**Evidence to decision table for cord management at birth for preteRm infants (nls # 787)**

This evidence to decision (EtD) table will include evidence for three questions or comparisons: #1) later (delayed) cord clamping compared to early cord clamping (<30s), #2) intact-cord milking compared to early cord clamping (<30s), and #4) later (delayed) cord clamping (≥30s) compared to intact-cord milking. Evidence for the other questions included in the CoSTR will not be presented as there was insufficient evidence. Only one study was identified for comparison #3 – cut-cord milking compared to early cord clamping (<30s). No studies met inclusion criteria for comparisons #5 (later (delayed) cord clamping (≥30s) compared to cut-cord milking), #6 (intact-cord milking compared to cut-cord milking), #7 (later (delayed) cord clamping ≥60s versus later (delayed) cord clamping ≥30 and <60s), and #8 (later (delayed) cord clamping (≥30s) versus physiological approach).

|  |
| --- |
| Question #1  |
| **Should later (delayed) cord clamping compared to early cord clamping (<30s) be used for preterm infants (ILCOR)?** |
| **Population:** | Preterm infants born at <34 weeks gestational age |
| **Intervention:** | Later (delayed) cord clamping |
| **Comparison:** | Early cord clamping (based on timing of delaying clamping <30s) |
| **Main outcomes:** | Survival to discharge from hospitalMortality (post hoc analysis)Severe intraventricular hemorrhage (IVH): ultrasound diagnosis grades III and/or IVChronic lung disease (CLD): oxygen at 36 weeks' postmenstrual age (PMA)Necrotising enterocolitis (≥ Bell's Stage II)Hyperbilirubinemia (treated by phototherapy)Respiratory support (mechanical ventilation or continuous positive pressure ventilation)Inotropic support for hypotension during the first 24 hours of life (after birth)Lowest mean arterial blood pressure in the first 12 hours of lifeBlood transfusion (infant)Number of blood transfusions per infantHemoglobin concentrations within the first 24 h after birthHematocrit within the first 24 h after birthHemoglobin concentrations within 7 days after birthHematocrit within 7 days after birthPostpartum hemorrhage (clinically estimated blood loss of ≥ 500 mL)Severe postpartum hemorrhage (blood loss ≥ 1000 mL)Use of therapeutic uterotonic agentsBlood transfusion (maternal)Manual removal of the placentaPostpartum infection |
| **Setting:** | delivery room |
| **Perspective:**  | Infants and their familiesHealth care practitioners providing care for newborn infants |
| **Background:** | Umbilical cord management affects every one of the 130 million infants born in the world each year. Cord management at birth impacts not only the volume of placental transfusion to the baby, but also the cardiovascular transition around the onset of breathing and/or ventilation. {Bhatt 2013 2113, Yao 1969 871}. Placental transfusion at birth, through delayed cord clamping and cord milking, improves cardio-respiratory post-natal adaptation of preterm infants, hemoglobin concentration, and cerebral oxygenation. {Bhatt 2013 2113, Hooper 2015 147, Kluckow 2015 225, Niermeyer 2013 385} There is a growing body of evidence that suggests that cord management at birth influences survival, neonatal morbidities, and long-term neurodevelopment in preterm infants. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 CD003248} Meta-analyses to date have suggested that placental transfusion at birth significantly reduces mortality in preterm infants as well as improving cardiovascular and hematological parameters. A recent systematic review found that delayed cord clamping at birth for >30s reduced mortality in preterm infants <28 weeks’ gestation with number needed to treat for benefit (NNTB) of 20 infants, with a high GRADE level of evidence. {Fogarty 2018 1} Cord management at birth is not just a question of timing of cord clamping. Placental transfusion may be augmented by milking the intact cord or a segment of cut cord. The optimal cord management at birth for preterm infants remains unclear. Cord management and resuscitation interventions may be simultaneous or sequential in time, and each may impact the performance and outcomes of the other.History, values, and preferences significantly impact interpretation of cord management studies. So-called “natural” cord management is based on the supposition that nature does not practice immediate cord clamping and cutting but has natural delays between delivery and cord separation. As a result, technically, early clamping and milking are “medical interventions” superimposed on a natural phenomenon. This systematic review, however, chose early clamping as the control based on the historical precedent of commonest practice and therefore commonest comparison. |
| **Conflict of interests:** | None |

