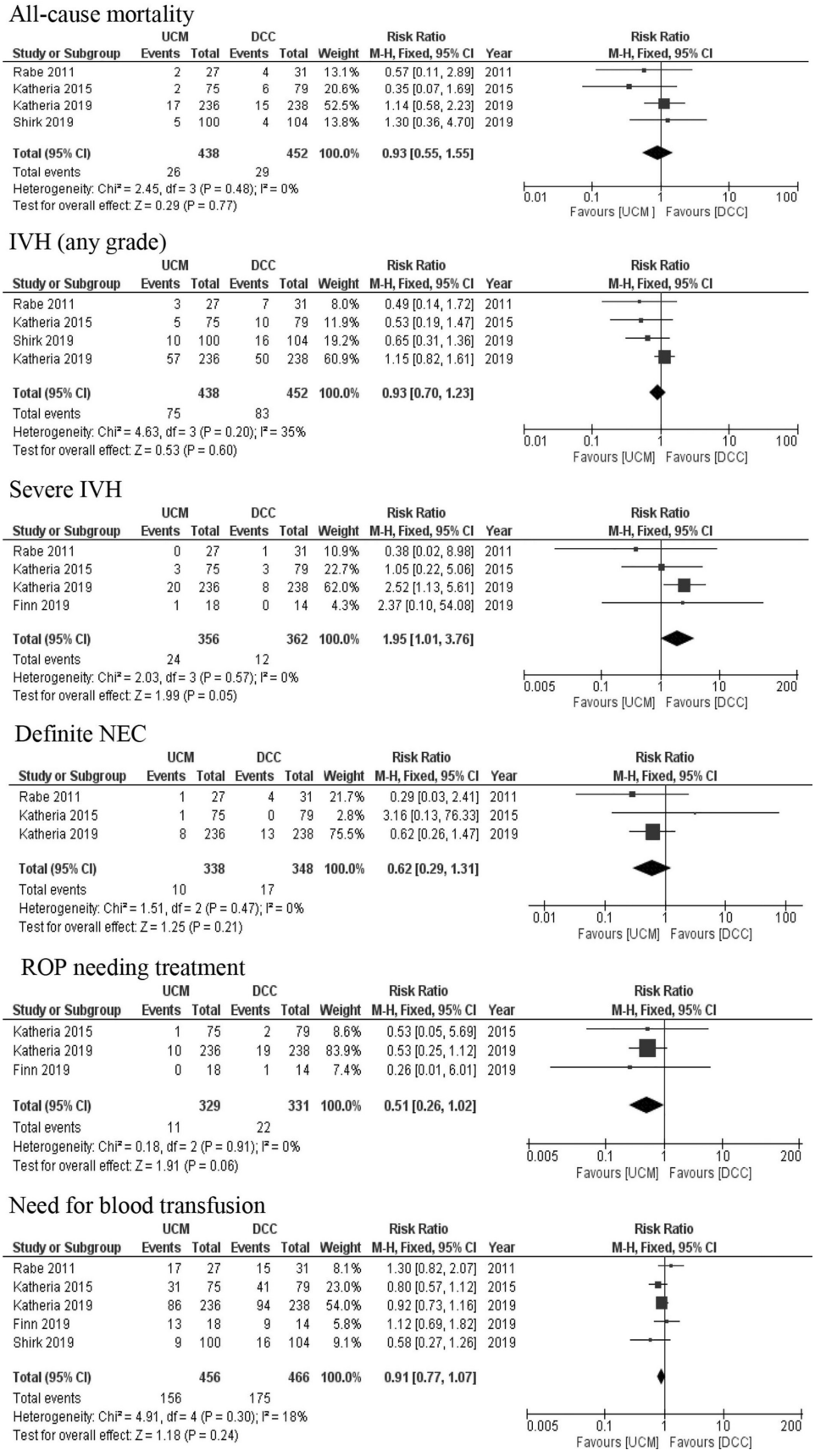


**Figure 2** UCM vs DCC in preterm infants—neonatal outcomes. DCC, delayed cord clamping; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; UCM, umbilical cord milking.

