 This template guides the Task Force Systematic Review (TFSR) team to create the consensus on science with treatment recommendation (CoSTR) for their respective task force(s), based on the evidence profile tables and discussion with the task force(s). The Scientific Advisory Committee representative for the team initially approves the document and then forwards this for approval by the Scientific Advisory Committee and then by ILCOR executive prior to posting on ILCOR.org.

This summary document includes some of the steps along the way, as it does not rely on that information to be published in a separate document (eg. published Systematic Review).

## Consensus on Science with Treatment Recommendations (COSTR) for [www.ilcor.org](http://www.ilcor.org) posting

**Cord Management at Birth for Term and Late Preterm infants (NLS#1551)-DRAFT**

This CoSTR is a final version prepared by ILCOR and is labelled “draft” to comply with copyright rules of journals. The ‘draft label’ will be removed from this website once a summary article has been published in a scientific journal.

## Conflict of Interest Declaration

The ILCOR Continuous Evidence Evaluation process is guided by a rigorous ILCOR Conflict of Interest policy. The following Task Force members and other authors were recused from the discussion as they declared a conflict of interest: None

## CoSTR Citation

El-Naggar W, Davis PG, Soll RF, Costa-Nobre DT, de Almeida MF, Fabres JG, Fawke J, Foglia EE, Guinsburg R, Hosono S, Isayama T, Kawakami MD, Kapadia VS, Kim HS, Liley HG, McKinlay CJD, Perlman JM, Rabi Y, Roehr CC, Schmölzer GM, Sugiura T, Trevisanuto D, Weiner GM, Wyckoff MH, Wyllie JP, Niermeyer S. Cord Management at Birth for Term and Late Preterm infants. International Liaison Committee on Resuscitation (ILCOR) Neonatal Life Support Task Force, Feb 2021. Available from: http://ilcor.org

## Collaborators

None

**Methodological Preamble (and Link to Published Systematic Review)**

The continuous evidence process for the production of Consensus of Science and Treatment Recommendations (CoSTR) started with a systematic review regarding Cord management at birth for term and late preterm infants (Gomersall J, et al 2020, PROSPERO CRD42018084902 https://www.crd.york.ac.uk/prospero/display\_record.php?ID=CRD42020155498) conducted by the Cochrane Knowledge Synthesis Unit with involvement of clinical content experts. Additional evidence for neonatal literature was sought and considered by the Neonatal Life Support Task Force. The resulting consensus on science was considered when formulating the Treatment Recommendations*.*

**Systematic Review**

Judith Gomersall, Slavica Berber, Philippa Middleton, Susan J McDonald, Susan Niermeyer, Walid El-Naggar, Peter G. Davis, Georg M. Schmölzer, Colleen Ovelman, Roger Soll on behalf of the International Liaison Committee on Resuscitation Neonatal Life Support Task Force. Cord management at birth for term and late preterm infants: A systematic review with meta-analysis. Pediatrics. 2021;143:e2020015404.

## Cord Management at Birth for Term and Late Preterm infants PICOST

## The PICOST (Population, Intervention, Comparator, Outcome, Study Designs, and Time Frame)

**Population:** Term and late preterm infants (≥34 weeks’ gestation) or equivalent birth weight.

**Interventions:**

1. Later (delayed) cord clamping - cord clamping after a delay of at least 30 seconds.
2. Intact-cord milking - repeated compression of the cord from the placental side toward the baby with the connection to the placenta intact.
3. Cut-cord milking - drainage of the cord by compression from the cut end toward the baby after clamping and cutting a long segment.

**Comparisons:**

1. Early clamping of the cord (clamping at less than 30 seconds after birth) without cord milking or initiation of respiratory support compared to each of the above interventions.
2. Between-intervention comparisons.
3. Later (delayed) cord clamping at <60 seconds compared to ≥60 seconds.
4. Later (delayed) cord clamping based on time since birth compared to physiological approach to cord clamping (until cessation of pulsation of the cord or based on vital signs monitoring/ initiation of breathing).

**Outcomes:**

***Selecting outcomes***

*The choice of outcomes using the GRADE classifications of critical, important, or less important were debated by the Task Force. Highest priority was given to survival without neurodevelopmental impairment, and maternal complications. Potential sub-groups were also defined a priori. {Strand 2020 328} These were converted into Main outcomes and Additional outcomes for submission to PROSPERO. The subsequent review divided outcomes into primary or secondary and presented a limited number of subgroup analyses.*

***Outcomes listed in the systematic review:***

***Primary outcomes***

*Infant*

1. Survival without moderate to severe neurodevelopmental impairment in early childhood.
2. Anemia by four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors).