# Assessment

|  |
| --- |
| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival, neonatal morbidities, and long-term neurodevelopment in preterm infants. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 CD003248} |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | The systematic review identified 23 trials (3513 infants). {Aladangady 2006 93, Armanian 2017 4909, Backes 2016 35, Baenziger 2007 455, Das 2017 157, Dipak 2017 112, Dong 2016 635, Duley 2018 F6, Finn 2019 121, Gokmen 2011 323, Hofmeyr 1988 104, Hofmeyr 1993 110, Kazemi 2017 , Kinmond 1993 172, Kugelman 2007 307, McDonnell 1997 308, Mercer 2003 466, Mercer 2006 1235, Oh 2011 S68, Rabe 2000 775, Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445} Although primary analysis of delaying cord clamping (≥30s) in infants who do not require immediate resuscitation **may have a survival benefit or may make no difference** over early clamping (16 trials; 2988 infants; risk ratio (RR) 1.02, 95% confidence interval (CI) 1.00 to 1.04; risk difference (RD) 0.02, 95% CI -0.00 to 0.04; number needed to treat for benefit (NNTB) 50, 95% CI 25 to >1,000; I2 = 0%; 18/1000 more infants survived when later cord clamping was intended than when early cord clamping was intended, 95% CI 0/1000 more to 36/1000 more), a post hoc analysis of mortality **could not exclude either benefit or harm** (16 trials; 2988 infants; RR 0.80, 95% CI 0.63 to 1.02; RD -0.02, 95% CI -0.04 to 0.00; NNTB 50, 95% CI 25 to >1,000 I2 = 0%). If CI were described to 4 decimal points one would see the lower confidence interval for survival cross 1.000 and reach 0.993.Delaying cord clamping results in fewer infants receiving inotropic support (6 trials, 351 infants; RR 0.36, 95% CI 0.17 to 0.75; RD -0.09, 95% CI -0.15 to -0.03; NNTB 11, 95% CI 7 to 33; I2 = 0%; 91/1000 fewer infants received inotropic support for hypotension within the first 24 hours after birth when later cord clamping was intended than when early cord clamping was intended, 95% CI 30/1000 fewer to 143/1000 fewer), higher hemoglobin within 24h (4 trials, 196 infants; MD 1.24g/dL, 95% CI 0.01 to 2.47g/dL; I2 = 79%), and higher hematocrit within 24h (14 trials, 1022 infants; MD 2.63%, 95% CI 1.85 to 3.42%; I2 = 5%) and 7 days (1 trial, 1550 infants; MD 2.70%, 95% CI 1.88 to 3.52%) with fewer infants receiving transfusions (12 trials, 780 infants; RR 0.83, 95% CI 0.77 to 0.90; RD -0.07, 95% CI -0.11 to -0.04; NNTB 14, 95% CI 9 to 25; I2 = 36%; 71/1000 fewer infants received any blood transfusions when later cord clamping was intended than when early cord clamping was intended, 95% CI 40/1000 fewer to 111/1000 fewer).  | Using the same data for a post hoc mortality analysis, a 2% survival benefit approximately equates to a 20% reduction in mortality: one inference is that mortality is less frequent than survival so there appears to be greater imprecision in the point estimate. Evidence on longer term neurodevelopmental outcomes was insufficient.   |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small● Trivial○ Varies○ Don't know | There is no significant effect on need for respiratory support after birth or need for phototherapy, nor on severe IVH, chronic lung disease of prematurity, or necrotizing enterocolitis. There is no impact on a limited number of critical maternal outcomes.  | Evidence on longer term neurodevelopmental outcomes was insufficient.  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low● Moderate○ High○ No included studies | The certainty of evidence varies by outcome. Evidence was moderate for the critical outcome of survival and ranged from low to high for the critical outcomes of severe IVH, necrotizing enterocolitis, and chronic lung disease. For the critical maternal outcome of postpartum hemorrhage (≥500 mL) evidence was very low. For all the important outcomes evidence ranged from moderate to high.  |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | The main outcomes are highly valued – they are critical outcomes. {Strand 2020 328, Webbe 2020 425}  |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison● Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | Delaying cord clamping for 30s or more in infants who do not require immediate resuscitation may have a survival benefit or may make no difference over early clamping (see above summary of desirable and undesirable effects). Delaying cord clamping results in less inotropic support, and higher hemoglobin and hematocrit within the first 24h and 7 days after birth with fewer infants receiving transfusions. |  |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings● Varies○ Don't know | There are no published cost data. However, for infants who do not require resuscitation, it is likely that delaying cord clamping (≥30s) compared to early clamping does not add cost. For infants requiring resuscitation during cord management additional equipment and additional training may be needed. | Cord clamping strategies in infants who do not require resuscitation need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. Training is required. |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | No data available. | We perceive the additional resource requirements and costs to be low for both this intervention and its comparison. |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | No data available. | Although there are no published cost data, it is unlikely that delayed cord clamping compared to early cord clamping will add costs for infants not requiring resuscitation. However, for infants requiring resuscitation additional equipment and additional training may be needed. |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact● Probably increased○ Increased○ Varies○ Don't know | The reduction in secondary, important outcomes, including need for inotropes and transfusions, may result in improved equity in low-resourced settings where these interventions may not be readily available. | Both the intervention and the comparison are widely available in all settings.  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | The 2015 CoSTR suggested delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence). Although umbilical cord clamping practices may vary across sites and providers, there has been an increase in the practice of DCC over recent years. {El-Naggar 2020 58, Ibrahim 2017 216, Ortiz-Esquinas 2020 1738} | The intervention may cause some anxiety in providers who have always clamped early. Need for resuscitation might change the acceptability of the intervention.  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Delayed (later) cord clamping is feasible. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072}. It should be noted that in many studies, infants randomized to later (delayed) clamping may have received early clamping if they were thought to require resuscitation. For example, in the largest study {Tarnow-Mordi 2017 2445} 19.5% (146 of 748) infants in the later cord clamping group had non-adherence to their allocated study arm because of clinical concern about infant well-being.  | It is current standard of care in some centers.  |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | **Probably increased** | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | ○  | ●  | ○  |

|  |
| --- |
| Question #2 |
| **COMPARISON 2: Should intact-cord milking compared to early cord clamping (<30s) be used for preterm infants?** |
| **Population:** | Preterm infants born at <34 weeks gestational age |
| **Intervention:** | Intact-cord milking |
| **Comparison:** | Early cord clamping (based on timing of delaying clamping <30s) |
| **Main outcomes:** | INFANT:Survival to discharge from hospitalMortality (post hoc analysis)Moderate to severe neurodevelopmental impairment in early childhoodCerebral palsySevere IVH: ultrasound diagnosis grades III and/or IVChronic lung disease (CLD): oxygen at 36 weeks' PMANecrotizing enterocolitis (≥ Bell's Stage II)Hyperbilirubinemia (treated by phototherapy)Respiratory support (mechanical ventilation or CPAP)Inotropic support for hypotension during the first 24 hours of life (after birth)Lowest mean arterial blood pressure in the first 12 hours of lifeBlood transfusion (infant)Total number of blood transfusions per infantHemoglobin concentrations within the first 24 h after birthHematocrit within the first 24 h after birthHemoglobin concentrations within 7 days after birthHematocrit within 7 days after birthMATERNAL:Severe postpartum hemorrhage (blood loss ≥ 1000 mL)Blood transfusion (maternal) |
| **Setting:** | delivery room |
| **Perspective:** | Infants and their familiesHealth care practitioners providing care for newborn infants |
| **Background:** | As for comparison #1 |
| **Conflict of interests:** | None |