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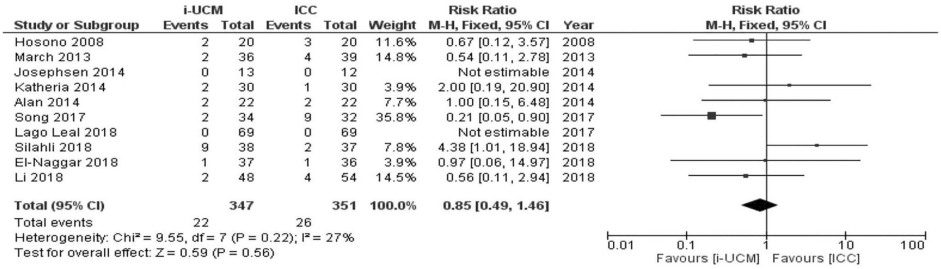
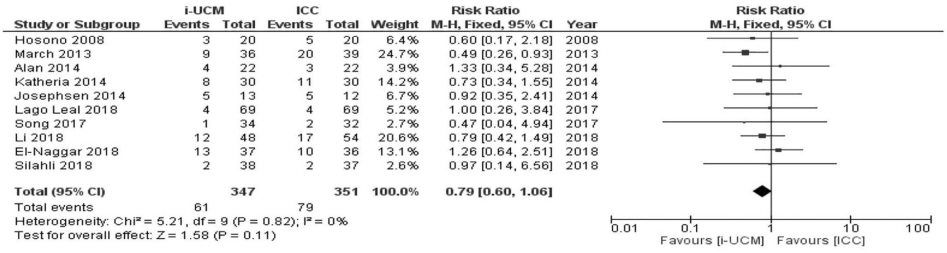
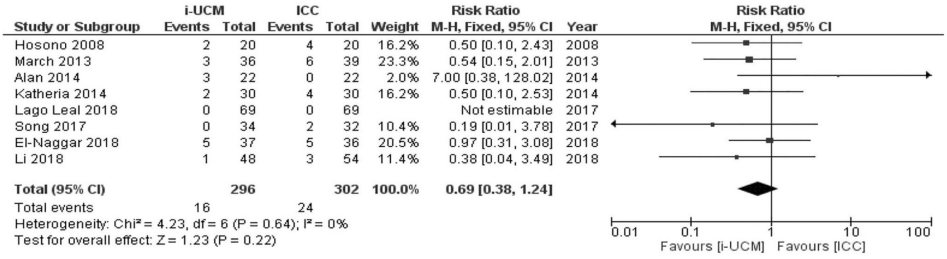
All-cause mortality



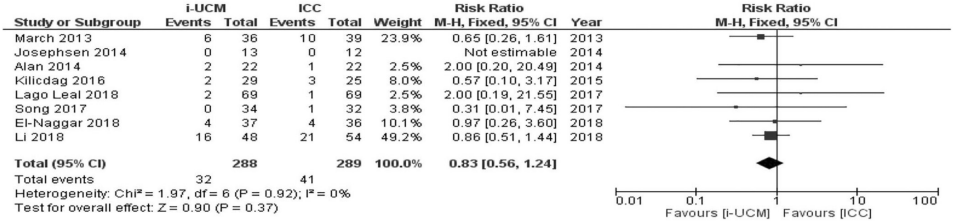

IVH (all grades)