*Maternal*

1. Postpartum haemorrhage (PPH) - clinically estimated blood loss of at least 500 mL or as defined by the trial authors.

***Secondary outcomes***

*Neonatal*

1. Neonatal mortality
2. Moderate to severe hypoxic ischaemic encephalopathy.
3. Resuscitation (defined as positive pressure ventilation ± intubation ± chest compression).
4. Respiratory distress of any type or duration as described by the authors.
5. Admission to neonatal intensive care unit or special care nursery.
6. Hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth.
7. Hematocrit (%) within the first 24 hours and within 7days after birth after birth.
8. Hyperbilirubinemia treated with phototherapy.
9. Polycythaemia (hematocrit greater than 65%).
10. Partial exchange transfusion.
11. Exchange transfusion.

*Infant*

1. Moderate to severe neurodevelopmental impairment in early childhood.
2. Ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L).

*Maternal*

1. Maternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors).
2. Severe postpartum hemorrhage: clinically estimated blood loss of at least 1000 mL.
3. Manual removal of the placenta.
4. Post-partum infection.

***A priori subgroups***

1. Mode of birth: 1) cesarean delivery 2) vaginal delivery.
2. Gestational age: 1) 340 to 366 weeks 2) ≥ 370 weeks 3) mixed gestational ages 4) not reported.
3. Respiratory support: 1) with the cord intact 2) after the cord is cut 3) unclear (whether with the cord intact, after the cord is cut or not recorded at all).
4. Timing of administration of uterotonic agent: 1) before clamping the cord 2) after clamping the cord 3) mixed 4) not reported.
5. Placement of the newborn relative to placenta: 1) below placenta level 2) at placenta level 3) above placenta level 4) unclear/not reported.
6. Whether or not there was later (delayed) cord clamping before milking/stripping: 1) cord clamping delayed before milking 2) no delay before milking 3) unclear/ not reported.
7. Number of fetuses: 1) multiples 2) singletons 3) multiples and singletons combined 4) not reported.
8. Newborn congenital anomalies or other conditions: anomalies/conditions noted at or prior to birth.
9. Fetal anemia: 1) anemia 2) no anemia 3) mixed 4) not reported.
10. Size for gestational age: 1) small for gestational age 2) appropriate for gestational age 3) large for gestational age 4) mixed 5) not reported).
11. Infant status at birth: 1) vigorous or breathing 2) non-vigorous or not breathing 3) mixed 4) not reported.
12. Infants born in different-resourced countries: 1) low-and middle-income countries 2) high-income countries 3) mixed 4) not reported.

**Study Designs:** Randomized controlled trials (RCTs), quasi randomized controlled trials and cluster RCTs assessing interventions regarding umbilical cord management (including timing of clamping and cord milking) in late preterm (340 to 366 weeks' gestational age) and/or term infants (≥ 370 weeks' gestational age) or infants with birth weight ≥ 2500 g were eligible for inclusion. For studies that reported on a broad population of infants (including both preterm infants < 34 weeks’ gestation, late preterm infants and term infants), we considered studies that had a preponderance of late preterm and term infants (defined as study populations comprising greater than 80% late preterm or term infants). Unpublished studies (e.g., conference abstracts, trial protocols) were excluded.

**Timeframe:** All years and all languages were included as long as there was an English abstract. Literature search updated to 26th July 2019.

**PROSPERO registration:**

The review was registered with PROSPERO [CRD4202015549]

**Risk of Bias:**

Most studies were at mixed to high risk of bias. The majority of studies were at low risk of selection bias, but most had unclear allocation concealment, lack of blinding of participants and personnel, a high level of attrition, as well as high or unclear risk of selective reporting due in part to a lack of prospectively registered protocols. All outcomes selected for GRADE assessment were rated as very low or low certainty of evidence. In addition to the risk of bias there was also considerable imprecision (low event rates for many outcomes and small numbers of studies per outcome) and some inconsistency in findings between studies due to unclear or missing definitions of outcomes. {Gomersall 2021 e2020015404}



**GRADE evaluations:**

With the possibility of at least 3 interventions (delayed cord clamping, intact-cord milking, and cut-cord milking) and one comparison (early cord clamping) and between-intervention comparisons, there were a large number of outcomes which were multiplied by several subgroup comparisons. No correction for multiple comparisons was undertaken, therefore measures of statistical significance should be interpreted cautiously. GRADE evaluations were performed post hoc for subgroup comparisons that were considered likely to contribute to the Justification and the Values and Preferences sections.

## Consensus on Science

**COMPARISON 1: LATER (DELAYED) CORD CLAMPING AT ≥ 30 SECONDS COMPARED TO EARLY CORD CLAMPING AT <30 SECONDS AFTER BIRTH.**

The systematic review identified 33 studies (5263 mothers and their infants) in this category.

*For the critical outcome of* ***survival without moderate to severe neurodevelopmental impairment***, no evidence was identified.

*For the critical outcome of* ***neonatal mortality****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **4 trials** involving 537 infants {Backes 2015 826, Ceriani Cernadas 2006 e779, Chopra 2018 234, Datta 2017 418} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (risk ratio (RR) =2.54, 95% confidence interval (CI) 0.50 to 12.74, I2 = 0%).

