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Umbilical cord clamping at one minute, allowing stem cell harvesting, compared with delayed cord clamping- infant and maternal outcomes

Bergdahl E, Friberg H, Frändberg S, Holmberg A, Jivegård L, Seyed Alikhani V, Svanberg T, Wessberg A, Sjögren P

Sahlgrenska Universitetssjukhuset
413 45 Göteborg
031-342 10 00 - sahlgrenska.se

Umbilical cord clamping at one minute, allowing stem cell harvesting, compared with delayed cord clamping - infant and maternal outcomes [Avnavling vid en minut, vilket möjliggör stamcellsskörd, jämfört med senare avnavling – utfall för moder och barn]

Bergdahl E[1*], Friberg H[2], Frändberg S[3], Holmberg A[4], Jivegård L[5], Seyed Alikhani V[6], Svanberg T[4], Wessberg A[7], Sjögren P[5]

[1] Region Västra Götaland, Sahlgrenska University Hospital, Department of Gynaecology and Obstetrics, Gothenburg, Sweden

[2] Region Västra Götaland, Sahlgrenska University Hospital, Department of Gynaecology and Obstetrics, Gothenburg, Sweden

[3] Region Västra Götaland, Sahlgrenska University Hospital, Dept of Clinical Immunology and Transfusion Medicine, Gothenburg, Sweden

[4] Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden

[5] Region Västra Götaland, HTA-centrum, Gothenburg, Sweden

[6] Region Västra Götaland, Sahlgrenska University Hospital, Department of Neonatology, Gothenburg, Sweden

[7] Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital, Gothenburg, Sweden and Department of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden

* Corresponding author Elin Bergdahl, Region Västra Götaland, Sahlgrenska University Hospital, Department of Gynaecology and Obstetrics, Gothenburg, Sweden

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Innehållsförteckning

1 Abstract

Background At the time of birth, the infant is attached to the placenta through the umbilical cord, which is then clamped and cut. The timing of this in healthy newborns varies, but recent guidelines often recommend delayed >1 minutes (min) cord clamping. This may be beneficial for the infant, reducing the risk of anaemia and iron deficiency. By contrast, early compared with delayed cord clamping improves the possibility to obtain umbilical cord blood allowing harvest of stem cells. After cord clamping, umbilical blood is collected, and made available for treatment of different conditions through international registries. Haematopoietic stem cell transplantation is used to treat severe hereditary and malignant diseases.

Question at issue Effects of umbilical cord clamping at 1 min compared with clamping at >1 min in newborn infants and healthy mothers with term pregnancy (≥37+0), concerning infant and maternal morbidity?

Methods After definition of PICO, systematic literature searches in Medline, Embase, the Cochrane Library and Cinahl were conducted. Two authors screened the obtained abstracts and made a first selection of full-text reports. All authors read these full-text reports and decided in consensus which reports should be included. Included studies were critically appraised using checklists. The results of each study were summarised per outcome and when possible, data were pooled in a meta-analysis. The certainty of evidence for each outcome was assessed using the GRADE approach. Summary of the results per outcome and the associated certainties of evidence were presented in a Summary-of-findings table.

Results Seven RCTs and one non-RCT were included, with a total of 1,818 individuals. The RCTs had some problems with directness (countries with a different level of development or health care settings than Sweden), and some to major problems with risk of bias and precision. All comparisons were clamping at 1 min (defined as early clamping) vs. after more than 1 min (delayed clamping).
Critical infant outcomes: Mortality, long-term cognitive function, neonatal intensive care unit care >4 days, and Apgar score <5 at 5 min were not reported.
Critical maternal outcomes: Postpartum haemorrhage >1,000 ml did not differ significantly between the groups, relative risk RR 5.12 (95%CI: 0.73 to 35.85), n.s. (2/81 at 1 min vs. 2/415 events at >1 min). It is uncertain whether postpartum haemorrhage >1,000 ml is affected by early compared with delayed umbilical cord clamping (GRADE ⊕○○○). Mortality, severe morbidity, organ failure, and ICU admission were not reported.
Important infant outcomes: Infant immediate haematocrit showed a mean difference of -3.09 (95%CI: -3.87 to -2.30) percentage points (pp.), p<0.00001, and short-term haemoglobin had a mean difference of -1.36 g/dl (95%CI: -1.48 to -1.24), p<0.00001, both in favour for clamping at >1 min. Infant immediate haematocrit and short-term haemoglobin probably decrease with early, compared with delayed umbilical cord clamping (GRADE ⊕⊕⊕○). The need for phototherapy did not differ significantly between the groups, RR 0.81 (95%CI: 0.55 to 1.19), n.s. There is probably little or no difference in the frequency of phototherapy with early, compared with delayed umbilical cord clamping (GRADE ⊕⊕⊕○).
There may be little or no difference in long-term haematocrit and ferritin levels and in

short-term anaemia with early, compared with delayed umbilical cord clamping (GRADE ⊕⊕◯◯).
It is uncertain whether there is any difference in long-term haemoglobin, iron deficiency and occurrence of admission to neonatal department with early, compared with delayed umbilical cord clamping (GRADE ⊕◯◯◯).

Economic aspects Costs associated with clamping at 1 minute compared with >1 minute are very unlikely to differ. Thus, there are no expected costs of the health technology at issue**.**

Ethical aspects This analysis was unable to answer the question if there is increased risk of morbidity among children with cord clamping at 1 min compared with >1 min although the present results did not suggest major differences. With umbilical clamping at 1 min, it is possible to harvest cord blood for the collection of stem cells but there could be a risk of infant iron deficiency and anaemia. However, if no cord blood donations are available this affects the possibility to offer treatment to patients with severe hereditary and malignant diseases in need of a stem cell transplantation at Sahlgrenska University Hospital and worldwide.