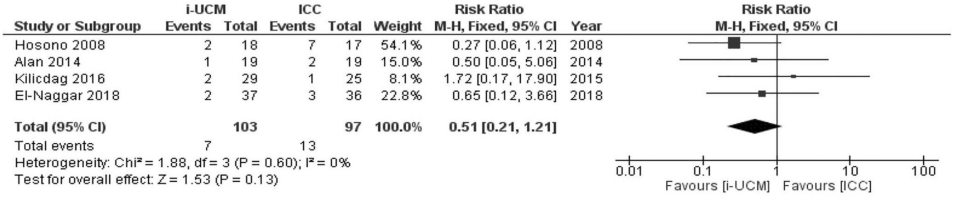

Severe IVH (grade 3 or more)




NEC (Stage not reported)




ROP needing treatment




Need for packed RBC transfusion

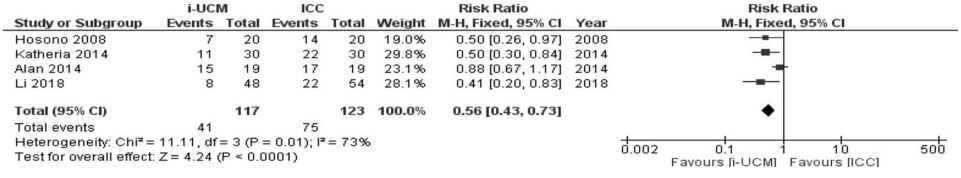



**Figure 3** Intact UCM vs immediate cord clamping in preterm infants—neonatal outcomes. DCC, delayed cord clamping; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; UCM, umbilical cord milking.

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III or more) in preterm infants born <34 weeks of gestation. When compared with ICC, milking significantly reduced the need for packed RBC transfusions but did not result in improved clinical outcomes.

To our knowledge, this is the most recent and comprehensive systematic review of UCM with exclusive focus on clinical outcomes in preterm infants. The consistency of our results even after excluding studies involving mature preterm neonates (>32 weeks of gestation), and those with high ROB, is another strength.

We identified at least four systematic reviews published on UCM in preterm infants. The systematic review by Dang *et al* compared UCM vs ICC (6 studies, 587 preterm infants<37 weeks) and found a reduced incidence of mortality and IVH, besides the reduced need for packed RBC transfusions in the UCM group. However, of the six included studies in their review, two were non-RCTs that contributed to nearly 63% of the total sample size.[7]

The systematic review on UCM by Al-Wassia *et al* (5 RCTs, 277 preterm infants<33 weeks of gestation) reported a lower risk of IVH of any grade and lower oxygen requirement at 36 weeks postmenstrual age with UCM,[6] without a significant reduction in the need for RBC transfusions. However, the control intervention in their review was ICC or DCC, whereas in our review, the effects of UCM were analysed separately with respect to the control intervention—immediate or delayed cord clamping. The systematic review by Nagano *et al* (2 RCTs, 255 preterm infants<33 weeks) reported that UCM may lower the risk of IVH and improve long term neurodevelopmental outcomes, when compared with DCC.[33]

The recent Cochrane review (2019) on placental transfusion strategies in preterm neonates included 14 RCTs comparing cord milking with either ICC (11 trials, n=1183) or DCC (3 trials, n=322). The authors found no significant benefits or harms from UCM; however, the overall quality of evidence was graded low to very low.[34] In our systematic review, 10 additional studies[8 15 18 20 21 27 28 30–32] have been included besides those summarised in the Cochrane review. While the Cochrane review included few studies that allowed cord milking as a cointervention in the DCC group,[35 36] we excluded those studies in order to determine the standalone effects of UCM in preterm neonates.

DCC is now considered the standard of care in vigorous preterm infants; however, its implementation in high risk preterm infants could be challenging.[37] Approximately 70% of moderately preterm infants born less than 34 weeks and nearly 90% of extremely preterm infants born <29 weeks are reported to require resuscitation at birth.[38] Second, placental transfusion from DCC in the absence of tonic uterine contractions as in caesarean delivery may be insufficient or ineffective.[16] Hence, there remains a need to identify an alternative to DCC in high risk preterm infants.