*For the important outcome of* ***receiving resuscitation after birth****,* the evidence of **very low** certainty (downgraded for serious risk of bias, indirectness and imprecision) from **3 trials** involving 329 infants {Datta 2017 418, Salari 2014 287, Withanathantrige 2017 5} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR=5.08, 95% CI 0.25 to 103.58, heterogeneity not applicable as two of the studies reported 0 infants receiving resuscitation).

*For the important outcome of* ***respiratory distress***, the poor definition, missing data, and inconsistency of the outcome in the available studies led to a decision not to pool the data for meta-analysis.

*For the important outcome of* ***admission to******neonatal intensive care unit or special care nursery****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **10 trials** involving 1968 infants {Andersson 2011 d7157, Ceriani Cernadas 2006 e779, Chen 2018 251, De Paco 2011 1011, Mercer 2017 260, Mohammad 2021 231, Salari 2014 287, Vural 2019 555} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 1.16, 95% CI 0.69 to 1.95, I2 = 0%).

*For the important outcomes of* ***hemoglobin concentrations (g/dL) and hematocrit values (%)*** *within the first 24 hours after birth*, the evidence of **very low** certainty (downgraded for serious risk of bias and inconsistency) from **9 trials** involving 1352 infants reporting hemoglobin {Al-Tawil 2012 319, Chaparro 2006 1997, De Paco 2016 153, Emhamed 2004 218, Fawzy 2015 , Mohammad 2021 231, Salari 2014 287, Ultee 2008 F20, Yadav 2015 720} and **12 trials** involving 2183 infants reporting hematocrit {Al-Tawil 2012 319, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chen 2018 251, Chopra 2018 234, Emhamed 2004 218, Jahazi 2008 523, Philip 1973 334, Salari 2014 287, Ultee 2008 F20, Vural 2019 555, Yadav 2015 720} showed **higher** hemoglobin concentrations and hematocrit values in the later cord clamping group compared to early cord clamping (mean difference (MD)= 1.17 g/dL, 95% CI 0.48 to 1.86 (corresponds to MD of 11.7 g/L, 95% CI 4.8 to 18.6), I2= 89% (random effects) and MD= 3.38% 95% CI 2.08 to 4.67, I2= 81% (random effects) respectively).

*For the important outcome of* ***polycythemia (hematocrit > 65%)****,* the evidence of **low** certainty (downgraded for serious risk of bias) from **13 trials** involving 1335 infants {Backes 2015 826, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chopra 2018 234, Emhamed 2004 218, Grajeda 1997 425, Krishnan 2015 183, Mercer 2017 260, Saigal 1972 406, Salae 2016 S159, Salari 2014 287, Ultee 2008 F20, van Rheenen 2007 603} showed **higher** rates of polycythemia in the later cord clamping group compared to early cord clamping (RR=2.26, 95% CI 1.56 to 3.28; number needed to harm (NNTH) 20 (95% CI 13 to 33); I2 = 0%, RD= 0.05 (95% CI 0.03 to 0.08); 50/1000 more infants had polycythemia after later cord clamping for ≥ 30 seconds compared to early cord clamping [95% CI: 30 more to 80 more per 1000]).

*For the important outcome of* ***partial exchange transfusion****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **two trials** involving 164 infants {Chopra 2018 234, Vural 2019 555} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR=2.11, 95% CI 0.55 to 8.02).

*For the important outcome of* ***exchange transfusion****,* the evidence from **one trial** involving 86 infants {Salae 2016 S159} showed no events.

*For the important outcomes of* ***hemoglobin concentrations (g/dL) and hematocrit values******(%) within the first 7 days after birth****,* the evidence of **very low certainty** (downgraded for serious risk of bias, inconsistency, and imprecision) from **3 trials** involving 695 infants reporting hemoglobin concentrations {Andersson 2011 d7157, Mercer 2017 260, Yadav 2015 720} and **5 trials** involving 590 infants reporting hematocrit values {Cavallin 2019 252, Mercer 2018 266, Philip 1973 334} showed **higher** hemoglobin concentrations and hematocrit values in the later cord clamping group compared to early cord clamping (MD= 1.11 g/dL, 95% CI 0.40 to 1.82 (corresponds to MD of 11.1 g/L, 95% CI 4.0 to 18.2), I2= 82% (random effects) and MD= 5.84%, 95% CI 2.74 to 8.95, I2= 91%; random effects) respectively.

*For the important outcome of* ***hyperbilirubinemia treated with phototherapy****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **15 trials** involving 2814 infants {Al-Tawil 2012 319, Andersson 2011 d7157, Backes 2015 826, Cavallin 2019 252, Chen 2018 251, Emhamed 2004 218, Krishnan 2015 183, Mercer 2017 260, Oxford Midwives Research Group 1991 167, Salae 2016 S159, Ultee 2008 F20, van Rheenen 2007 603, Vural 2019 555, Withanathantrige 2017 5, Yadav 2015 720} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 1.28 95%, CI 0.90 to 1.82, I2=19%).