# Assessment

|  |
| --- |
| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | As for comparison #1 |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ● Trivial○ Small○ Moderate○ Large○ Varies○ Don't know | The systematic review identified 13 trials (1170 infants). {Mercer 2016 50, Finn 2019 121, Alan 2014 e493, El-Naggar 2019 F145, Elimian 2013 S22, Hosono 2008 F14, Katheria 2014 e94085, Kilicdag 2016 615, Lago Leal 2018 , Li 2020 184, March 2013 763, Silahli 2018 1560, Song 2017 527} For the critical outcomes of both survival to discharge (RR 1.02, 95% CI 0.98 to 1.06; I2=24%) and mortality (post hoc RR 0.77, 95% CI 0.49 to 1.23) 10 trials involving 945 infants (moderate certainty, downgraded for imprecision) **could not exclude benefit or harm** from intact-cord milking compared to early cord clamping. Only one study (26 infants) looked at moderate to severe neurodevelopmental impairment in early childhood and was non-contributory. No other critical outcomes were significant.It is noteworthy that for the critical outcome of severe IVH, evidence of low certainty (downgraded for very serious imprecision) from 10 trials involving 889 infants **could not exclude benefit or harm** with intact-cord milking compared to early cord clamping (RR 0.72, 95% CI 0.44 to 1.19; I2 = 0%). {Mercer 2016 50, Finn 2019 121, Alan 2014 e493, El-Naggar 2019 F145, Elimian 2013 S22, Hosono 2008 F14, Katheria 2014 e94085, Li 2020 184, March 2013 763, Song 2017 527} With respect to important outcomes, intact-cord milking resulted in fewer infants receiving inotropic support for hypotension in the first 24 hours after birth (5 trials, 431 infants; RR 0.61, 95% CI 0.44 to 0.84; RD -0.12, 95% CI -0.19 to -0.05; NNTB 8, 95% CI 5 to 20; I2 = 0%; 125/1000 fewer infants received inotropic support for hypotension within the first 24 hours after birth when intact-cord milking was intended than when early cord clamping was intended, 95% CI 50/1000 fewer to 200/1000 fewer), higher hemoglobin concentrations within 24h after birth (10 trials, 914 infants; MD 1.18g/dL, 95% CI 0.65 to 1.71g/dL; I2 = 71%; random effects), higher hematocrit within 24h after birth (7 trial, 774 infants; MD 3.04%, 95% CI 1.28 to 4.80%; I2 = 69%; random effects), and fewer infants receiving blood transfusions (7 trial, 545 infants; RR 0.73, 95% CI 0.56 to 0.94; RD -0.17, 95% CI -0.30 to -0.04; NNTB 6, 95% CI 3 to 25; I2 = 54%; random effects; 167/1000 fewer infants received any blood transfusions when intact-cord milking was intended than when early cord clamping was intended, 95% CI 40/1000 fewer to 333/1000 fewer). | The important cardiovascular and hematologic outcomes may be confounded by unreported variation in clinical practices such as fluid administration and transfusion thresholds, raising concerns about indirectness; thus clinical variation may be a reason for the inconsistency (I2 values range from 21% to 77%). |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small● Trivial○ Varies○ Don't know | No significant undesirable effects were noted in the analyses. | For this comparison of intact-cord milking with early cord clamping no subgroup analysis by gestation was done. It is not known whether the signal of harm identified in comparison #4 (later (delayed) cord clamping vs intact-cord milking) is mirrored in this comparison.No critical or important outcomes showed undesirable effects, in particular, there were no significant differences in the important outcomes of respiratory support after birth and hyperbilirubinemia requiring phototherapy.Only 2 studies reported maternal complications, and none were significant. |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low● Moderate○ High○ No included studies | Critical outcomes (all neutral to the question) ranged from very low to moderate certainty. Evaluation of the critical outcome of survival was based on a moderate level of certainty (downgraded for imprecision). The certainty of evidence for important outcomes varied from very low to moderate. |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | The main outcomes are highly valued – they are critical outcomes. {Strand 2020 328, Webbe 2020 425}For this comparison of intact cord milking with early cord clamping no subgroup analysis by gestation was done. It is not known whether the signal of harm identified in comparison #4 (later (delayed) cord clamping vs intact-cord milking) is mirrored in this comparison. |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison● Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | No critical outcomes differ significantly between intact-cord milking and early cord clamping.However, intact-cord clamping has benefits over early cord clamping with respect to hematological status, and the number of infants receiving inotropes or transfusion. | One needs to consider intact-cord milking vs early cord clamping in the context of a third cord management strategy, delayed (or later) cord clamping. |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | There are no published cost data. | Cord clamping strategies in infants who do not require resuscitation need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. Training is required. |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | There are no data available. | We perceive the additional resource requirements and costs to be low for both this intervention and its comparison. |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | There are no data available. | As fewer infants receive inotropic support or transfusion with intact-cord milking, the cost-effectiveness leans in favour of the intervention. |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact● Probably increased○ Increased○ Varies○ Don't know | The reduction in secondary, important outcomes, including need for inotropes and transfusions, may result in improved equity in low-resourced settings where these interventions may not be readily available. | Both the intervention and the comparison are widely available in all settings.  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | A recent retrospective multicenter study implies that this is an accepted practice among healthcare practitioners. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072} | There are no clear disadvantages to the caregiver or client with respect to the intervention. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | The intervention is feasible. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072} |  |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | **Probably increased** | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | ○  | ●  | ○  |

|  |
| --- |
| Question #4 |
| **COMPARISON 4: Should later (delayed) cord clamping (≥30s) compared to intact-cord milking be used for preterm infants?** |
| **Population:** | Preterm infants born at <34 weeks gestational age |
| **Intervention:** | Later (delayed) cord clamping (≥30s) |
| **Comparison:** | Intact-cord milking |
| **Main outcomes:** | INFANT:Survival to discharge from hospitalMortality (post hoc analysis)Survival without moderate to severe neurodevelopmental impairment in early childhoodCerebral palsySevere IVH: ultrasound diagnosis grades III and/or IVChronic lung disease (CLD): oxygen at 36 weeks' PMANecrotizing enterocolitis (≥ Bell's Stage II)Hyperbilirubinemia (treated by phototherapy)Respiratory support (mechanical ventilation or CPAP)Inotropic support for hypotension during the first 24 hours of life (after birth)Lowest mean arterial blood pressure in the first 12 hours of lifeBlood transfusion (infant)Total number of blood transfusions per infantHemoglobin concentrations within the first 24 h after birthHematocrit within the first 24 h after birthMATERNAL:Maternal death |
| **Setting:** | DELIVERY ROOM |
| **Perspective:** | Infants and their familiesHealth care practitioners providing care for newborn infants |
| **Background:** | As for Comparison #1 |
| **Conflict of interests:** | None |

