**Evidence to decision table for cord management at birth for Term and Late Preterm infants (nls # 1551)**

This evidence to decision (EtD) table will include evidence for three questions or comparisons examined in the review, as follows.

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| **Comparison 1: Later (delayed) cord clamping at ≥ 30 seconds compared to early cord clamping at < 30 seconds after birth** | **33 studies, 5263 mothers and their infants** | **EtD table included** |
| Comparison 2: Intact cord milking versus early cord clamping | 1 study, 24 infants | No |
| Comparison 3: Cut-cord milking vs early cord clamping | 1 study, 200 infants | No |
| Comparison 4: Later (delayed) cord clamping vs intact-cord milking | 1 study – serious methodological problems | No |
| **Comparison 5: Later (delayed cord clamping at ≥30 seconds versus cut-cord milking** | **3 studies, 740 infants** | **EtD table included** |
| Comparison 6: Intact-cord milking vs cut-cord milking | No studies | No |
| **Comparison 7: Later (delayed) cord clamping ≥60 seconds versus later (delayed) cord clamping at< 60 seconds** | **7 studies, 2745 mothers and their infants** | **EtD table included** |
| Comparison 8: Later (delayed) cord clamping at ≥ 30 seconds versus physiological approach to cord clamping (waiting until cessation of pulsation of the cord or based on vital signs monitoring or initiation of breathing) | 3 studies, 1113 mothers and their infants | No |

Evidence to Decision tables were not prepared for the other comparisons, because of insufficient data, or in the case of comparison #8, findings of very little difference between the intervention and control.

|  |  |
| --- | --- |
| Question #1 | |
| **Should later (delayed) cord clamping vs. early cord clamping be used for term and late preterm infants?** | |
| **Population:** | Term and late preterm infants. |
| **Intervention:** | Later (delayed) cord clamping at ≥ 30 seconds |
| **Comparison:** | Early cord clamping at <30 seconds after birth |
| **Main outcomes:** | Survival without moderate to severe neurodevelopmental impairment in early childhood; anemia four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL or as defined by the trial authors); neonatal mortality; moderate to severe hypoxic ischemic encephalopathy; resuscitation (positive pressure ventilation ± intubation ± chest compression); respiratory distress of any type or duration as described by the authors; admission to neonatal intensive care unit or special care nursery; hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth; hematocrit (%) within the first 24 hours and within 7days after birth after birth; hyperbilirubinemia treated with phototherapy; polycythemia (hematocrit greater than 65%); partial exchange transfusion; exchange transfusion; moderate to severe neurodevelopmental impairment in early childhood; ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L).  Maternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors); severe postpartum hemorrhage (clinically estimated blood loss of at least 1000 mL); manual removal of the placenta; post-partum infection. |
| **Setting:** | Delivery Room |
| **Perspective:** | Infants and their families  Health care practitioners providing care for newborn infants |
| **Background:** | Umbilical cord management affects every one of the 140 million babies born in the world each year. At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} |
| **Conflict of interests:** | None |