*For the critical outcome of* ***neurodevelopmental impairment in early childhood***, the evidence of **very low certainty** (downgraded for serious risk of bias and very serious risk of imprecision) from **one trial** involving 245 children including Ages and Stages Questionnaire (ASQ)-3 total scores at four years of age, {Andersson 2015 631} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (MD=3.40 points, 95% CI -2.86 to 9.66).

*For the important outcome of* ***anemia at 4-6 months of age****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **4 trials** involving 937 infants {Al-Tawil 2012 319, Andersson 2011 d7157, Chaparro 2006 1997, van Rheenen 2007 603} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR=1.01, 95% CI 0.75 to 1.37, I2 = 0%).

*For the important outcome of* ***ferritin concentrations at 3-6 months of age****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **3 trials** involving 286 infants {Al-Tawil 2012 319, Chopra 2018 234, Mercer 2018 266} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (MD=87.02 µg/L, 95% CI -1.89 to 175.94, I2= 96%; random effects) using random effects analysis (high heterogeneity). However, the high levels of ferritin in one study and the heterogeneity between the three studies made clinical interpretation difficult other than late cord clamping being associated with higher ferritin.

*For the important outcome of* ***low ferritin concentrations (<9 µg/L, <20* *µg/L and <50* *µg/L) at 3-6 months of age****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **2 trials** involving 610 infants reporting ferritin concentrations <9 µg/L {Ceriani Cernadas 2010 201, Chaparro 2006 1997}, **2 trials** involving 507 infants reporting ferritin concentrations <20 µg/L {Al-Tawil 2012 319, Andersson 2011 d7157} and **one trial** involving 82 infants reporting ferritin concentrations <50 µg/L {Chopra 2018 234}, showed **lower** rates of low ferritin concentrations. n the later cord clamping group compared to early cord clamping (RR= 0.46, 95% CI 0.26 to 0.82, I2 =47%; random effects, RR= 0.10, 95% CI 0.03 to 0.35, I2 = 0% and RR= 0.50, 95% CI 0.26 to 0.95 respectively); 60/1000, 90/1000 and 240/1000 fewer infants had low ferritin concentrations (<9 µg/L, <20 µg/L and <50 µg/L) at 3-6 months of age after later cord clamping compared to early cord clamping (95% CI: 100/1000 fewer to 10/1000 fewer, 130/1000 fewer to 50/1000 fewer 440/1000 fewer to 40/1000 fewer, respectively).

*For the critical composite outcome of* ***maternal mortality or severe morbidity****,* no evidence was identified.

*For the critical outcomes of* ***maternal* *postpartum hemorrhage****,* the evidence of **low** certainty (downgraded for serious risk of bias and indirectness) from **10 trials** involving 2675 women {Andersson 2013 567, Backes 2015 826, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chen 2018 251, Krishnan 2015 183, Mohammad 2021 231, Oxford Midwives Research Group 1991 167, van Rheenen 2007 603, Withanathantrige 2017 5} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 0.89, 95% CI 0.70 to 1.13, I2 =13%).

*For the critical outcomes of* ***maternal* *severe* *postpartum hemorrhage****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **6 trials** involving 1828 women {Andersson 2015 631, Backes 2015 826, Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chen 2018 251, Withanathantrige 2017 5} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 0.75, 95% CI 0.42 to 1.35, I2 =0%).

*For the important outcomes of manual removal of placenta,* the evidence of **low** certainty (downgraded for serious risk of imprecision) from **2 trials** involving 247 women {van Rheenen 2007 603, Withanathantrige 2017 5} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 0.58, 95% CI 0.21 to 1.65, heterogeneity not applicable).

**COMPARISON 2: INTACT-CORD MILKING VERSUS EARLY CORD CLAMPING**

The systematic review identified one small study of 24 infants.

*For the important outcomes of* ***hemoglobin concentrations (g/dL) and hematocrit values (%)******within the first 7 days after birth****,* the evidence from **one trial** involving 24 infants {Erickson-Owens 2012 580} showed **higher** hemoglobin concentrations and hematocrit values in the intact-cord milking group compared to early cord clamping (MD= 2.2 g/dL 95%, CI 0.48 to 3.92 (corresponds to MD of 22.0 g/L 95% CI 4.8 to 39.2) and MD= 7.50%, 95% CI 2.30 to 12.70) respectively.

**COMPARISON 3: CUT-CORD MILKING VERSUS EARLY CORD CLAMPING.**

The systematic review identified one study (200 infants) in this category.

*For the critical outcome of* ***neonatal mortality****,* the evidence from **one trial** involving 200 infants {Upadhyay 2013 120.e1} **could not exclude benefit or harm** from cut-cord milking compared to early cord clamping(RR= 0.20, 95% CI 0.01 to 4.11).