# Assessment

|  |
| --- |
| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival, neonatal morbidities, and long-term neurodevelopment in preterm infants. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 CD003248}  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ● Trivial○ Small○ Moderate○ Large○ Varies○ Don't know | The systematic review identified **7 trials** (1073 infants). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Krueger 2015 394.e1, Pratesi 2018 364, Rabe 2011 205, Shirk 2019 482.e1} For the critical outcome of both survival to discharge (RR 0.99, 95% CI 0.95 to 1.02; I2=14%) and mortality (post hoc RR 1.21, 95% CI 0.76 to 1.94; I2=14%), the evidence of moderate certainty (downgraded for imprecision) from 5 trials involving 1000 infants, **could not exclude benefit or harm** with delayed cord clamping compared to intact-cord milking. There were no differences between delayed cord clamping compared to intact-cord milking for any of the outcomes: cerebral palsy (2 trials, 193 infants, RR 0.36, 95% CI 0.01 to 8.65); severe intraventricular hemorrhage (4 trials, 761 infants, RR 0.60, 95% CI 0.32 to 1.12; I2 = 23%); chronic lung disease (4 trials, 734 infants, RR 0.91, 95% CI 0.67 to 1.25; I2 = 0%); necrotizing enterocolitis (5 trials, 922 infants, RR 1.57, 95% CI 0.83 to 2.97; I2 = 0%); hyperbilirubinemia receiving phototherapy (2 trials, 236 infants, RR 1.05, 95% CI 0.90 to 1.24; I2 = 43%); hemoglobin at 24h after birth (6 trials, 914 infants, MD -0.002g/dL, 95% CI -0.56 to 0.53g/dL; I2 = 52%); and hematocrit at 24h after birth (5 trials, 841 infants, MD -0.18%, 95% CI -1.90 to 1.54%; I2 = 51%). | In summary, no differences were noted between delayed cord clamping and intact-cord milking. |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial● Varies○ Don't know | Overall, there were no undesirable effects of delayed cord clamping compared to intact-cord milking. For the critical outcome of severe intraventricular hemorrhage, evidence of moderate certainty (downgraded for imprecision) from 4 trials involving 761 infants **could not exclude benefit or harm** with later (delayed) cord clamping compared to intact-cord milking (RR 0.60, 95% CI 0.32 to 1.12; I2 = 23%). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205} One large clinical trial comparing intact-cord milking with later (delayed) cord clamping closed recruitment before completion because of an increased rate of severe IVH in infants born at <28 weeks gestational age who received intact-cord milking. {Katheria 2019 1877} | A recent randomized controlled trial comparing delayed cord clamping with intact-cord milking was stopped early due to a higher incidence of severe IVH in the milking group in the subgroup of very preterm infants (<28 weeks’ gestation). {Katheria 2019 1877}  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low● Moderate○ High○ No included studies | Evidence was moderate for the critical outcome of survival and for the critical outcomes of severe IVH, necrotizing enterocolitis, and chronic lung disease. It was also moderate for the important outcomes of hyperbilirubinemia receiving phototherapy, hemoglobin concentration and hematocrit within 24h after birth. | For some important outcomes, the GRADE analysis was post hoc.  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | The main outcomes are highly valued – they are critical outcomes. {Strand 2020 328, Webbe 2020 425} |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention● Varies○ Don't know | Overall, there were no undesirable effects of delayed cord clamping compared to intact-cord milking. For the critical outcome of severe IVH, evidence of moderate certainty (downgraded for imprecision) from 4 trials involving 761 infants **could not exclude benefit or harm** with later (delayed) cord clamping compared to intact-cord milking (RR 0.60, 95% CI 0.32 to 1.12; I2 = 23%). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205}One large clinical trial comparing intact-cord milking with later (delayed) cord clamping closed recruitment before completion because of an increased rate of severe IVH in infants born at <28 weeks gestational age who received intact-cord milking. {Katheria 2019 1877} | A recent randomized controlled trial comparing delayed cord clamping with intact-cord milking was stopped early due to a higher incidence of severe IVH in the milking group in the subgroup of very preterm infants (<28 weeks’ gestation). {Katheria 2019 1877} |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings● Varies○ Don't know | There are no published cost data. However, for infants who do not require resuscitation, it is likely that delaying cord clamping (30s) compared to intact-cord milking does not add cost. For infants requiring resuscitation additional equipment and additional training may be needed. | Cord clamping strategies in infants who do not require resuscitation need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. Training is required. |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | No data available. | We perceive the additional resource requirements and costs to be low for both this intervention and its comparison. |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | No data available | Although there are no published cost data, it is unlikely that delayed cord clamping compared to intact-cord milking will add costs for infants not requiring resuscitation. However, for infants requiring resuscitation additional equipment and additional training may be needed. |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced● Probably no impact○ Probably increased○ Increased○ Varies○ Don't know | No data available | Both the intervention and the comparison are widely available in all settings. |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | The 2015 CoSTR suggest delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence); and suggest against the routine use of cord milking for infants born at 28 weeks of gestation or less, because there is insufficient published human evidence of benefit. {Perlman 2015 S204‒S241}Although umbilical cord clamping practices may vary across sites and providers, there has been an increase in the practice of DCC over the last years. Cord milking is a less common practice of cord management. {El-Naggar 2020 58, Ortiz-Esquinas 2020 1738} | Both the intervention and the comparison are practiced. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | The intervention is feasible. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072}Later cord clamping and cut cord milking appeared to be feasible in the context of the included trials. It should be noted that in many studies, infants randomized to later (delayed) clamping may have received early clamping if they were thought to require resuscitation. For example, in the Tarnow-Mordi study {Tarnow-Mordi 2017 2445} 19.5% (146 of 748) infants in the later cord clamping group had non-adherence to their allocated study arm because of clinical concern about infant well-being. This is less likely to be the case with intact-cord milking, where the baby is more likely to have received a placental transfusion before the need for resuscitation was determined. | Current standard of care in some centers.  |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | **Varies** | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | **Varies** | Don't know |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

# Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | ●  | ○  | ○  |

# Type of recommendation (OVERALL)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for later (delayed) cord clamping > intact-cord milking > early clamping | Strong recommendation for the intervention |
| ○  | ○  | ○  | ●  | ○  |

# OVERALL Conclusions

|  |
| --- |
| Recommendation |
| **In infants born at less than 34 weeks’ gestational age who do not require immediate resuscitation after birth, we suggest deferring clamping the cord for at least 30 seconds (weak recommendation, low certainty of evidence).****In infants born at 28+0 to 33+6 weeks’ gestational age who do not require immediate resuscitation after birth, we suggest intact-cord milking as a reasonable alternative to deferring cord-clamping (weak recommendation, moderate certainty of evidence).** **We suggest against intact cord milking for infants born at less than 28 weeks’ gestational age (weak recommendation; very low certainty of evidence).**In infants born at less than 34 weeks’ gestational age who require immediate resuscitation, there is insufficient evidence to make a recommendation with respect to cord management. There is also insufficient evidence to make recommendations on cord management for maternal, fetal, or placental conditions that were considered exclusion criteria in many studies (in particular multiple fetuses, congenital anomalies, placental abnormalities, alloimmunization and/or fetal anemia, fetal compromise, and maternal illness). In these situations, we suggest individualized decisions based on severity of the condition and assessment of maternal and neonatal risk (weak recommendation; very low certainty of evidence). |
|  |
| Justification |
| The Task Force debated the certainty of evidence for the overall recommendation of later (delayed) cord clamping. Even though evidence for survival was ‘moderate certainty’ we felt that the doubt raised by the post hoc analysis of mortality justified downgrading our primary recommendation to ‘low certainty of evidence’.Exclusion criteria from clinical trials were a significant concern for the Task Force. Many pregnancies were excluded from studies for the following reasons:* Multiple fetuses
* Congenital anomalies and hydrops
* Placental abnormalities, including placenta previa, vasa previa, and abruption
* Alloimmunization and/or fetal anemia
* Fetal compromise including fetal growth restriction
* Maternal conditions or obstetrical concern

We were unable to draw conclusions from subgroup analyses with respect to these exclusion criteria. We therefore suggest caution when making cord management decisions in the presence of any of these conditions. In the absence of evidence from these subgroups, decisions regarding cord management should be individualized and based on the severity of the presenting condition(s) and an assessment of risk to the mother or baby during and after delivery. Our suggestions/recommendations were justified based on several inferences that included the following:1. The critical outcome of survival with later (delayed) clamping versus early clamping suggests benefit or neutrality from delaying clamping.
2. There are no significant differences in other critical outcomes for all comparisons.
3. There is improvement in important cardiovascular (blood pressure), therapeutic (inotropic support and/or transfusions), and hematological outcomes with delayed (later) clamping and/or intact-cord milking versus early clamping.
4. There are no significant differences between later (delayed) clamping and intact-cord milking (except for the presence of a “signal for harm” from intact-cord milking in infants born at <28 weeks’ gestational age in a single large study).
5. Only one small study was available for cut-cord milking.
6. Post hoc and subgroup analyses and GRADE evaluations did not conflict with our suggestions or recommendations.
7. There is a paucity of evidence available to make recommendations for cord management in the preterm infant needing immediate resuscitation.