# Assessment

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| --- | --- | --- |
| Problem Is 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 140 million babies born in the world each year.{https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} | The widespread practice of early umbilical cord clamping is not evidence-based. Umbilical cord management varies greatly among professional groups and across different regions. |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | The prevalence of iron deficiency and iron deficiency anemia has been reported to be as high as 26% and 3-7%, respectively among young children in Europe {Bramhagen 1999 1333, Persson 1998 618, Thane 2000 433} The global prevalence of iron deficiency anemia has been reported to be 33%, with the highest burden in children less than five years of age.{Kassebaum 2014 615} Iron deficiency in young children has been associated with impaired motor development, behavioral problems and cognitive delay. {Grantham-McGregor 2001 649S, Gunnarsson 2007 391, Lozoff 2006 1108} A delay in cord clamping at birth may improve iron status, reduce iron deficiency in infancy and may consequently improve long-term neurodevelopmental outcomes. {Andersson 2011 d7157, Andersson 2015 631}  Our review of the evidence of benefits of later cord clamping identified higher hemoglobin and hematocrit concentration during the neonatal period and lower iron deficiency in infancy without significant maternal adverse effects. However, no evidence was found to support a significant benefit of later cord clamping for the other critical and important outcomes. | Cord management and placental transfusion at birth may play a significant role, at no cost, in reducing iron deficiency in both well-resourced and resource-limited countries. This could potentially have a global impact on neurodevelopment later in childhood. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know | Our review of the evidence found later cord clamping increased polycythemia (hematocrit >65%) and possibly increased the use of phototherapy for treatment of hyperbilirubinemia compared to early cord clamping. However, there was no evidence of increased rates of exchange transfusion and there was no evidence of harm found in other important or critical outcomes. | It is not clear if there is any clinical impact of the increased rates of polycythemia (hematocrit >65%) with the later cord clamping. Rates of *symptomatic* polycythemia were not available and there was no evidence of an increase in the rates of partial exchange transfusion.  The outcome of phototherapy for treatment of jaundice is not objectively and consistently defined. This area merits further research with measurement of bilirubin concentrations and thresholds for treatment.  More research is required in middle- and low-income countries to refine our estimates of the risks of undesirable effects. |
| Certainty of evidence What 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 was very low for the critical outcomes of neonatal mortality and neurodevelopmental impairment in childhood and was low for the critical outcome of maternal postpartum hemorrhage.  The certainty of evidence ranged from very low to low for the important outcomes as resuscitation at birth and hematological status in neonatal period and in infancy. |  |
| Values Is 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 of the systematic review were: anemia at four to six months after birth, survival without moderate to severe neurodevelopmental impairment in early childhood, and maternal postpartum hemorrhage. Given that the intervention is simple and at no cost, and considering the main outcomes are critical, there is no important uncertainty or variability in how much people value the main outcomes despite the very low certainty of evidence of the effects. | Collection of cord blood for banking may pose a competing interest. |
| Balance of effects Does 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 | The improved hemoglobin and iron status associated with later cord clamping in the neonatal period and in early infancy, may help in the prevention of the complications of iron deficiency, such as anemia and developmental delay. Rates of iron deficiency are highest in resource-limited settings and therefore the potential benefits of later cord clamping may be greatest in these areas.  However, as later cord clamping is associated with increased rates of polycythemia and a possible increase in use of phototherapy for hyperbilirubinemia, monitoring for hyperbilirubinemia should be conducted for all newborns, with access to treatment when indicated. This may necessitate strengthening of monitoring and referral systems in some settings. |  |
| Resources required How 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 | No studies have reported resource implications | The intervention is simple and of no cost, however, there is limited data about the possible cost-saving associated with the potential benefits (reducing iron deficiency and the consequent neurodevelopmental impairments) and the possible costs of monitoring and managing the adverse effects of increased polycythemia and hyperbilirubinemia. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does 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 studies have examined cost-effectiveness | The costs associated with iron deficiency and its consequences vs. the possible increase in monitoring and treatment of hyperbilirubinemia, are not known in any setting.  In middle- and low-income countries, the benefit-risk assessment can be complicated and different from one setting to another depending on the available resources and the prevalence of iron deficiency. More research is needed to address this important area. |
| Equity What 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 | This is a simple, easy and inexpensive intervention that can be implemented by health care providers in any place in the world to improve the hematological status and prevent iron deficiency which is prevalent globally (in high- as well as middle- and low-income countries). Embracing such intervention would foster health equity.  Research studies conducted thus far, reflect the high interest from low- and 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} as well as high-income countries. {Al-Tawil 2012 319, Andersson 2011 d7157, Chen 2018 251, Philip 1973 334}  However, there might be disparity in monitoring and management of the potential adverse effects (hyperbilirubinemia treated with phototherapy) related to the lack of resources in the lower income countries. |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | The intervention has been recommended by many governing bodies including WHO and has been practiced as the standard of care for most infants at birth over the past decade?  The research studies related to the intervention (later cord clamping) were conducted in different settings with variable resources. | There is a high level of interest in later cord clamping among pregnant women, as reflected on social media sites and childbirth education courses. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | The intervention is simple and easy to implement at no cost.  The intervention is feasible for any health care provider worldwide after minimal guidance/training and has been recommended by WHO since 2012. {World Health Organization 2012 }  The research studies related to the intervention (later cord clamping) were conducted in different settings with variable resources which shows that the intervention is feasible. | The intervention has been the standard practice in many centers providing childbirth care worldwide. |