Conclusion Regarding outcomes critical for decision making there was only inconclusive data for maternal postpartum haemorrhage >1,000 ml, and no data on the other critical outcomes, neither for newborn infants nor for mothers with term pregnancy, comparing cord clamping at 1 min with clamping at >1 min. For important infant outcomes, with moderate certainty of evidence, significant differences were seen for infant immediate haematocrit, with a mean difference of -3.09 (95%CI: -3.87 to -2.30) pp., p<0.00001, and short-term haemoglobin with a mean difference of -1.36 g/dl (95%CI: -1.48 to -1.24), p<0.00001, both (<10% differences between the groups) in favour for clamping at >1 min. Early umbilical cord clamping (here defined as at 1 min), versus delayed clamping (here defined as > 1 min) allows collection of umbilical cord blood improving the possibility of stem cell harvesting. In summary, although current evidence regarding important infant outcomes does not suggest major infant or maternal risks, important knowledge gaps for critical outcomes preclude definitive conclusions regarding the safety of umbilical cord clamping at 1 min.

2 Populärvetenskaplig sammanfattning – Plain language summary in Swedish

I denna rapport har vi utvärderat frågeställningen: Påverkan av avnavling vid precis en minut (då insamling av stamceller möjliggörs), jämfört med avnavling efter en minut, hos nyfödda spädbarn och mödrar vid fullgången graviditet (⩾37+0), avseende spädbarns- och mödrasjuklighet.

Bakgrund: Vid födseln är barnets cirkulation kopplad till moderkakan i livmodern via navelsträngen. Navelsträngen delas efter födseln, och valet av tidpunkt för denna avnavling hos friska nyfödda varierar. De senaste riktlinjerna rekommenderar fördröjd (>1 minut efter födseln) avnavling, vilket kan vara fördelaktigt för barnet genom att minska risken för blod- och järnbrist. Sannolikheten att kunna samla in navelsträngsblod med en tillräcklig mängd stamceller är större med avnavling vid en minut jämfört med senare tidpunkter. Efter att navelsträngen delats samlas navelsträngsblod in för stamcellsskörd, och stamceller görs sedan tillgängliga för patienter genom internationella biobanker och register. Denna typ av (hematopoetisk) stamcellstransplantation används för att behandla svåra ärftliga och elakartade sjukdomar.

Metod: Efter definition av frågeställningen (PICO) gjordes systematiska litteratursökningar i databaserna Medline, Embase, Cochrane Library och Cinahl. Två författare gick igenom de erhållna sökresultaten och gjorde ett första urval av rapporter. Alla författare läste dessa rapporter i fulltext och beslutade i samförstånd (konsensus) vilka rapporter som skulle inkluderas. Inkluderade studier kvalitetsgranskades med hjälp av checklistor. Resultaten i studierna sammanfattades för varje studerat utfall och när det var möjligt redovisades data från studierna i en sammanförd statistisk analys (metaanalys). Det samlade resultatets tillförlitlighet bedömdes enligt GRADE metoden. Sammanfattning av resultatet för varje utfall, med tillhörande bedömd tillförlitlighet, presenteras i en resultattabell (SoF-Table).

Resultat: Sju randomiserade kontrollerade studier (RCT) och en icke-randomiserad kontrollerad studie inkluderades. De randomiserade studierna hade vissa problem med överförbarhet mot bakgrund av att de gjorts i länder med annan utvecklingsnivå och andra hälso- och sjukvårdssystem än Sveriges, och varierande grad av problem med studiekvalitet och precision. För samtliga utfall jämfördes avnavling vid precis 1 minut (tidig avnavling) med avnavling efter mer än 1 minut (sen avnavling).
Kritiska spädbarnsutfall: Dödlighet, kognitiv funktionsnedsättning senare i livet, intensivvård >4 dagar och barnets vitalitet 5 minuter efter födseln, rapporterades inte i de inkluderade studierna.
Kritiska utfall för modern: Det är osäkert huruvida förekomsten av blödning >1 000 ml hos mamman efter förlossningen påverkas av tidig, jämfört med sen avnavling (GRADE ⊕○○○). Dödlighet, allvarlig sjuklighet, organsvikt och intensivvård rapporterades inte i de inkluderade studierna.
Viktiga spädbarnsutfall: Spädbarnets tidiga hematokrit- (andelen röda blodkroppar i blodet) och hemoglobinvärde (blodvärde) minskar troligen, medan det troligen är liten eller ingen skillnad i frekvensen av fototerapi (ljusbehandling för nyföddhetsgulsot) med tidig, jämfört med sen avnavling (GRADE ⊕⊕⊕○). Det kan vara liten eller ingen skillnad i hematokrit 2–6 månader efter födseln, hemoglobin 0–48 timmar efter födseln,

järndepåer, samt blodbrist vid tidig, jämfört med sen avnavling (GRADE ⊕⊕◯◯). Det är osäkert huruvida det finns någon skillnad i blodvärde efter längre tid, järnbrist och förekomst av inläggning på nyföddhetsavdelning med tidig, jämfört med sen avnavling (GRADE ⊕◯◯◯).

Kostnader: Kostnaden för avnavling vid precis 1 minut jämfört med efter >1 minut skiljer sig sannolikt inte. Det finns alltså ingen förväntad kostnadsändring för den utvärderade metoden.

Etiska aspekter: Med avnavling vid 1 minut är det möjligt att samla navelsträngsblod för insamling av stamceller, men det finns en möjlig risk för järnbrist och blodbrist hos det nyfödda barnet på kort sikt. Efter 2–6 månader kan det vara liten eller ingen skillnad. Det är oklart om denna skillnad på kort sikt innebär något på längre sikt. Barnet skulle kunna utsättas för en risk av en åtgärd som en annan individ har nytta av. Vår aktuella HTA-analys kunde inte svara på frågan om det finns en ökad risk för sjuklighet för barn med avnavling vid precis 1 minut jämfört med >1 minut, även om resultaten inte antydde några större skillnader. Om inga navelsträngsbloddonationer finns att tillgå påverkar det dock möjligheten att erbjuda behandling till patienter med svåra ärftliga och elakartade sjukdomar i behov av stamcellstransplantation på Sahlgrenska Universitetssjukhuset och över hela världen.