*1:**Survival with delayed (later) clamping versus early clamping* This analysis was based on the preference of ILCOR to use survival to discharge as the primary outcome rather than mortality. It showed that later (delayed) cord clamping for 30 seconds or more in infants who do not require immediate resuscitation may have a survival benefit or make no difference when compared to early clamping (moderate certainty evidence, RR 1.02 and lower confidence interval just reaching 1.00). However, for mortality, the confidence intervals were wider and crossed 1.00.When calculating confidence intervals around a relative risk, events that occur frequently (such as survival) will result in a narrower confidence interval than events that occur infrequently (in this case, mortality). In the included studies, survival was much more common than mortality. As a result, we anticipated that the confidence interval around survival and mortality would appear to have different precision. For transparency, we included the estimate for both outcomes. As a consequence of the wider confidence intervals, a post hoc analysis of mortality was unable to exclude benefit or harm (RR 0.80, 95% CI 0.63 to 1.02).Our inference is that delayed cord clamping is safe and may be beneficial when compared to early clamping in infants born at <34 weeks who do not require immediate resuscitation. With a 2% increase in survival, the number needed to benefit is 50 (confidence interval 25 to >1000).Overall, we interpret the data to suggest that later (delayed) cord clamping is likely to be safe and may have a benefit whether the outcome is described as survival or mortality.*2: No significant differences in other critical outcomes with any other comparison*With the exception of survival to discharge when later (delayed) clamping and early cord clamping were compared, no comparisons showed significant benefit or harm for any critical neonatal (or maternal) outcomes including severe intraventricular hemorrhage, chronic lung disease, necrotizing enterocolitis, neurodevelopment and maternal postpartum hemorrhage and infection.*3: Possible benefits in important outcomes with later (delayed) clamping or intact-cord milking versus early clamping.*Although there were no significant effects for all but one critical neonatal outcome, there were significant effects on some important outcomes. Later (delayed) cord clamping and intact-cord milking resulted in fewer infants receiving inotropic support, higher hemoglobin and hematocrit by 24 hours and 7 days, and fewer infants receiving blood transfusions. There were no significant effects on use of respiratory support after birth or use of phototherapy. However, 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. These beneficial effects have a clinically important impact on inpatient care. Together with the potential benefit for the critical outcome of survival to discharge, they influenced us to suggest either later (delayed) cord clamping or intact-cord milking (in the case of infants born at 28+0 to33+0 weeks’ gestational age) over early clamping, despite the lack of evidence for benefit for other critical outcomes.*4: Lack of significant differences between later (delayed) clamping and intact-cord milking*The analysis, with moderate certainty, showed no significant differences in outcomes between later (delayed) clamping and intact-cord milking.We noted that one large clinical trial comparing intact-cord milking with later (delayed) cord clamping closed recruitment before completion because of an increased rate of severe intraventricular hemorrhage in infants born at <28 weeks gestational age who received intact-cord milking. {Katheria 2019 1877} However, meta-analysis of **4 trials** involving 761 infants **could not exclude benefit or harm** from later (delayed) cord clamping compared to intact-cord milking (RR 0.60, 95% CI 0.32 to 1.12; I2 = 23%). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205}These findings influenced us to suggest intact-cord milking as a reasonable alternative to delayed cord clamping, except for infants born at <28 weeks’ gestational age.*5: Cut-cord milking*Only one study was included in this comparison (60 infants). Given the small numbers and nonsignificant findings, this comparison was not considered in our suggestions or recommendations. {Ram Mohan 2018 88}*6: Post hoc and subgroup analyses and GRADE evaluations*Subgroup analyses are exploratory and must be interpreted with caution.The p-values for interaction did not suggest important influences of gestational age (p = 0.26 for interaction) or duration of deferral of cord clamping on survival to discharge (p = 0.27 for interaction).There was some evidence that the effect of later cord clamping on survival to discharge may be influenced by setting, with treatment effect being apparent only in studies performed in high-income countries (p= 0.01 for interaction; studies in high-income countries: RR 1.06, 95% CI 1.02 to 1.11; I2 = 0%; studies in low-and-middle income countries: RR 0.97, 95% CI 0.92 to 1.01; I2 = 39%). We caution that the difference in effect direction, size and significance between low-and-middle- and high- income countries could be a result of variation in resources available to individual participating hospitals within each country.We do not have sufficient confidence in these findings to make separate recommendations for cord management by country income, by gestational age, or interval from birth to cord clamping (beyond 30s). We consider that the beneficial effect of delayed clamping in high-income countries is likely to be widely generalizable and should therefore be offered in all settings. *7: Cord management when immediate resuscitation is required*There is insufficient evidence to make any recommendation for cord management in preterm infants who require immediate resuscitation.**Overall justification:**In 2015, the ILCOR Neonatal Task Force stated: *“We suggest delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence). There is insufficient evidence to recommend an approach to cord clamping for preterm infants who do receive resuscitation immediately after birth, because many infants who were at high risk of requiring resuscitation were excluded from or withdrawn from the studies.”* {Perlman 2015 S204‒S241} An updated review of the evidence does not substantially change this recommendation.As all critical outcomes but one (survival to discharge with later (delayed) cord clamping versus early clamping) did not show either benefit or harm, we drew our conclusions from that one outcome and the important neonatal outcomes of fewer infants receiving inotropic support, higher hemoglobin and hematocrit concentrations, fewer blood transfusions, and otherwise no evidence of harm for the mother or neonate. Limited subgroup analyses were non-contributory but did not contradict the results of critical or important comparisons. Two previous systematic reviews suggest benefits from later (delayed) clamping over early clamping in preterm infants for survival and other outcomes. {Fogarty 2018 1, Rabe 2008 138} The systematic review that informed this statement of Consensus on Science with Treatment Recommendations {Seidler 2021 } included an additional 11 studies, while removing studies with substantial late preterm populations. All three reviews are in general accord in suggesting that benefits outweigh harms of later (delayed) cord clamping in preterm infants resembling those enrolled in the included trials. A large systematic review derived from individual patient data is underway and may improve the certainty of evidence for some critical and important outcomes. {Seidler 2020 e034595}It should be noted that in many studies, infants randomized to later (delayed) clamping may have received early clamping if they were thought to require resuscitation. For example, in the largest study {Tarnow-Mordi 2017 2445} 19.5% (146 of 748) infants in the later cord clamping group had non-adherence to their allocated study arm because of clinical concern about infant well-being. This is less likely to be the case with intact-cord milking, where the baby is more likely to have received a placental transfusion before the need for resuscitation was determined. We await the results of studies that are underway or planned that examine resuscitation with the cord intact, which may help determine the optimal umbilical cord management for infants at highest risk for mortality and neonatal morbidity.There is currently insufficient evidence to make a recommendation with respect to cord management for preterm infants who require immediate resuscitation. There is also uncertainty regarding the optimal cord management strategy in deliveries complicated by multiple pregnancies, infants who have major congenital abnormalities, fetal anemia, or other conditions that may impact maternal or fetal well-being at the time of birth. There is also uncertainty regarding optimal cord management in the setting of placental problems including abruption, incision through an anterior placenta, placenta previa, or abnormalities of placental vasculature or insertion. Until more data are available for specific situations such as these, decisions about cord management in the presence of maternal, placental, or fetal complications need to be individualized, based on severity of presentation and clinical assessment of risk to the mother or baby.The uncertainty of the updated evidence (including its generalisability to infants at highest risk for adverse outcomes) influences the decision to continue to make a ‘weak’ recommendation. |