# 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 |
| ○ | ○ | ○ | **●** | ○ |

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| Question 5 | |
| **Should later (delayed) cord clamping vs. cut-cord milking be used for term and late preterm infants ?** | |
| **Population:** | Term and late preterm babies |
| **Intervention:** | Later (delayed) cord clamping at ≥ 30 seconds |
| **Comparison:** | Cut-cord milking |
| **Main outcomes:** | Survival without moderate to severe neurodevelopmental impairment in early childhood; anemia four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL or as defined by the trial authors); neonatal mortality; moderate to severe hypoxic ischemic encephalopathy; resuscitation (positive pressure ventilation ± intubation ± chest compression); respiratory distress of any type or duration as described by the authors; admission to neonatal intensive care unit or special care nursery; hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth; hematocrit (%) within the first 24 hours and within 7days after birth after birth; hyperbilirubinemia treated with phototherapy; polycythemia (hematocrit greater than 65%); partial exchange transfusion; exchange transfusion; moderate to severe neurodevelopmental impairment in early childhood; ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L).  *Maternal; m*aternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors); severe postpartum hemorrhage (clinically estimated blood loss of at least 1000 mL); manual removal of the placenta; post-partum infection. |
| **Setting:** | Delivery Room |
| **Perspective:** | Infants and their families  Health care practitioners providing care for newborn infants |
| **Background:** | Umbilical cord management affects every one of the 140 million babies born in the world each year. {https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266}. Cut-cord milking may be an alternative to later cord clamping as a means for added blood transfusion to the baby at birth {Jaiswal 2015 1159, Yadav 2015 720} especially when later cord clamping is not feasible or contraindicated. |
| **Conflict of interests:** | None |

# Assessment

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| --- | --- | --- |
| Problem Is 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 140 million babies born in the world each year. {https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} Cut-cord milking may be an alternative to later cord clamping as a means for added blood transfusion to the baby at birth {Jaiswal 2015 1159, Yadav 2015 720} especially when later cord clamping is not feasible or contraindicated. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | The prevalence of iron deficiency and iron deficiency anemia has been reported to be as high as 26% and 3-7%, respectively among young children in Europe.{Bramhagen 1999 1333, Persson 1998 618, Thane 2000 433} The global prevalence of iron deficiency anemia has been reported to be 33%, with the highest burden in children less than five years of age (Kassebaum 2014 615). Iron deficiency in young children has been associated with impaired motor development, behavioral problems and cognitive delay {Grantham-McGregor 2001 649S, Gunnarsson 2007 391, Lozoff 2006 1108} A delay in cord clamping at birth may improve iron status, reduce iron deficiency in infancy and may consequently improve long-term neurodevelopmental outcomes. {Andersson 2011 d7157, Andersson 2015 631}  Cut-cord milking may be an alternative to later cord clamping as a means for added blood transfusion to the baby at birth {Jaiswal 2015 1159, Yadav 2015 720} especially when later cord clamping is not feasible or is contraindicated.  Our review of the evidence of benefits of cut-cord milking identified higher hemoglobin and hematocrit concentration during the neonatal period. However, no evidence was found to support a significant benefit of later cord clamping on the other critical and important outcomes. | Assisted ventilation in combination with cut-cord milking, may provide a more physiological approach to facilitate placental transfusion when newborn infants are not breathing at birth. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | The few available studies comparing later cord clamping to cut-cord milking {Jaiswal 2015 1159, Vatansever 2018 877, Yadav 2015 720} did not report significant adverse effects.  The available evidence did not exclude benefit or harm related to hyperbilirubinemia treated with phototherapy, when cut-cord milking was compared to later cord clamping. Since later cord clamping was found to increase polycythemia and hyperbilirubinemia treated with phototherapy when compared to early cord clamping, these may represent potential undesirable effects of cut-cord milking as well. | It is unclear whether cut-cord milking causes adverse effects if conducted before establishing breathing at birth. |
| Certainty of evidence What 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 was very low for the reported outcomes. |  |
| Values Is 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 of the systematic review were: anemia at four to six months after birth, survival without moderate to severe neurodevelopmental impairment in early childhood, and maternal postpartum hemorrhage. Given that the interventions are simple and of no cost, and considering the main outcomes are critical, there is no important uncertainty or variability in how much people value the main outcomes despite the very low certainty of evidence of the effects. | Collection of cord blood for banking may pose a competing interest. |
| Balance of effects Does 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 | - The number of the studies (3) and the studied population (740) included in the systematic review were low.  - Apart from neonatal mortality, which was addressed only by one small study {Yadav 2015 720}, no other critical outcomes were reported.  - Compared to later cord clamping, two small studies {Jaiswal 2015 890, Yadav 2015 720} showed an increase in neonatal hemoglobin and hematocrit in the cut-cord milking group, without a significant increase in phototherapy-treated hyperbilirubinemia.  - The improved hemoglobin with cut-cord milking in the neonatal period, may help in the prevention of the complications of iron deficiency, such as anemia and developmental delay. However, there are no available studies to address the long-term effects of cut-cord milking on iron deficiency, anemia or neurodevelopment in infancy or childhood. | It is unclear if there are long-lasting benefits or harms from either intervention when compared to the other. |
| Resources required How 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 | No studies have reported resource implications | Both interventions can be conducted at no cost and with minimal training but there is limited data on the potential costs related to their outcomes as not all the important outcomes were studied/reported. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does 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 studies have addressed cost effectiveness | Both interventions can be conducted at no cost and with minimal training but there is limited data on the potential costs related to their outcomes as not all the important outcomes were studied/reported. |
| Equity What 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 | There are no studies examining health equity | Both interventions are feasible and accessible at no cost for any health care provider regardless of resource availability.  Not all the outcomes that might affect health equity have been studied. |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | The intervention is simple, inexpensive and practical but may need minimal training. Cut-cord milking has the potential to be an alternative to later cord clamping in situations where later cord clamping is not feasible or contraindicated. | More research is needed as currently there are only a few small studies which inform this question. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | The intervention is simple, easy to implement at no cost. It may need minimal training. It is feasible for all health care providers worldwide. |  |