Slutsatser: Tidig avnavling (här definierad som vid precis 1 minut), jämfört med sen avnavling (här definierad som >1 minut) tillåter uppsamling av navelsträngsblod vilket ger möjlighet till stamcellsdonation. I denna systematiska översikt studeras risker för barnet och modern med tidig kontra sen avnavling. Förutom för blödning efter förlossningen för mamman, fanns det inga data för utfall som är kritiska för beslutsfattande angående effekter av tidig kontra sen avnavling hos nyfödda spädbarn och mödrar med fullgången graviditet. Det fanns sparsamt med data för viktiga spädbarnsutfall, dock sågs skillnader, med måttlig vetenskaplig tillförlitlighet, avseende vissa blodvärden för barnet (omedelbar hematokritnivå och blodvärde kort tid efter födseln) med <10% minskning och medelvärden inom normalområdet i såväl gruppen med tidig som med sen avnavling, med högre värden för sen avnavling. Sammanfattningsvis, även om befintliga resultat inte tyder på några större viktiga risker för barn eller modern, medför viktiga kunskapsluckor vad gäller kritiska utfall att definitiva slutsatser om säkerheten med avnavling vid precis 1 minut inte kan dras.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers and is ended with a concluding summary.

Ylva Carlsson
Head of HTA-centrum of Region Västra Götaland, Sweden, 2024-12-19

Regional board for quality assurance of activity based HTA

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Wartenberg, Constanze	Psychologist, PhD
Wide, Ulla	Psychologist, Professor

DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
RN Registered Nurse

3 Summary of findings

Outcomes	Study design Number of studies	Effect estimate (absolute respectively relative effect as available in publication)	Certainty of evidence* GRADE
Umbilical cord clamping at 1 minute (min) compared with clamping at >1 min			
Postpartum haemorrhage >1,000 ml	1 RCT n=496	Postpartum haemorrhage >1,000 ml RR: 5.12 (95%CI: 0.73 to 35.85), n.s.	Low (GRADE ⊕⊕◯◯) [1]
Infant haematocrit – immediate	5 RCT n=695	Haematocrit %, mean difference: -3.09 (95%CI: -3.87 to -2.30) pp., p<0.00001, (in favour for umbilical cord clamping at >1 min)	Moderate (GRADE ⊕⊕⊕◯) [2]
Infant haematocrit – long-term	1 non-RCT n=283	Haematocrit %, at 4 months, mean (95%CI) 1 min group: 33.1% (95%CI: 32.8 to 33.5) >1 min group: 32.7% (95%CI: 32.4 to 33.1), n.s.	Low (GRADE ⊕⊕◯◯) [3]
Infant ferritin – long-term	1 RCT n=55 1 non-RCT n=295	Serum ferritin levels at 12 weeks, median (IQR) µg/l 1 min group: 101.0 (67.4-211.5) >1 min group: 101.7 (52.2-173.8) µg/l, n.s.	Low (GRADE ⊕⊕◯◯) [4]
Infant iron deficiency – long-term	1 RCT n=55 1 non-RCT n=295	Iron deficiency at 12 weeks: RR: 1.04 (95%CI: 0.34 to 3.18), n.s. Iron deficiency, at 4 months: 1 min group: 7/147 (4.8%) >1 min group: 1/148 (0.7%), p=0.04	Very low (GRADE ⊕◯◯◯) [5]
Infant anaemia – short-term	1 RCT n=179	RR: 0.67 (95%CI: 0.12 to 3.94), n.s.	Low (GRADE ⊕⊕◯◯) [4]
Infant anaemia – long-term	1 non-RCT n=286	Anaemia at 4 months 1 min group: 16/140 (11.4%) >1 min group: 20/144 (13.9), n.s.	Very low (GRADE ⊕◯◯◯) [3]
Infant haemoglobin – short-term	2 RCT n=306	Mean difference: -1.36 (95%CI: -1.48 to -1.24), g/dl[#], p<0.00001, in favour for clamping at >1 min	Moderate (GRADE ⊕⊕⊕◯) [6]
Infant haemoglobin – long-term	1 non-RCT n=295	Haemoglobin at 4 months, mean (95%CI), g/dl[#]: 1 minute group: 11.4 (11.3 to 11.6) >1 minute group: 11.3 (11.2 to 11.4) g/dl, n.s.	Low (GRADE ⊕⊕◯◯) [3]
Phototherapy	3 RCT n=882	RR: 0.81 (95%CI: 0.55 to 1.19), n.s.	Moderate (GRADE ⊕⊕⊕◯) [3]
Admission to neonatal department	1 RCT n=496	RR: 0.34 (95%CI: 0.01 to 8.26), n.s.	Very low (GRADE ⊕◯◯◯) [7]
Postpartum haemorrhage >500 ml	2 RCT n=635	RR: 0.74 (95%CI: 0.19 to 2.98), n.s.	Low (GRADE ⊕⊕◯◯) [1]

The infant outcomes: mortality, long-term cognitive function; NICU care ≥4 days; Apgar score <5 at five minutes; and infant ferritin level – short-term, were not reported. The maternal outcomes: mortality; severe morbidity; organ failure; ICU admission; manual removal of retained placenta; blood transfusion, were not reported. The methodological outcome: successful stem cell harvest, was not reported.

Footnotes:
pp.=percentage points; RCT=randomised controlled trial; RR=relative risk.

[#] The amount of haemoglobin is here expressed in grams per deciliter (g/dl).

[1] Downgraded one step for serious indirectness (population not clearly described) and one step for serious imprecision (not reported sample size calculation).

[2] Downgraded one step for serious indirectness (population not clearly described).

[3] Not downgraded.

[4] RCT downgraded two steps for very serious imprecision regarding this outcome.

[5] RCT downgraded two steps for very serious imprecision regarding this outcome, and one step for some study limitations (no blinding) and some indirectness (population not clearly described).

[6] Downgraded one step for serious study limitations (unclear randomisation, no blinding, no protocol) and one step for serious imprecision (not reported sample size calculation).

[7] Downgraded one step for serious indirectness (population not clearly described) and two step very for serious imprecision (very few events, not reported sample size calculation).