|  |
| --- |
| Subgroup considerations |
| As described in the “Justification” (preceding section) |
| Implementation considerations |
| Early cord clamping, and the 3 cord management approaches evaluated as interventions appear to be feasible in the context of the included trials.It should be noted that in many studies, infants randomized to later (delayed) clamping may have received early clamping if they were thought to require resuscitation. For example, in the largest study{Tarnow-Mordi 2017 2445} 19.5% (146 of 748) infants in the later cord clamping group had non-adherence to their allocated study arm because of clinical concern about infant well-being. This is less likely to be the case with intact-cord milking, where the baby is more likely to have received a placental transfusion before the need for resuscitation was determined. We await the results of studies that are underway or planned that examine resuscitation with the cord intact, which may help determine the optimal umbilical cord management for infants at highest risk for mortality and neonatal morbidity. |

|  |
| --- |
| Monitoring and evaluation |
| 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. |
| Research priorities |
| We identified the following knowledge gaps: * There are insufficient data on long-term neurodevelopment outcomes, or any other post-discharge outcomes.
* There are insufficient data on cord management as a public health strategy to impact child health and development
* There are insufficient data for cord management among preterm infants who require immediate resuscitation.
* There are insufficient data for cord management among preterm infants with specific conditions, such as congenital heart or lung disease.
* The long-term neurodevelopmental outcomes of intact-cord milking in extremely preterm infants is uncertain.
* The optimal timing of cord clamping is not known, nor is how it should be determined with different maternal or fetal conditions.
* There are limited numbers of studies of cut-cord milking as a management strategy
* The impact of cord management on vertical transmission of infectious diseases is uncertain
* There is a need for widely agreed 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”.
 |

**References**

1. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol. 2013;591(8):2113.

2. Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. Lancet. 1969;2(7626):871.

3. Hooper SB, Polglase GR, Roehr CC. Cardiopulmonary changes with aeration of the newborn lung. Paediatr Respir Rev. 2015;16(3):147.

4. Kluckow M, Hooper SB. Using physiology to guide time to cord clamping. Semin Fetal Neonatal Med. 2015;20(4):225.

5. Niermeyer S, Velaphi S. Promoting physiologic transition at birth: re-examining resuscitation and the timing of cord clamping. Semin Fetal Neonatal Med. 2013;18(6):385.

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(1):18.

7. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, 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.

8. Mercer JS, Erickson-Owens DA, Vohr BR, Tucker RJ, Parker AB, Oh W, et al. Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial. J Pediatr. 2016;168:50.

9. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. 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.

10. Aladangady N, McHugh S, Aitchison TC, Wardrop CA, Holland BM. Infants' blood volume in a controlled trial of placental transfusion at preterm delivery. Pediatrics. 2006;117(1):93.

11. Armanian AM, Tehrani H, Ansari M, Ghaemi S. Is "Delayed Umbilical Cord Clamping" Beneficial for Premature Newborns? International Journal of Pediatrics. 2017;5:4909.

12. Backes CH, Huang H, Iams JD, Bauer JA, Giannone PJ. Timing of umbilical cord clamping among infants born at 22 through 27 weeks' gestation. Journal of perinatology : official journal of the California Perinatal Association. 2016;36(1):35.

13. Baenziger O, Stolkin F, Keel M, Von Siebenthal K, Fauchere J-C, Das Kundu S, et al. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. Pediatrics. 2007;119(3):455.

14. Das S, Sarkar N, Bhattacharya M, Basu S, Sanyal D, Chatterjee A, et al. Neurological outcome at 30 months of age after mild hypothermia via selective head cooling in term neonates with perinatal asphyxia using low-cost coolcap: a single-center randomized control pilot trial in India. J Pediatr Neurol. 2017;15(04):157.

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

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

17. Duley L, Dorling J, Pushpa-Rajah A, Oddie SJ, Yoxall CW, Schoonakker B, et al. Randomised trial of cord clamping and initial stabilisation at very preterm birth. Arch Dis Child Fetal Neonatal Ed. 2018;103(1):F6.

18. Finn D, Ryan DH, Pavel A, O'Toole JM, Livingstone V, Boylan GB, 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.

19. Gokmen Z, Ozkiraz S, Tarcan A, Kozanoglu I, Ozcimen EE, Ozbek N. Effects of delayed umbilical cord clamping on peripheral blood hematopoietic stem cells in premature neonates. Journal of Perinatal Medicine. 2011;39(3):323.

20. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clampings. Findings and hypothesis. South African Medical Journal. 1988;73(2):104.

21. Hofmeyr GJ, Gobetz L, Bex PJ, Van der Griendt M, Nikodem C, Skapinker R, et al. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. Online J Curr Clin Trials. 1993:110.

22. Kazemi M, Akbarianrad Z, Zahedpasha Y, Mehraein R, Mojaveri M. Effects of Delayed Cord Clamping on Intraventricular Hemorrhage in Preterm Infants. Iranian Journal of Pediatrics. 2017;In Press.

23. Kinmond S, Aitchison TC, Holland BM, Jones JG, Turner TL, Wardrop CA. Umbilical cord clamping and preterm infants: a randomised trial. Bmj. 1993;306(6871):172.

24. Kugelman A, Borenstein-Levin L, Riskin A, Chistyakov I, Ohel G, Gonen R, et al. Immediate versus Delayed Umbilical Cord Clamping in Premature Neonates Born < 35 Weeks: A Prospective, Randomized, Controlled Study. American Journal Of Perinatology. 2007;24(05):307.

25. McDonnell M, Henderson-Smart DJ. Delayed umbilical cord clamping in preterm infants: a feasibility study. J Paediatr Child Health. 1997;33(4):308.

26. Mercer JS, McGrath MM, Hensman A, Silver H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. J Perinatol. 2003;23(6):466.

27. Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics. 2006;117(4):1235.

28. Oh W, Fanaroff AA, Carlo WA, Donovan EF, Mcdonald SA, Poole WK. Effects of delayed cord clamping in very-low-birth-weight infants. Journal of Perinatology. 2011;31(S1):S68.

29. Rabe H, Wacker A, Hülskamp G, Hörnig-Franz I, Schulze-Everding A, Harms E, et al. A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. Eur J Pediatr. 2000;159(10):775.

30. Rana A, Agarwal K, Ramji S, Gandhi G, Sahu L. Safety of delayed umbilical cord clamping in preterm neonates of less than 34 weeks of gestation: a randomized controlled trial. Obstet Gynecol Sci. 2018;61(6):655.