*For the important outcomes of* ***hemoglobin concentrations (g/dL) and hematocrit values (%)******within the first 24 hours after birth****,* the evidence from **one trial** involving 200 infants {Upadhyay 2013 120.e1} showed **higher** hemoglobin concentration and hematocrit value in the cut-cord milking group compared to early cord clamping (MD= 1.60 g/dL, 95% CI 0.96 to 2.24 (corresponds to MD of 16.0 g/L, 95% CI 9.6 to 22.4) and MD= 4.30%, 95% CI 2.36 to 6.24) respectively.

For *the important outcomes of* ***hemoglobin concentrations (g/dL) and hematocrit values (%)******within the first 7 days after birth****,* the evidence from **one trial** involving 200 infants {Upadhyay 2013 120.e1} showed **higher** hemoglobin concentration and hematocrit value in the cut-cord milking group compared to early cord clamping (MD= 1.10 g/dL, 95% CI 0.74 to 1.46 (corresponds to MD of 11.0 g/L, 95% CI 7.4 to 14.6) and MD= 4.00%, 95% CI 2.29 to 5.71) respectively.

**COMPARISON 4: LATER (DELAYED) CORD CLAMPING VERSUS INTACT-CORD MILKING.**

The systematic review identified one study {Alzaree 2018 1399}. No reliable assessment of treatment effects could be drawn because of serious methodologic concerns with the study.

**COMPARISON 5: LATER (DELAYED) CORD CLAMPING AT ≥ 30 SECONDS VERSUS CUT-CORD MILKING**

The systematic review identified 3 studies (740 infants) in this category.

*For the critical outcome of* ***neonatal mortality****,* the evidence of **very low** certainty (downgraded for risk of bias) from **one trial** involving 300 infants {Yadav 2015 720} **could not exclude benefit or harm** from later cord clamping compared to cut-cord milking (RR= 1.00, 95% CI 0.09 to 10.90).

*For the important outcome of* ***admission to neonatal intensive care unit or special care nursery****,* the evidence of **very low** certainty (downgraded for risk of bias) from **one** trial involving 200 infants {Jaiswal 2015 1159} **could not exclude benefit or harm** from later cord clamping compared to cut-cord milking (RR= 1.83, 95% CI 0.71 to 4.77).

*For the important outcomes of* ***hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 24 hours after birth****,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and imprecision) from **2 trials** involving 500 infants {Jaiswal 2015 1159, Yadav 2015 720} showed **lower** hemoglobin concentrations and hematocrit values in the later cord clamping group compared to cut-cord milking (MD= -0.56 g/dL, 95% CI -0.92 to -0.21 (corresponds to MD of -5.6 g/L 95% CI -9.2 to -2.1), I2 =9% and MD= -1.60%, 95% CI -3.11 to -0.09, I2= 45%; random effects) respectively.

*For the important outcome of* ***hyperbilirubinemia treated with phototherapy****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **2 trials** involving 500 infants {Jaiswal 2015 1159, Yadav 2015 720} **could not exclude benefit or harm** from later cord clamping compared to cut-cord milking (RR=1.36, 95% CI 0.66 to 2.81, I2 = 0%).

*For the important outcome of* ***hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth****,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and imprecision) from **2 trials** involving 500 infants {Jaiswal 2015 1159, Yadav 2015 720} showed **lower** hemoglobin concentrations and hematocrit values in the later cord clamping group compared to cut-cord milking (MD= -0.47 g/dL, 95% CI -0.81 to -0.13 (corresponds to MD of -4.7 g/L, 95% CI -8.1 to -1.3), I2 = 0% and MD= -1.11%, 95% CI -2.12 to -0.09, I2= 0%) respectively.

**FOR COMPARISON 6: INTACT-CORD MILKING VERSUS CUT-CORD MILKING**

No trials were identified.

**COMPARISON 7: LATER (DELAYED) CORD CLAMPING ≥ 60 SECONDS VERSUS LATER (DELAYED) CORD CLAMPING <60 SECONDS**

The systematic review identified 7 studies (2745 mothers and their infants) in this category.

*For the critical outcome of* ***neonatal mortality****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 231 infants {Andersson 2019 15}**could not exclude benefit or harm** from later cord clamping ≥ 60 seconds compared to later cord clamping <60 seconds (RR= 0.10, 95% CI 0.01 to 1.98).

*For the important outcome of* ***receiving resuscitation after birth****,* the evidence of **very low** certainty (downgraded for risk of bias) from one trial {Katheria 2017 313} involving 60 infants **could not exclude benefit or harm** from later cord clamping ≥ 60 seconds compared to later cord clamping <60 seconds (RR= 0.04, 95% CI 0.08 to 1.90).