* Certainty of evidence

High certainty ⊕⊕⊕⊕: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty ⊕⊕⊕◯: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty ⊕⊕◯◯: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty ⊕◯◯◯: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

4 Abbreviations

CBU= Cord blood unit

ID = Iron deficiency

Min = Minutes

NICU = Neonatal intensive care unit

N.s. = Not significant

NSCBB= National Swedish Cord Blood Bank

Pp.=Percentage points

RCT – Randomised Controlled Trial

RD = Risk difference

RR= Risk ratio

SBF = The Swedish Association of Midwives [Svenska barnmorskeförbundet]

SCB = Statistics Sweden (Statistikmyndigheten)

SFOG = Swedish Society of Obstetrics and Gynecology [Svensk Förening för Obstetrik och Gynekologi]

SoF = Summary of Findings

VGR = Region Västra Götaland [Västra Götalandsregionen]

5 Background

At the time of birth, the infant is attached to the placenta through the umbilical cord, which is then clamped and cut, disconnecting the newborn from the placenta and mother. The timing of cord clamping in healthy newborn infants varies worldwide, but recent guidelines often recommend so called delayed cord clamping. There is no international consensus regarding the definition of delayed cord clamping, but early cord clamping is usually defined as clamping <1 minute (min) after birth and delayed cord clamping as clamping ≥1 min after birth. There is evidence that delayed cord clamping compared to early cord clamping is beneficial for the infant, since blood is transfused to the infant from the placenta. This transfusion helps the infant in the physiological adjustment to life outside the uterus and increases haemoglobin and iron storage, reducing the risk of anaemia and iron deficiency. Although no causal relationship has been shown in infants, iron deficiency and anaemia in children is associated with cognitive and psychological impairments later in life (Lozoff et al., 2006, Bayer, 2016, Andersson and Mercer, 2021). This association has been shown for lower hemoglobin levels (Hb <110 g/l, or lower) than those observed after umbilical cord clamping at 1 minute. There are possible confounding factors such as nutritional deficiency, poor socioeconomic background, illness and poor care giving that could explain these negative outcomes in the mentioned studies (Grantham-McGregor and Ani, 2001, McCann et al., 2020). In systematic reviews which studied the effect of iron supplementation (McCann et al., 2020, Walker et al., 2007, Sant-Rayn et al., 2013) on neurodevelopment in children and infants the results are inconsistent, some of the studies reported improvement in neurodevelopment and some studies did not. The UK National Screening Committee in 2017 concluded the available evidence suggests that the policy not to screen for iron deficiency anaemia in children under 5 years should not be changed (Screening for iron deficiency anaemia in children under 5 years. UK National Screening Committee, 2017). To summarise, there is a correlation between anaemia (Hb <110 g/l) and negative effects on neurodevelopment in infants and children but a causal negative effect has not been shown.

Umbilical cord blood is rich in haematopoietic stem cells with unique biological properties (Sanchez-Petitto et al., 2023). Early compared with delayed cord clamping improves the possibility to harvest stem cells. Haematopoietic stem cell transplantation is performed to treat severe hereditary and malignant diseases in both children and adults. After cord clamping, umbilical blood is collected, processed, frozen and stored in cord blood banks, thereby made available for treatment through international registries.

Prevalence and incidence

In year 2023 100,151 children were born in Sweden, whereof 17,427 in Region Västra Götaland (VGR) (Statistikmyndigheten (SCB), Statistics Sweden). According to a recent review the iron status in children in the Nordic countries seems to have improved since the 1990s. Studies in Norway, Iceland and Sweden from 2004 to 2011 showed iron deficiency prevalence of 6-18% in 12-month-olds and 13% in 2-year-olds. The causes of iron deficiency are multifactorial (Domellöf and Sjöberg, 2024).

The National Swedish cord blood bank (NSCBB) was founded after a governmental decision in 2006 and is the only active cord blood bank in Scandinavia, located at

Sahlgrenska university hospital, Sweden. NSCBB is an altruistic (public) bank funded in solidarity by the Swedish healthcare regions. The bank currently holds approximately 5,000 cord blood units (CBU) available for transplantation through the Swedish international registry for stem cell donations (Tobias registry). The number of yearly donations to NSCBB have varied greatly since its inauguration. The range during years 2007 to 2022 was 112-1,195 collections (data from NSCBB), with higher numbers during the early years when the ambition was to quickly increase the number of available CBU:s. The future ambition of the NSCBB is to hold a stable inventory of around 5000-6000 CBU. This would require annual collections of between 200-300 CBU:s (i.e. 200-400 labours per annually). Collection activities have been suspended since March 2023 due to staff shortage, recruitment is ongoing with the goal of starting again at the turn of the year 2024-2025.

Present treatment

Umbilical cord clamping at Sahlgrenska University Hospital is currently performed according to the Swedish national guidelines, see paragraph below: *Present recommendations from medical societies or health authorities* (Rekommendationer om avnavling av det nyfödda barnet, Swedish Association of Obstetrics and Gynaecology [SFOG], 2022) The timing of the clamping of the umbilical cord was until recently not routinely registered in the patient records after birth, but according to new recommendations this data is now recommended to be registered.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

Following normal pregnancy and delivery the hospital stay is usually 6-48 hours. No screening for iron deficiency is performed on healthy infants during the first years of life in VGR.

Number of patients per year who undergo current treatment regimen

During 2023, 8,609 children were born at Sahlgrenska University Hospital/Östra, in Gothenburg, after ≥37+0 weeks of gestation. Since, until recently, the timing of cord clamping was not registered routinely in the patient records, it is not possible to give an exact number of infants that have had cord clamping at different time points (e.g. at >1 min, or at ≤1 min).

Infants delivered vaginally at ≥37+0 gestational weeks by healthy mothers with a normal pregnancy, rarely need respiratory support and resuscitation and are thus likely to get the cord clamped after >1 min.

During an elective caesarean section an assistant nurse tells the obstetrician or gynaecologist when 1 minute has passed, whereafter the cord is clamped. The procedure is the same during an emergency caesarean section as a vaginal birth, but since the indications for an emergency caesarean section can be signs of fetal distress or acute maternal indication it is more common with cord clamping at <1 min.

Present recommendations from medical societies or health authorities

In 2022, the Swedish Association of Midwifes (SBF), the SFOG and the Swedish Neonatal Association published recommendations concerning timing of umbilical cord clamping. The recommendation for umbilical cord clamping for healthy newborn infants, born vaginally >35+0 weeks of gestation, and not in need of resuscitation, is that it should be performed when the umbilical cord is pale and limp. At the latest, the umbilical cord should be clamped concurrent with the expulsion of the placenta. The recommendation for cord clamping after delivery by caesarean section for healthy newborns >35+0 weeks of gestation without need of resuscitation is at 1 min.