Our meta-analysis demonstrated a significantly increased risk of severe IVH with cord milking in preterm infants, primarily driven by the results of the recently published PREMOD 2 (premature infants receiving cord milking or DCC) trial. This multicentre non-inferiority trial[8] involving preterm infants born at 23–$31^{+6}$ weeks of gestation randomised to UCM or DCC at birth was prematurely terminated, since the first interim analysis revealed a significantly increased risk of severe IVH with cord milking (22% vs 6%, p=0.002) among infants born at 23–$27^{+6}$ weeks of gestation. This risk was not evident in the 27–$31^{+6}$ weeks subgroup and there were no differences in mortality between the UCM and the DCC group.

The results of our meta-analysis are in contrast to the findings from previous systematic reviews,[6 7] recently published observational studies[39 40] and even the recently published Cochrane review (2019)[34] on cord milking practices. This is predominantly because we included the recent PREMOD 2 trial that contributed to 50% of the overall sample size in the UCM vs DCC comparison. Second, the risk of severe IVH with milking was apparent only in PREMOD 2 trial where the study population was representative of preterm infants at risk of IVH.

Cord milking-induced rapid changes in the blood volume has remained a matter of concern, especially in the context of extreme prematurity. In the first experimental study on the physiological effects of placental transfusion strategies, Blank *et al* studied 29 fetal lambs exposed to (1) UCM with placental refill, (2) UCM without placental refill, (3) Physiology based cord clamping (ventilation before DCC) and (4) ICC.[41] Placental transfusion was the least in the UCM group without placental refill. Both UCM groups experienced large fluctuations in the mean arterial blood pressure and cerebral blood flows. This led them to predict that extremely preterm infants subjected to UCM could be susceptible to IVH. The largest clinical trial to date[8] also reached that outcome. These findings could warrant restriction of milking related research to preterm neonates born greater than 30 weeks of gestation.

Reduction in the need for RBC transfusions, demonstrated with cord milking in our meta-analysis, could be an important clinical benefit. However, majority of the study infants were vigorous at birth and eligible for DCC. In addition, there were no benefits with milking over ICC for other clinically relevant outcomes. Thus, our meta-analysis lends support to the criticism over the current clinical relevance of comparing cord milking with ICC, especially when the feasibility of DCC has been demonstrated even in non-vigorous preterm neonates.[42]

Placental transfusion with cut UCM has been reported to be inferior to that with intact cord milking.[43] In an observational cohort of 106 preterm neonates<35 weeks of gestation, cut UCM neither improved haemoglobin levels nor reduced neonatal morbidities when compared with historical controls exposed to early cord clamping.[44] Hence, the effect of cut UCM was analysed separately in our meta-analysis.

The main limitations of our review are the relatively small sample size and the lack of adequate information from extremely preterm infants. This also precluded assessment of the effects of UCM across GA categories. Neonatal mortality or morbidity was the primary outcome in only 1 of the 19 included studies.[8] The other limitation is the heterogeneity in the milking techniques employed in the included studies. The frequency, speed of the milking manoeuvre and the length of cord that was stripped varied between the studies. Few of the included trials allowed cord refill after each milking attempt. The time frame for completion of the cord milking procedure was reported only in four studies.[8 16 18 32]

In summary, UCM cannot be recommended as a placental transfusion strategy in preterm infants based on current evidence. Safety monitoring of ongoing trials and reporting of long-term neurodevelopmental outcomes of participants of RCTs would be essential.