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

32. Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, et al. Delayed versus Immediate Cord Clamping in Preterm Infants. N Engl J Med. 2017;377(25):2445.

33. Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2020;105(3):328.

34. Webbe JWH, Duffy JMN, Afonso E, Al-Muzaffar I, Brunton G, Greenough A, et al. Core outcomes in neonatology: development of a core outcome set for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020;105(4):425.

35. El-Naggar W, Afifi J, Dorling J, Bodani J, Cieslak Z, Canning R, et al. A Comparison of Strategies for Managing the Umbilical Cord at Birth in Preterm Infants. J Pediatr. 2020;225:58.

36. Ibrahim NO, Sukkarieh HH, Bustami RT, Alshammari EA, Alasmari LY, Al-Kadri HM. Current umbilical cord clamping practices and attitudes of obstetricians and midwives toward delayed cord clamping in Saudi Arabia. Ann Saudi Med. 2017;37(3):216.

37. Ortiz-Esquinas I, Gómez-Salgado J, Pascual-Pedreño AI, Rodríguez-Almagro J, Ballesta-Castillejos A, Hernández-Martínez A. Variability and associated factors in the management of cord clamping and the milking practice among Spanish obstetric professionals. Sci Rep. 2020;10(1):1738.

38. Alan S, Arsan S, Okulu E, Akin IM, Kilic A, Taskin S, 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(8):e493.

39. El-Naggar W, Simpson D, Hussain A, Armson A, Dodds L, Warren A, et al. Cord milking versus immediate clamping in preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2019;104(2):F145.

40. Elimian A, Goodman J, Escobedo M, Nightingale L, Knudtson E, Williams M. 35: A randomized controlled trial of immediate versus delayed cord clamping in the preterm neonate. American Journal of Obstetrics and Gynecology. 2013;208(1, Supplement):S22.

41. Hosono S, Mugishima H, Fujita H, Hosono A, Minato M, Okada T, 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(1):F14.

42. Katheria A, Blank D, Rich W, Finer N. Umbilical cord milking improves transition in premature infants at birth. PLoS One. 2014;9(4):e94085.

43. Kilicdag H, Gulcan H, Hanta D, Torer B, Gokmen Z, Ozdemir SI, et al. Is umbilical cord milking always an advantage? J Matern Fetal Neonatal Med. 2016;29(4):615.

44. Lago Leal V, Pamplona Bueno L, Cabanillas Vilaplana L, Nicolás Montero E, Martín Blanco M, Fernández Romero C, et al. Effect of Milking Maneuver in Preterm Infants: A Randomized Controlled Trial. Fetal Diagnosis and Therapy. 2018;45.

45. Li J, Yu B, Wang W, Luo D, Dai QL, Gan XQ. Does intact umbilical cord milking increase infection rates in preterm infants with premature prolonged rupture of membranes? J Matern Fetal Neonatal Med. 2020;33(2):184.

46. March MI, Hacker MR, Parson AW, Modest AM, de Veciana M. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. J Perinatol. 2013;33(10):763.

47. Silahli M, Duman E, Gokmen Z, Toprak E, Gokdemir M, Ecevit A. The relationship between placental transfusion, and thymic size and neonatal morbidities in premature infants - A Randomized Control Trial. J Pak Med Assoc. 2018;68(11):1560.

48. Song SY, Kim Y, Kang BH, Yoo HJ, Lee M. Safety of umbilical cord milking in very preterm neonates: a randomized controlled study. Obstet Gynecol Sci. 2017;60(6):527.

49. Kumbhat N, Eggleston B, Davis AS, DeMauro SB, Van Meurs KP, Foglia EE, et al. Umbilical Cord Milking vs Delayed Cord Clamping and Associations with In-Hospital Outcomes among Extremely Premature Infants. J Pediatr. 2021.

50. Katheria A, Reister F, Essers J, Mendler M, Hummler H, Subramaniam A, et al. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. Jama. 2019;322(19):1877.

51. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical Cord Milking Versus Delayed Cord Clamping in Preterm Infants. Pediatrics. 2015;136(1):61.

52. Krueger MS, Eyal FG, Peevy KJ, Hamm CR, Whitehurst RM, Lewis DF. Delayed cord clamping with and without cord stripping: a prospective randomized trial of preterm neonates. Am J Obstet Gynecol. 2015;212(3):394.e1.

53. Pratesi S, Montano S, Ghirardello S, Mosca F, Boni L, Tofani L, et al. Placental Circulation Intact Trial (PCI-T)-Resuscitation With the Placental Circulation Intact vs. Cord Milking for Very Preterm Infants: A Feasibility Study. Front Pediatr. 2018;6:364.

54. Rabe H, Jewison A, Fernandez Alvarez R, Crook D, Stilton D, Bradley R, et al. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. Obstet Gynecol. 2011;117(2 Pt 1):205.

55. Shirk SK, Manolis SA, Lambers DS, Smith KL. Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. Am J Obstet Gynecol. 2019;220(5):482.e1.

56. Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: neonatal resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2015;132(suppl 1)(16):S204‒S241.

57. Ram Mohan G, Shashidhar A, Chandrakala BS, Nesargi S, Suman Rao PN. Umbilical cord milking in preterm neonates requiring resuscitation: A randomized controlled trial. Resuscitation. 2018;130:88.

58. Rabe H, Reynolds G, Diaz-Rossello J. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology. 2008;93(2):138.

59. Seidler AL, Gyte GM, Rabe H, Diaz-Rossello J, Duley L, Aziz K, et al. Umbilical Cord Management for Newborns < 34 weeks' Gestation: a meta-analysis. . Pediatrics. 2021;In press.

60. Seidler AL, Duley L, Katheria AC, De Paco Matallana C, Dempsey E, Rabe H, et al. Systematic review and network meta-analysis with individual participant data on cord management at preterm birth (iCOMP): study protocol. BMJ Open. 2020;10(3):e034595.