The national recommendations include maternal and neonatal indications for earlier cord clamping. The decision of earlier cord clamping is made by a clinical assessment of the mother and/or the neonate by the midwife, obstetrician, and/or neonatologist (if present) at the time of birth. (Rekommendationer om avnavling av det nyfödda barnet, SFOG, 2022).

The World Health Organization guidelines on cord clamping states a strong recommendation, that in newborn infants not in need of resuscitation, the cord should not be clamped earlier than 1 min after birth. These guidelines also recognize the potential conflict of the practice of delayed umbilical cord clamping and collection of cord blood for stem cell banking (Guideline: Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. WHO, 2014).

Concerning stem cell harvesting there is currently no national or international recommendations.

6 Health Technology at issue: Umbilical cord clamping at 1 min of newborn infants eligible for stem cell harvesting.

This HTA-report focuses on comparing neonatal and maternal outcomes after umbilical cord clamping at 1 min (=Health technology at issue) with >1 min in infants not in need of resuscitation, born after uncomplicated term pregnancy ($\geq$37+0 weeks) by healthy mothers. This group of infants are hypothetically eligible for stem cell harvesting.

On the reintroduction of cord blood donation there is a well-established procedure. Pre-donation material including information material, medical questionaries and consent forms will be available in 12 different languages at all the maternity care centres in the Gothenburg region and expecting parents will be informed by their maternity care midwife. If parents are interested in donation these documents are filled in by the parents and sent to the NSCBB. When the parents arrive at the obstetric ward to give birth, the consent and medical questionnaire are updated if the parents still wish to donate. Midwifes collecting cord blood are employed by the NSCBB and dedicated to cord blood collecting only. The cord is clamped at 1 min for both vaginal and caesarean section deliveries, enabling collection of sufficient numbers of stem cells for banking (Frändberg et al., 2016). The collected cord blood is transported to the Stemcell Laboratory at Sahlgrenska University Hospital for processing, freezing and storage.

At term pregnancy, the total blood volume in the placenta, cord and fetus is approximately 110 ml/kg with one third of the fetal blood volume located in the placenta. Studies show that at 1 min after birth approximately 90% of the blood has been transfused to the child (Palethorpe et al., 2010) and for the majority the placental transfusion is completed at 2 min (Farrar et al., 2011). There is no evidence that delaying cord clamping >1 min affects complications during the third stage of labour such as postpartum haemorrhage (McDonald et al., 2013). The evidence also points towards no increase in infant hyperbilirubinemia when the cord clamping is delayed (Wilander et al., 2023). Multiple studies have shown benefits with delayed cord clamping >1 min with lower frequency of anaemia and iron deficiency and increased myelin content in regions of the brain involved in motor function, visual/spatial and sensory processing (Andersson et al., 2011). In most of these studies early (<1 min, often <30s) cord clamping is compared with cord clamping at >1 min, leaving a knowledge gap concerning the difference in the beneficial effect for the newborn and the risk for the mother of postpartum haemorrhage when the cord is clamped *at* 1 min as compared with >1 min.

Donating umbilical cord blood for stem cell harvesting is an altruistic action that potentially can be lifesaving. After parental consent, donations are accepted from newborn infants not in need of resuscitation, born after uncomplicated term pregnancy ($\geq$37+0 weeks) to healthy mothers. Studies have shown that it is possible to collect cord blood units with sufficient cell numbers, if clamping is performed at 1 min, but to a lesser extent at later timepoints (Allan et al., 2016, Frändberg et al., 2016).

This HTA report seeks to investigate to what extent the beneficial effects of delayed cord clamping are achieved within the first min after birth as compared to delaying cord clamping >1 min, seeking to provide both the expecting parents and health care professionals with adequate information for well-grounded decisions when considering donation.

7 Focused question

Frågeställning
Effects of umbilical cord clamping in newborn infants and mothers with term pregnancy (≥37+0) at 1 min, compared with clamping at >1 min concerning infant and maternal morbidity and mortality?

PICO	
P	Newborn infants not in need of stabilisation, and mothers with uncomplicated term pregnancy (≥37+0).
I	Umbilical cord clamping at 1 min
C	Umbilical cord clamping at >1 min
O	<u>Outcomes critical for decision-making</u> <u>Infant</u> Mortality Long-term cognitive function NICU care ≥4 days Apgar score <5 at five min <u>Mother</u> Mortality Severe morbidity, organ failure, ICU admission Severe postpartum haemorrhage ≥1,000ml <u>Outcomes important for decision-making</u> <u>Infant</u> • Haematocrit – immediate and long-term • Ferritin – immediate and long-term • Iron-deficiency, anaemia: immediate and long-term* and haemoglobin level, immediate and long-term. (*Immediate defined as within 0-48 hours and long-term as after 2-6 months) Phototherapy Admission to neonatal units Apgar score <7 at five min Neurodevelopment, long term <u>Mother</u> Manual removal of retained placenta Blood transfusion Maternal blood loss >500 ml <u>Methodological outcomes</u> Successful stem cell harvest

Study design
Randomised controlled trials – (All outcomes) Cohort studies with ≥100 patients per group.

8 Method

Systematic literature search (Appendix 1)

During December 2023 two authors (AH, TS) performed systematic searches in Medline, Embase, the Cochrane Library and Cinahl. Websites of Scandinavian national and regional HTA-organisations were visited. Reference lists of relevant reports were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, and independently of one another screened the obtained abstracts and made a first selection of full-text reports to be assessed for inclusion or exclusion. All abstracts were screened using the Rayyan tool (Ouzzani et al., 2016). Any disagreements were resolved by consensus. The remaining reports were sent to all the participants of the project group. All authors read these reports independently of one another and it was finally decided in a consensus meeting which reports should be included in the assessment.

Critical appraisal and certainty of evidence

Included studies were critically appraised using an adjusted checklist from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) for assessment of randomised controlled trials, and for assessment of non-randomised controlled studies. The results of each study were summarised per outcome in Appendix 4. When possible, data were pooled in meta-analysis (RevMan 5.4) using the random effects model. The certainty of evidence for each outcome was assessed using the GRADE approach (Atkins et al., 2004; GRADE Working group). Summary of the results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (Chapter 3).