*For the important outcome of* ***admission to neonatal intensive care unit or special care nursery****,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and imprecision) from **2 trials** involving 291 infants {Andersson 2019 15, Katheria 2017 313} **could not exclude benefit or harm** from later cord clamping ≥ 60 seconds compared to later cord clamping <60 seconds (RR=0.73, 95% CI 0.40 to 1.35, I2 = 26%).

*For the important outcome of* ***hemoglobin concentration (g/dL) within the first 24 hours after birth****,* the evidence of **very low** certainty (downgraded for risk of bias) from **one trial** involving 60 infants {Katheria 2017 313} showed **higher** hemoglobin concentrations in the later cord clamping group ≥60 seconds compared to later cord clamping <60 seconds (MD=1.30 g/dL, 95% CI 0.14 to 2.46, corresponds to MD of 13.0 g/L, 95% CI 1.4 to 24.6).

*For the important outcome of* ***hyperbilirubinemia treated with phototherapy****,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and imprecision) from **2 trials** involving 906 infants {Kc 2017 264, Nouraie 2019 45} showed **higher (or no difference)** in rates of **treatment with phototherapy** after later cord clamping ≥ 60 seconds compared to later cord clamping <60 seconds (RR=1.93, 95% CI 1.00 to 3.72, I2 = 60%; random effects). 70/1000 more infants had hyperbilirubinemia treated with phototherapy after later cord clamping for ≥ 60 seconds compared to later cord clamping <60 seconds (95% CI: 0/1000 more to 204/1000 more).

*For the important outcome of* ***receiving respiratory support****,* the evidence of very low certainty (downgraded for risk of bias) from **one trial** involving 60 infants {Katheria 2017 313} **could not exclude benefit or harm** from later cord clamping ≥ 60 seconds compared to later cord clamping <60 seconds (RR=0.53, 95% CI 0.27 to 1.07).

*For the critical outcome of* ***neurodevelopmental outcomes in early childhood****,* the evidence of **very low** certainty (downgraded for serious risk of bias and very serious risk of imprecision) from **one trial** {Rana 2019 36} involving 540 infants at 12 months of age showed infants in the later cord clamping for ≥ 60 seconds group had **higher** proportion ofASQ-3 scores >279 compared to later cord clamping for <60 seconds (RR=2.33, 95% CI 1.44 to 3.78; 103/1000 more infants would have ASQ-3 scores >279 after later cord clamping for ≥ 60 seconds compared with later cord clamping for <60 seconds (95% CI: 34/1000 more to 216/1000 more).

**COMPARISON 8: LATER (DELAYED) CORD CLAMPING AT ≥ 30 SECONDS VERSUS PHYSIOLOGICAL APPROACH** **TO CORD CLAMPING (UNTIL CESSATION OF PULSATION OF THE CORD OR BASED ON VITAL SIGNS MONITORING/INITIATION OF BREATHING).**

The systematic review identified 3 studies (1113 mothers and their infants) in this category.

*For the critical outcome of* ***neonatal mortality****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 338 infants {Sun 2017 14} **could not exclude benefit or harm** from later cord clamping ≥ 30 seconds compared to physiological approach (RR=5.00, 95% CI 0.24 to 103.37).

*For the important outcome of* ***receiving resuscitation after birth****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 338 infants {Sun 2017 14} **could not exclude benefit or harm** from later cord clamping ≥ 30 seconds compared to physiological approach (RR=1.67, 95% CI 0.84 to 3.30).

*For the important outcome of* ***admission to******neonatal intensive care unit or special care nursery****,* the evidence of **very low** certainty (downgraded for serious risk of bias, inconsistency and imprecision) from **2 trials** involving 878 infants {Chen 2018 251, Sun 2017 14} **could not exclude benefit or harm** from later cord clamping ≥ 30 seconds compared to physiological approach (RR= 2.58, 95% CI 0.04 to 163.65, I2 = 80%; random effects).

*For the important outcome of* ***hematocrit values (%) within the first 24 hours after birth****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 540 infants {Chen 2018 251} showed **lower** hematocrit values in the later cord clamping ≥ 30 seconds group compared to the physiological approach (MD= -1.40%, 95% CI -2.79 to -0.01).

*For the important outcome of* ***hyperbilirubinemia treated with phototherapy****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **3 trials** involving 932 infants {Chen 2018 251, Nelson 1980 655, Sun 2017 14} **could not exclude benefit or harm** from later cord clamping ≥ 30 seconds compared to physiological approach (RR=0.88, 95% CI 0.53 to 1.44, I2 = 0%).

*For the important outcome of* ***hemoglobin concentrations (g/dL) and hematocrit values (%) within the first 7 days after birth****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 338 infants {Sun 2017 14} showed **lower** hemoglobin concentrations and hematocrit values in the later cord clamping ≥ 30 seconds group compared to the physiological approach (MD= -1.70 g/dL, 95% CI -1.97 to -1.43 (corresponds to MD of -17.0 g/L, 95% CI -19.7 to -14.3) and MD= -6.50%, 95% CI -7.64 to -5.16).