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**Contributors** HB designed the study and drafted the initial manuscript. AA and VJ collected the data and carried out the initial analysis. NK conceptualised the study and critically reviewed the manuscript. SCR conducted literature search



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and critically reviewed the manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

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## REFERENCES


1 Katheria AC, Lakshminrusimha S, Rabe H, *et al*. Placental transfusion: a review. *J Perinatol* 2017;37:105–11.
2 Rabe H, Diaz-Rossello JL, Duley L, *et al*. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2012;8:Cd003248.
3 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;218:1–18.
4 World Health Organization. *Who guideline: delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes*. Geneva, 2014.
5 Royal college of obstetricians and gynaecologists. *Clamping of the umbilical cord and placental transfusion. scientific impact paper No. 14*, 2015.
6 Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: a systematic review and meta-analysis. *JAMA Pediatr* 2015;169:18–25.
7 Dang D, Zhang C, Shi S, *et al*. Umbilical cord milking reduces need for red cell transfusions and improves neonatal adaptation in preterm infants: meta-analysis. *J Obstet Gynaecol Res* 2015;41:890–5.
8 Katheria A, Reister F, Essers J, *et al*. Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants. *JAMA* 2019;322:1877–86.
9 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
10 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
11 Guyatt GH, Oxman AD, Schünemann HJ, *et al*. Grade guidelines: a new series of articles in the Journal of clinical epidemiology. *J Clin Epidemiol* 2011;64:380–2.
12 Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions. version 5.1.0 (updated March 2011). The Cochrane collaboration; 2011. London, England. Available: Www. Cochrane- handbook.Org
13 Sedgwick P, Marston L. How to read a funnel plot in a meta-analysis. *BMJ* 2015;351:h4718.
14 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
15 Finn D, Ryan DH, Pavel A, *et al*. Clamping the Umbilical Cord in Premature Deliveries (CUPiD): Neuromonitoring in the Immediate Newborn Period in a Randomized, Controlled Trial of Preterm Infants Born at <32 Weeks of Gestation. *J Pediatr* 2019;208:121–6.
16 Katheria AC, Truong G, Cousins L, *et al*. Umbilical cord milking versus delayed cord clamping in preterm infants. *Pediatrics* 2015;136:61–9.
17 Rabe H, Jewison A, Alvarez RF, *et al*. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. *Obstet Gynecol* 2011;117:205–11.
18 Shirk SK, Manolis SA, Lambers DS, *et al*. Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. *Am J Obstet Gynecol* 2019;220:482.e1–8.
19 Alan S, Arsan S, Okulu E, *et al*. Effects of umbilical cord milking on the need for packed red blood cell transfusions and early neonatal hemodynamic adaptation in preterm infants born ≤1500 G: a prospective, randomized, controlled trial. *J Pediatr Hematol Oncol* 2014;36:e493–8.
20 Alavi A, Diuband A, Etaati Z, *et al*. Investigating the effect of umbilical cord milking on neonatal outcomes among the preterm infants born in shariati hospital of bandar Abbas. *Journal of Research in Medical and Dental Science* 2018;6:133–9.
21 El-Naggar W, Simpson D, Hussain A, *et al*. Cord milking versus immediate clamping in preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F145–50.
22 Hosono S, Mugishima H, Fujita H, *et al*. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F14–19.
23 Josephsen J, Vlastos E, Potter S, *et al*. *Milking the umbilical cord in extreme preterm infants. paper presented at: 34th annual meeting of the Society for Maternal-Fetal medicine (the pregnancy meeting); 3-8 February 2014, 2014; New Orleans, LA*.
24 Katheria AC, Leone TA, Woelkers D, *et al*. The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates. *J Pediatr* 2014;164:1045–50.