Ongoing research

A search in Clinicaltrials.gov was done (07 April 2024) using the search terms (cord AND (clamping OR clamp OR cutting OR cut OR detachment OR separation) AND (immediate OR prompt OR early OR late OR delay OR delayed OR time OR timing OR deferred)) OR "cord management".

9 Results

Search results and study selection (Appendix 1)

The literature search identified 1894 records after removal of duplicates. After reading the abstracts 1798 records were excluded. Another 43 reports were excluded by two authors after reading the reports in full text. The remaining 53 reports were sent to all participants of the project group. Six reports were finally included in the assessment. In addition, two reports from the previous HTA report (Wennerholm et al., 2012) fulfilling our present PICO criteria were also included, which makes a total of eight reports (Appendix 2).

Included studies

Seven RCTs and one non-RCT were included (Appendix 1 and 2). The RCTs by Chen et al. (2017), and Chaudary et al. (2023), had some problems with directness (population not

clearly described countries with different levels of development, healthcare systems, and maternal background factors compared to Sweden), and precision (sample size calculations not reported). Katariya et al. (2021), Rao et al. (2018), and Saigal et al. (1972), also RCTs, had some problems with directness (population not clearly described), and major study limitations (mainly unclear randomisation and allocation concealment, no blinding, no reported study protocol, and unclear primary outcome), and some problems with precision (e.g. sample size calculations not reported). The RCT by Songtham et al. (2020) had some problems with precision, and in addition no reported study protocol and unclear primary outcome). The RCT by Cerinai Cernadas et al. (2006), and the non-RCT (Askelöf et al., 2017) had no or minor problems regarding study quality.
Specific issues related to each outcome are stated separately in respective contexts below.

Results per outcome

Infant outcomes critical for decision-making

The outcomes: **Mortality, Long-term cognitive function, NICU care ≥4 days**, and **Apgar score <5 at five min**, were not reported.

Maternal outcomes – critical for decision-making

The outcomes**: Mortality, Severe morbidity, Organ failure,** and **ICU admission** were not reported.

Postpartum haemorrhage >1,000 ml (Appendix 4:1)

Postpartum haemorrhage (PPH) >1,000 ml, after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in one RCT (Chen et al., 2017) with 496 participants. Regarding this outcome the study had serious indirectness and imprecision.
The risk difference (RD) between the groups was 0.02 (95%CI: -0.01 to 0.05, n.s., and the risk ratio (RR) was 5.12 (95%CI: 0.73 to 35.85), n.s., (Figures 1 and 2).

Figure 1. Postpartum haemorrhage >1,000 ml - risk difference for umbilical cord clamping at 1 min compared with clamping at >1 min

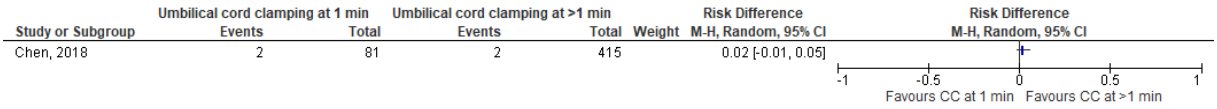
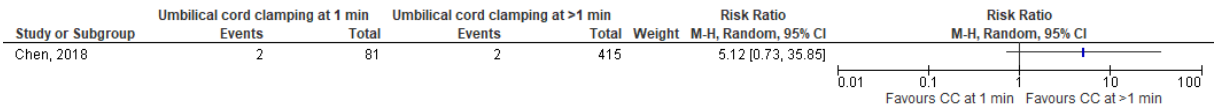


Figure 2. Postpartum haemorrhage >1,000 ml - risk ratio for umbilical cord clamping at 1 min compared with clamping at >1 min



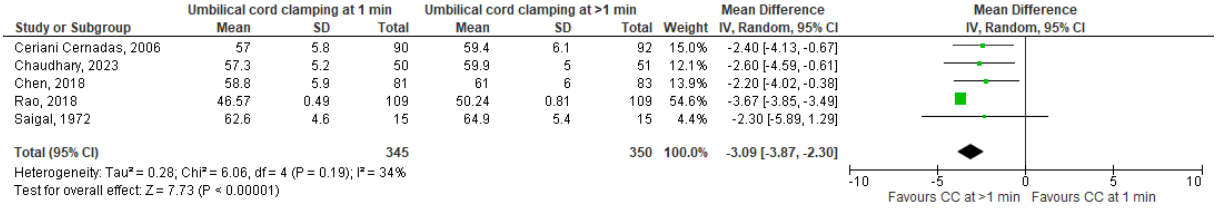
Conclusion: Postpartum haemorrhage >1,000 ml may not be affected when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Low certainty of evidence (GRADE ⊕⊕◯◯).

Infant outcomes important for decision-making

Infant haematocrit – immediate (Appendix 4:2)

The outcome infant haematocrit – immediate, after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in 5 RCTs, with a total of 695 infants. Across studies, there was serious indirectness (see above). The mean difference in venous haematocrit was -3.09 (95%CI: -3.87 to -2.30) pp., p<0.00001, in favour of umbilical cord clamping at >1 min (Figure 3).

Figure 3. Infant haematocrit (%) – immediate, after umbilical cord clamping at 1 min compared with clamping at >1 min



Conclusion: Infant immediate haematocrit probably decreases when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

Infant haematocrit – long-term (Appendix 4:3)

The outcome infant haematocrit – long-term (at four months age), after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in one non-RCT (Askelöf et al., 2017), with 283 infants. The long-term venous haematocrit (%) in the group with umbilical cord clamping at 1 min was mean 33.1% (95%CI: 32.8 to 33.5), and in the >1 min group mean 32.7% (95%CI: 32.4 to 33.1), n.s.

Conclusion: There may be little or no difference in infant long-term haematocrit when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Low certainty of evidence (GRADE ⊕⊕◯◯).

Infant ferritin level, short-term

The outcome was not reported.