*For the critical outcome of* ***maternal* *postpartum haemorrhage****,* the evidence of **very low** certainty (downgraded for serious risk of bias and imprecision) from **2 trials** involving 594 women {Chen 2018 251, Nelson 1980 655} **could not exclude benefit or harm** from latercord clamping ≥ 30 seconds compared to physiological approach (RR 0.92, 95% CI 0.40 to 2.07, I2 = 0%).

*For the critical outcome of* ***maternal* *severe* *postpartum haemorrhage****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 540 women {Chen 2018 251} **could not exclude benefit or harm** from latercord clamping ≥ 30 seconds compared to physiological approach (RR 1.82, 95% CI 0.10 to 33.4).

*For the critical outcome of* ***postpartum infection****,* the evidence of **very low** certainty (downgraded for serious risk of bias) from **one trial** involving 54 women {Nelson 1980 655} **could not exclude benefit or harm** from later cord clamping ≥ 30 seconds compared to physiological approach (RR 0.15, 95% CI 0.01 to 2.83).

**SUBGROUP ANALYSES**

The number of pre-specified subgroup analyses was large and was multiplied by the number of comparisons. The p-values were not adjusted for multiple comparisons. As a consequence, GRADE evaluations were not done for all subgroup analyses: instead, post hoc GRADE evaluations were requested for outcomes considered important for our justification, values and preferences statements.

We assessed the influence of key factors on the intervention effect using a test of interaction, including gestational age (full-term vs. late preterm), resource setting (low- or middle income vs. high-income countries), timing of uterotonic administration (before vs. after cord clamping) and size for gestational age (small vs. appropriate for gestational age). We planned to test for subgroup interactions within and between studies where appropriate. We noted whether randomization was stratified by the characteristic of interest. If subgroup data were not available, we performed subgroup analysis according to study characteristics, where applicable. These subgroup analyses are exploratory and must be interpreted with caution, especially for interaction tests between studies and by strata that were not used in randomization.

**SUBGROUP COMPARISONS FOR: LATER (DELAYED) CORD CLAMPING AT ≥ 30 SECONDS COMPARED TO EARLY CORD CLAMPING AT <30 SECONDS AFTER BIRTH**

**A- Subgroups according to gestational age**

*For the important outcome of* ***hyperbilirubinemia treated with phototherapy among term infants (≥ 37 weeks’ gestation)***, the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **13 trials** involving 2691 infants {Al-Tawil 2012 319, Andersson 2011 d7157, Backes 2015 826, Cavallin 2019 252, Chen 2018 251, Emhamed 2004 218, Krishnan 2015 183, Mercer 2017 260, Oxford Midwives Research Group 1991 167, van Rheenen 2007 603, Vural 2019 555, Withanathantrige 2017 5, Yadav 2015 720} showed **more** term infants in the later cord clamping group received phototherapy for hyperbilirubinemia compared to early cord clamping group (RR=1.54, 95% CI 1.01 to 2.34; RD= 0.01 [0.00, 0.03; NNTH= 100; I2= 15%); 10/1000 more term infants had hyperbilirubinemia treated with phototherapy after later cord clamping compared to early cord clamping [95% CI: 0 to 30 more per 1000]).

Among **late** **preterm infants (34 – 36+6 weeks’ gestation**), the evidence of **low** certainty (downgraded for serious risk of bias and imprecision) from **2 trials** involving 123 infants {Salae 2016 S159, Ultee 2008 F20} **could not exclude benefit or harm** from later cord clamping compared to early cord clamping (RR= 0.72, 95% CI 0.37 to 1.40, I2 = 0%). The p-value for interaction between subgroups was 0.06.

**B- Subgroups according to different resource settings, based upon World Bank country classifications**

*For the important outcomes of* ***hematocrit values (%)******within the first 24 hours after birth***, the evidence from **8 trials** involving 1279 infants **in low- or middle- income countries** {Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chopra 2018 234, Emhamed 2004 218, Jahazi 2008 523, Salari 2014 287, Vural 2019 555, Yadav 2015 720} and from **4 trials** involving 904 infants in **high-income countries**; {Al-Tawil 2012 319, Chen 2018 251, Philip 1973 334, Ultee 2008 F20} showed **higher** hematocrit values in the later cord clamping group compared to early cord clamping (MD= 2.42%, 95% CI 1.11 to 3.73, I2=71% (random effects) and MD= 5.75%, 95% CI 2.90 to 8.58, I2= 88%; random effects) respectively. The effect was **greater** in studies performed in high-income countries than in studies performed in low- or middle-income countries (p-value for interaction between subgroups was 0.04).

**C- Subgroup analyses according to the timing of uterotonic medication administration** **and according to size for gestational age did not reveal significant differences between subgroups.**

**Treatment Recommendations**

* For term and late preterm infants born at ≥34 weeks’ gestation who are vigorous or deemed not to require immediate resuscitation at birth, we suggest later (delayed) clamping of the cord at ≥ 60 seconds (weak recommendation, very low certainty evidence).