# 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 7 | |
| **Should Delayed cord clamping ≥ 60 seconds vs. < 60 seconds be used for term and late preterm infants** | |
| **Population:** | Term and late preterm babies |
| **Intervention:** | Later (delayed) cord clamping at ≥ 60 seconds |
| **Comparison:** | Later (delayed) cord clamping at < 60 seconds |
| **Main outcomes:** | Survival without moderate to severe neurodevelopmental impairment in early childhood; anemia four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL or as defined by the trial authors); neonatal mortality; moderate to severe hypoxic ischemic encephalopathy; resuscitation (positive pressure ventilation ± intubation ± chest compression); respiratory distress of any type or duration as described by the authors; admission to neonatal intensive care unit or special care nursery; hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth; hematocrit (%) within the first 24 hours and within 7days after birth after birth; hyperbilirubinemia treated with phototherapy; polycythemia (hematocrit greater than 65%); partial exchange transfusion; exchange transfusion; moderate to severe neurodevelopmental impairment in early childhood; ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L).  Maternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors); severe postpartum hemorrhage (clinically estimated blood loss of at least 1000 mL); manual removal of the placenta; post-partum infection. |
| **Setting:** | Delivery Room |
| **Perspective:** | Infants and their families  Health care practitioners providing care for newborn infants |
| **Background:** | Umbilical cord management affects every one of the 140 million babies born in the world each year. {https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} The optimal duration of later cord clamping was among knowledge gaps identified by ILCOR in the 2015 statement. |
| **Conflict of interests:** | None |

# Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is 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 140 million babies born in the world each year. At the time of birth, a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} The optimal timing of later cord clamping is unknown and was considered among knowledge gaps identified by ILCOR in the 2015 statement. | The optimal timing of cord clamping after birth has not been determined. Early studies of the time course of placental transfusion {Yao 1969 871} suggest that the rate of transfer is most rapid in the first minute, but transfer continues beyond this time. |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | The prevalence of iron deficiency and iron deficiency anemia has been reported to be as high as 26% and 3-7%, respectively among young children in Europe. {Bramhagen 1999 1333, Persson 1998 618, Thane 2000 433} The global prevalence of iron deficiency anemia has been reported to be 33%, with the highest burden in children less than five years of age. {Kassebaum 2014 615} Iron deficiency in young children has been associated with impaired motor development, behavioral problems and cognitive delay. {Grantham-McGregor 2001 649S, Gunnarsson 2007 391, Lozoff 2006 1108} A delay in cord clamping at birth may improve iron status, reduce iron deficiency in infancy and may consequently improve long-term neurodevelopmental outcomes. {Andersson 2011 d7157, Andersson 2015 631}  Our review of the evidence of benefits of later cord clamping ≥ 60 seconds vs. < 60 seconds, identified higher hemoglobin and hematocrit concentration during the neonatal period and higher neuro-developmental scores in childhood, in the group that received later cord clamping for ≥ 60 seconds. However, no evidence was found to support a significant benefit of later cord clamping for ≥ 60 seconds on the other critical and important outcomes. |  |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know | Our review of the evidence found later cord clamping for ≥ 60 seconds possibly increased the use of phototherapy for treatment of hyperbilirubinemia compared to later cord clamping for < 60 seconds. | The possible increase in the rates of phototherapy-treated hyperbilirubinemia may have less impact in high- income countries where resources are in place for detecting and managing affected infants. In middle- and low-income countries, the benefit-risk assessment can be complicated and different from one setting to another depending on available resources. More research is needed to address this important area. |
| Certainty of evidence What 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 was very low for the critical outcomes of neonatal mortality and neurodevelopmental impairment in early childhood as well as for the important outcomes of resuscitation at birth, hemoglobin concentration in the first 24 hours after birth and hyperbilirubinemia treated with phototherapy. |  |
| Values Is 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 of the systematic review were: anemia at four to six months after birth, survival without moderate to severe neurodevelopmental impairment in early childhood, and maternal postpartum hemorrhage. Given that the intervention is simple and at no cost, and considering the main outcomes are critical, there is no important uncertainty or variability in how much people value the main outcomes despite the very low certainty of evidence of the effects. | Collection of cord blood for banking may pose a competing interest. |
| Balance of effects Does 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 | The improved hemoglobin associated with later cord clamping ≥ 60 seconds in the neonatal period may help in the prevention iron deficiency and its complications, such as anemia and developmental delay. Rates of iron deficiency are highest in resource-limited settings and therefore the potential benefits of later cord clamping ≥ 60 seconds may be greatest in these areas. There is some evidence that later cord clamping for ≥ 60 seconds may improve neurodevelopment in early childhood as evidence by higher ASQ 3 scores at 12 months of age.  However, as later cord clamping for ≥ 60 seconds is associated with possible increase in use of phototherapy for hyperbilirubinemia, the potential for harm may be more pronounced in settings where resources for monitoring and treatment of hyperbilirubinemia are limited.  It is crucial to weigh the benefits vs. the risks of later cord clamping for ≥ 60 seconds in different resource settings | Collection of cord blood for banking may pose a competing interest. |
| Resources required How 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 | No studies have reported resource implications | Both interventions are simple and of no cost, however, there is limited data about the possible cost-saving associated with the potential benefits of higher hemoglobin (reduced iron deficiency and the consequent neurodevelopmental impairments) and the possible costs of monitoring and managing the adverse effects of the possibly increased hyperbilirubinemia. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does 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 studies have examined cost-effectiveness | The intervention itself is low-cost, but studies to examine cost-benefit await additional data on neurodevelopment and the objective need for treatment of hyperbilirubinemia. |
| Equity What 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 | This is a simple, easy and inexpensive intervention that can be implemented by health care providers in any place in the world to improve the hematological status and prevent iron deficiency which is prevalent globally (in high- as well as middle- and low-income countries). Embracing such intervention would foster health equity.  Research studies conducted to date reflect the high interest from low- and middle- income countries {Kc 2017 264, Nouraie 2019 45, Rana 2019 36} as well as high-income countries. {Katheria 2017 e0187730}  However, there might be disparity in monitoring and management of the possible adverse effects (hyperbilirubinemia treated with phototherapy) related to the lack of resources in the lower income countries. |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | The intervention (later cord clamping ≥ 60 seconds) has been recommended by many governing bodies including WHO {World Health Organization 2012 } and in many countries, has been practiced as the standard of care for many infants at birth for years.  Research studies related to the intervention (later cord clamping ≥ 60 seconds) were conducted in different settings with variable resources. | There is a high level of interest in delayed cord clamping among pregnant women, as reflected on social media sites and childbirth education courses. |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | - The intervention is simple, easy to implement at no cost.  - The intervention is feasible for any health care provider worldwide after minimal guidance/training and has been recommended by WHO since 2012. {World Health Organization 2012 }  - Research studies related to the intervention were conducted in different settings with variable resources which shows that the intervention is feasible. | The intervention has been the standard practice in many centers providing childbirth care. |