Infant ferritin level, long term (Appendix 4:4)

The outcome infant ferritin – long-term, after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in one RCT with 55 infants (Chaudhary et al., 2023), and in one non-RCT (Askelöf et al., 2017), with 295 infants. The RCT had very serious imprecision regarding this outcome. Serum ferritin levels, at 12±2 weeks, were median (IQR): 101.0 (67.4-211.5) µg/L, after umbilical cord clamping at 1 min compared with clamping at >1 min 101.7 (52.2-173.8) µg/l, n.s. Serum ferritin levels at 4 months reported in the non-RCT were, geometric mean (95%CI): 96 (44 to 208) µg/L, for infants with umbilical cord clamping at 1 min, versus geometric mean (95%CI): 117 (58 to 232) µg/l, n.s. at >1 min (Askelöf et al., 2017).

Conclusion: There may be little or no difference in infant long-term ferritin level, when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Low certainty of evidence (GRADE ⊕⊕◯◯).

Infant iron deficiency, long-term (Appendix 4:5)

Infant iron deficiency – long-term, after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in one RCT with 55 infants (Chaudhary et al., 2023), and in one non-RCT (Askelöf et al., 2017), with 295 infants. Regarding this outcome, the RCT had very serious imprecision. In the subgroup of infants after full-term delivery, for iron deficiency at 12 weeks, the RD between the groups was 0.01 (95%CI: -0.20 to 0.21), n.s., and the RR was 1.04 (95%CI: 0.34 to 3.18), n.s. (Figures 4a and 4b).
In the non-RCT by Askelöf et al. (2017), iron deficiency, at 4 months, was seen in 7 out of 147 (4.8%) infants after umbilical cord clamping at 1 min compared with 1 out of 148 (0.7%) infants (p=0.04) after clamping at >1 min.

Figure 4a. Infant iron deficiency – long-term, risk difference for umbilical cord clamping at 1 min compared with clamping at >1 min

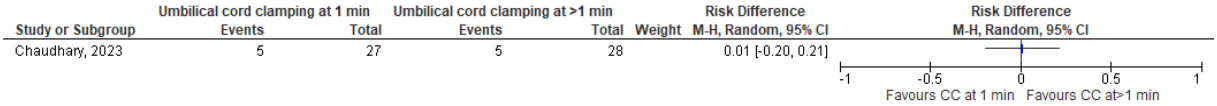
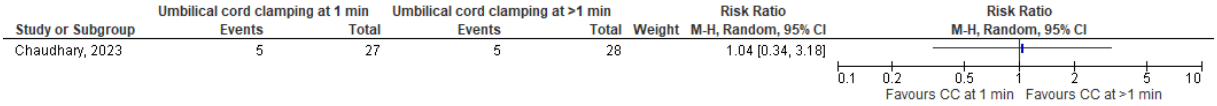


Figure 4b. Infant iron deficiency – long-term, risk ratio for umbilical cord clamping at 1 min compared with clamping at >1 min



Conclusion: It is uncertain whether there is any difference in infant long-term iron deficiency when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at > 1 min. Very low certainty of evidence (GRADE ⊕◯◯◯).

Infant anaemia, short-term (Appendix 4:6)

Infant anaemia – short-term, was reported in one RCT with 179 infants (Ceriani Cernadas et al., 2006), with very serious imprecision for this outcome. The difference in anaemia at 24 to 48 h for infants with umbilical cord clamping at 1 min, compared with clamping at >1 min the RD was -0.01 (95%CI: -0.06 to 0.04), n.s., and the RR was 0.67 (95%CI: 0.12 to 3.94), n.s. (Figures 5a and 5b).

Figure 5a. Infant anaemia – short-term, risk difference for umbilical cord clamping at 1 min compared with clamping at >1 min

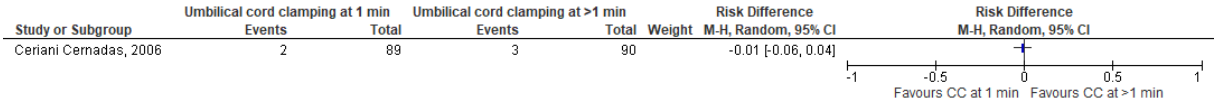
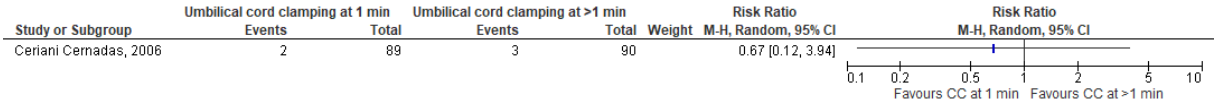


Figure 5b. Infant anaemia – short-term, risk ratio for umbilical cord clamping at 1 min compared with clamping at >1 min



Conclusion: There may be little or no difference in short-term infant anaemia after umbilical cord clamping at 1 min, compared with umbilical cord clamping at >1 min. Low certainty of evidence (GRADE ⊕⊕◯◯).

Infant anaemia, long-term (Appendix 4:7)

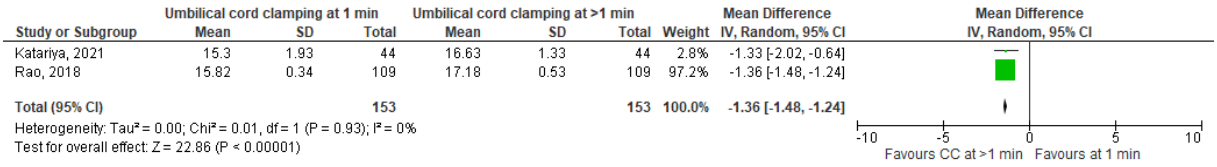
Infant anaemia – long-term, was reported in one non-RCT by Askelöf et al. (2017), with 284 infants, and serious imprecision for this outcome. Anaemia at 4 months was seen in 16/140 (11.4%) infants with umbilical cord clamping at 1 min, compared with 20/144 (13.9%), n.s. infants with clamping at >1 min.

Conclusion: It is uncertain whether infant long-term anaemia is different when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Very low certainty of evidence (GRADE ⊕◯◯◯).