## Justification and Evidence to Decision Framework Highlights

In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:

* Most studies comparing later (delayed) cord clamping to early cord clamping in late preterm and/or full-term infants delayed clamping of the cord for ≥ 60 seconds.
* Later (delayed) cord clamping facilitates postnatal cardiovascular transition {Bhatt 2013 2113},increases hemoglobin and hematocrit in the neonatal period and improves iron status in early infancy. Although there were no studies that showed that later cord clamping prevented the complications of iron deficiency anemia or associated developmental delay, we value the benefits of increased hemoglobin and the potential for improved iron status to benefit neurodevelopment during early infancy. These potential benefits may be greatest in settings where resources for evaluation of nutritional status are limited and iron deficiency and anemia are prevalent.
* Later cord clamping is associated with increased rates of polycythemia and possible increase in use of phototherapy for hyperbilirubinemia. Although there was no reported increase in the rates of exchange transfusions, these considerations are important in settings where resources for evaluation and treatment of hyperbilirubinemia are limited.
* Only a few studies examined a physiological approach to cord clamping (delaying clamping until cessation of pulsation of the cord or based on vital signs monitoring/initiation of breathing). Compared with early, or time-based later cord clamping, this intervention improved neonatal hemoglobin and hematocrit. However, the effect on iron status, anemia in infancy, or neurodevelopment is uncertain.
* Although cut-cord milking improves neonatal hemoglobin and hematocrit, it is unknown if the intervention facilitates the post-natal cardiovascular transition in the same way as later cord clamping. There are only a few small studies and no long-term outcomes were addressed, limiting assessment of safety. Although cut-cord milking may be useful when later (delayed) cord clamping is contraindicated or not feasible, no included studies report its use in these situations.
* There is insufficient evidence to recommend milking of the attached cord for term and late preterm infants.
* Across all comparisons, there was no evidence that any of the studied cord management strategies improved the primary infant outcome of survival without neurodevelopmental impairment. Likewise, there was no evidence that cord management strategies altered important maternal outcomes including post-partum hemorrhage. The small sample size of most trials and the associated risks of bias and imprecision limited the certainty of evidence for all outcomes of interest. Analysis of many outcomes could not exclude benefits or harms.

**Values, Preferences, and Task Force Insights**

Suggestions and recommendations are provided in the context of both early cord clamping and later clamping being commonly practiced. There have been historical and regional changes in cord management practices over past decades {Downey 2012 325}. We acknowledge the perception of early clamping as a medical intervention, and of later clamping as a ‘natural’ or ‘physiological’ approach, and the paradox that many studies defined early clamping as the control {Hooper 2016 4}.

We accept the influence of current cord management practices on the recommendations. If the current norm for cord management were later clamping, evidence evaluation likely would have rejected early clamping. However, when the control is defined as early clamping, recommendations to change practice need to be more cautious given the weak evidence.

Animal studies and small observational studies provide evidence that cardiovascular transition after birth occurs more effectively when cord clamping is deferred {Bhatt 2013 2113, Ersdal 2014 265}. Societal, maternal, and practitioner preferences may also influence decisions about the timing of cord clamping.

With respect to equity, acceptability, accessibility, and cost, later cord clamping is an inexpensive, readily available, universally applicable intervention that can be performed irrespective of setting {Bhutta 2013 452}.

Many of the included studies did not record the exact time of cord clamping. The details of cord management including the timing of clamping should be routinely recorded in clinical practice and research studies.

## Knowledge Gaps

High quality studies are needed to determine the following;

* whether the demonstrated reduction in early iron deficiency seen after later (delayed) cord clamping improves long-term neurodevelopment. These studies need to be performed in low-resource and high-resource settings.
* the effects of cord management practices on polycythemia and hyperbilirubinemia using standardized protocols for diagnosis and management.
* the optimal timing of later cord clamping and effects on important outcomes in the neonatal period, infancy, childhood and for mothers.
* optimal cord management practices (i) for infants who are not vigorous or are deemed to require immediate resuscitation at birth and (ii) when there are contraindications to later cord clamping (e.g. interrupted placental circulation). These studies should report the important outcomes in the neonatal period, infancy, childhood and for mothers.
* optimal cord management practice in cesarean deliveries (under regional or general anesthesia), intrauterine growth restriction, multiple gestations, fetal anemia, fetal anomalies.
* the impact of cord management on vertical transmission of infectious diseases.
* the economic impact of different cord management practices.
* parents’ views regarding cord management practices at birth.

Finally, there is a need (in the settings of both clinical practice and research) to widely agree on nomenclature and definition of different interventions including “delayed”, “deferred”, “later”, “optimal”, and “physiological” cord clamping, as well as “milking”, “stripping”, “intact-cord”, and “cut-cord”.

**Attachments:**

**References:**