# 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 |
| ○ | ○ | **●** | ○ | ○ |

# Overall conclusions

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| Recommendation |
| For term and late preterm infants born at ≥34 weeks’ gestation who are vigorous or deemed not require immediate resuscitation at birth; we suggest later (delayed) clamping the cord at ≥ 60 seconds (weak recommendation, very low certainty evidence). |
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| Justification |
| 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 (delayed) 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 the critical periods of 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 (delayed) 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 to 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 postnatal cardiovascular transition in the same way as later (delayed) cord clamping. The number and size of studies is small and no long-term outcomes were addressed, limiting assessment of safety. Although cut-cord milking may be useful when later 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 intact 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. |

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| Subgroup considerations |
| The number of pre-specified subgroup analyses was large, was multiplied by the number of comparisons, and their 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 that were significant or that contributed positively or negatively to 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.  A- Subgroups according to gestational age: More term infants in the later cord clamping group received phototherapy for hyperbilirubinemia compared to early cord clamping group (low certainty evidence). Among late preterm infants (34 – 36+6 weeks’ gestation), there was no benefit or harm from later cord clamping compared to early cord clamping (low certainty evidence). However, the test of interaction between the two subgroups was non-significant.  B- Subgroups according to different resource settings, based upon World Bank country classifications: Later cord clamping resulted in higher hematocrit values in the compared to early cord clamping in both low- or middle- income countries and high-income countries. The effect was greater in studies performed in high-income countries than in low- or middle-income countries. However, we do not have sufficient confidence in these findings to make separate recommendations for cord management by country income. We consider that the beneficial effect of delayed clamping is likely to be widely generalizable and should therefore be offered in all settings.  C- Subgroup analyses according to the timing of uterotonic administration and according to size for gestational age did not reveal significant differences between subgroups. |
| Implementation considerations |
| Later (delayed) cord clamping for at least 60 seconds for term and late preterm infants who are vigorous or do not require immediate resuscitation at birth is a simple, easy to implement and feasible intervention that requires no added equipment or special skills.  The intervention has been in practice for many years as it was recommended by WHO in 2012. {World Health Organization 2012 }  The implementation in lower-resources settings should be considered after carefully weighing the benefit/risk ratio for each setting. |

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| Monitoring and evaluation |
| Continuous monitoring and evaluation of both desired and undesired effects of the intervention are needed. This includes:   * Monitoring the possible impact of the increased phototherapy-treated hyperbilirubinemia especially in low- and middle-income countries. * Monitoring the long-term effects of the intervention in reducing iron deficiency complications such as anemia and neurodevelopmental impairment in childhood. * Evaluating the associated costs and the potential economic impact of implementing later cord clamping >60 seconds or intact or cut-cord miking on the short- and long-term outcomes in different settings. * Investigating the effects of the intervention, if implemented, in the less studied populations including non-vigorous babies (including resuscitation with cord intact), multiple births, small for gestational age babies.   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 |
| High quality studies are needed,   * to determine if the demonstrated reduction in early iron deficiency seen after later cord clamping improves long-term neurodevelopment and to determine the impact of cord management practices on these outcomes. These studies need to be performed in low-resourced and high-resourced settings. * to address the effects of cord management practices on polycythemia and hyperbilirubinemia using standardized protocols for diagnosis and management. * to define the optimal duration of later cord clamping and address important outcomes in the neonatal period, infancy, childhood and for mothers. * to identify 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 important short and long-term child outcomes including hyperbilirubinemia, polycythemia, anemia and neurodevelopmental outcomes as well as maternal outcomes. * to address optimal cord management practice in cesarean deliveries (under spinal or general anesthesia), intrauterine growth restriction, multiple gestations, fetal anemia, fetal anomalies. * to address the impact of cord management on vertical transmission of infectious diseases. * to address the economic impact of different cord management practices. * 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”. * to ascertain parents’ views regarding cord management practices at birth. |

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