25 Kilicdag H, Gulcan H, Hanta D, *et al*. Is umbilical cord milking always an advantage? *J Matern Fetal Neonatal Med* 2016;29:615–8.
26 Kumar B, Upadhyay A, Gothwal S, *et al*. Umbilical cord milking and hematological parameters in moderate to late preterm neonates: a randomized controlled trial. *Indian Pediatr* 2015;52:753–7.
27 Lago Leal V, Pamplona Bueno L, Cabanillas Vilaplana L, *et al*. Effect of milking maneuver in preterm infants: a randomized controlled trial. *Fetal Diagn Ther* 2019;45:57–61.
28 Li J, Yu B, Wang W, *et al*. Does intact umbilical cord milking increase infection rates in preterm infants with premature prolonged rupture of membranes? *J Matern Fetal Neonatal Med* 2020;33:1–7.
29 March MI, Hacker MR, Parson AW, *et al*. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. *J Perinatol* 2013;33:763–7.
30 Ram Mohan G, Shashidhar A, Chandrakala BS, *et al*. Umbilical cord milking in preterm neonates requiring resuscitation: a randomized controlled trial. *Resuscitation* 2018;130:88–91.
31 Silahli M, Duman E, Gokmen Z, *et al*. The relationship between placental transfusion, and thymic size and neonatal morbidities in premature infants - A Randomized Control Trial. *J Pak Med Assoc* 2018;68:1560–5.
32 Song S-Y, Kim Y, Kang B-H, *et al*. Safety of umbilical cord milking in very preterm neonates: a randomized controlled study. *Obstet Gynecol Sci* 2017;60:527–34.
33 Nagano N, Saito M, Sugiura T, *et al*. Benefits of umbilical cord milking versus delayed cord clamping on neonatal outcomes in preterm infants: a systematic review and meta-analysis. *PLoS One* 2018;13:e0201528.
34 Rabe H, Gyte GM, Díaz-Rossello JL, *et al*. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev* 2019;9:Cd003248.
35 Elimian A, Goodman J, Escobedo M, *et al*. Immediate compared with delayed cord clamping in the preterm neonate: a randomized controlled trial. *Obstet Gynecol* 2014;124:1075–9.
36 Mercer JS, Erickson-Owens DA, Vohr BR, *et al*. Effects of placental transfusion on neonatal and 18 month outcomes in preterm infants: a randomized controlled trial. *J Pediatr* 2016;168:50–5.
37 Tarnow-Mordi W, Morris J, Kirby A, *et al*. Delayed versus immediate cord clamping in preterm infants. *N Engl J Med* 2017;377:2445–55.
38 Walsh MC, Bell EF, Kandefer S, *et al*. Neonatal outcomes of moderately preterm infants compared to extremely preterm infants. *Pediatr Res* 2017;82:297–304.
39 Toledo JD, Rodilla S, Pérez-Iranzo A, *et al*. Umbilical cord milking reduces the risk of intraventricular hemorrhage in preterm infants born before 32 weeks of gestation. *J Perinatol* 2019;39:547–53.
40 Rodriguez CE, Metz TD, Patel S, *et al*. Neonatal outcomes associated with umbilical cord milking in preterm multiple gestations. *Am J Perinatol* 2019;36:990–6.
41 Blank DA, Polglase GR, Kluckow M, *et al*. Haemodynamic effects of umbilical cord milking in premature sheep during the neonatal transition. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F539–46.
42 Duley L, Dorling J, Pushpa-Rajah A, *et al*. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed* 2018;103:F6–14.
43 McAdams RM, Fay E, Delaney S. Whole blood volumes associated with milking intact and cut umbilical cords in term newborns. *J Perinatol* 2018;38:245–50.
44 Simonin A, Safarulla A, Farmer Z, *et al*. Cut umbilical cord milking: an ineffective method of placental transfusion in preterm infants? *J Matern Fetal Neonatal Med* 2019:1–4.
45 Rabe H, Sawyer A, Amess P, *et al*. Neurodevelopmental outcomes at 2 and 3.5 years for very preterm babies enrolled in a randomized trial of milking the umbilical cord versus delayed cord clamping. *Neonatology* 2016;109:113–9.
46 Katheria A, Garey D, Truong G, *et al*. A randomized clinical trial of umbilical cord milking vs delayed cord clamping in preterm infants: neurodevelopmental outcomes at 22-26 months of corrected age. *J Pediatr* 2018;194:76–80.




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