Infant haemoglobin, short-term (Appendix 4:8)

The outcome infant haemoglobin – short-term, after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in two RCTs, with a total of 306 infants (Katariya et al., 2021; Rao et al., 2018), with serious imprecision regarding this outcome. Katariya et al. (2021), reported haemoglobin data, at 24-48 hours, after umbilical cord clamping at 2 minu, mean (SD): 16.26 (2.03) g/dl, and at 3 min: 16.63 (1.33) g/dl, of which the latter was used in the meta-analysis for cord clamping at >1 min (Figure 6). The between group difference, after umbilical cord clamping at 1 min compared with clamping at >1 min, was RR -1.36 (95%CI: -1.48 to -1.24), p<0.00001, in favour for clamping at >1 min (Figure 6).

Figure 6. Infant haemoglobin (g/dl) – short-term, after umbilical cord clamping at 1 min compared with clamping at >1 min



Conclusion: Infant short-term haemoglobin probably decreases when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

Infant haemoglobin, long-term (Appendix 4:9)

Infant haemoglobin – long-term, was reported in one non-RCT by Askelöf et al. (2017), with 295 infants, and no or minor problems with indirectness, study limitations or precision for this outcome. Infant haemoglobin at 4 months was, mean (95%CI): 11.4 (11.3 to 11.6) g/dl for infants with umbilical cord clamping at 1 min, compared with 11.3 (11.2 to 11.4) g/dl, n.s., for infants with clamping at >1 min (Askelöf et al., 2017).

Conclusion: There may be little or no difference in infant long-term haemoglobin when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Low certainty of evidence (GRADE ⊕⊕◯◯).

Phototherapy (Appendix 4:10)

Phototherapy after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in four RCTs (Chaudhary et al., 2023; Chen at al., 2018; Katariya et al., 2021; Songthamwat et al., 2020), including a total of 882 infants, with serious imprecision regarding this outcome.
The difference in frequency of phototherapy after umbilical cord clamping at 1 min compared with clamping at >1 min, was RD-0.02 (95%CI: -0.05 to 0.00), n.s., and the RR was 0.81 (95%CI: 0.55 to 1.19), n.s. (Figures 7a and 7b).
A sensitivity analysis comparing umbilical cord clamping at 1 min with clamping at no visible or palpable pulsation in the umbilical cord, resulted in RR, 0.80 (95%CI: 0.54 to 1.18), n.s. (Figure 8).

Figure 7a. Frequency of phototherapy – risk difference for umbilical cord clamping at 1 min compared with clamping at >1 min

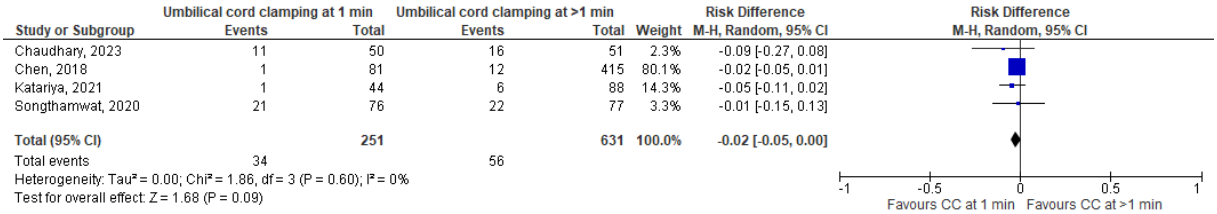


Figure 7b. Frequency of phototherapy – risk ratio for umbilical cord clamping at 1 min compared with clamping at >1 min

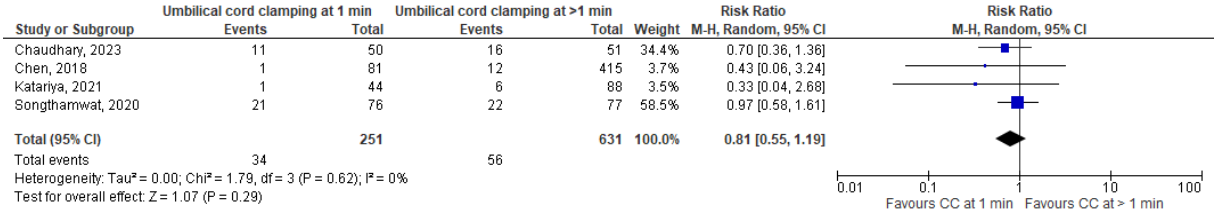
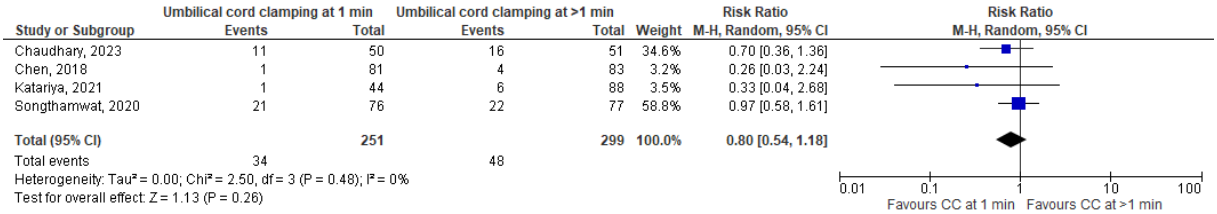


Figure 8. A sensitivity analysis for frequency of phototherapy (Appendix 4:10) – risk ratio for umbilical cord clamping at 1 min versus at no pulsation in the umbilical cord



Conclusion: There is probably little or no difference in the frequency of phototherapy when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

Admission to neonatal department (Appendix 4:11)

Admission to neonatal department was reported in one RCT (Chen et al., 2018), with 496 infants, with very serious imprecision for this outcome.
The difference in frequency of admission to neonatal department after umbilical cord clamping at 1 min compared with clamping at >1 minute, was RD -0.01 (95%CI: -0.03 to 0.01), n.n., and RR 0.72 (95%CI: 0.04 to 13.90), n.s. (Figures 9a and 9b).
A sensitivity analysis comparing umbilical cord clamping at 1 min with clamping at no pulsation in the umbilical cord, resulted in RR 0.34 (95%CI: 0.01 to 8.26), n.s. (Figure 10).

Figure 9b. Frequency of admission to neonatal department, risk difference for umbilical cord clamping at 1 min compared with clamping at >1 min

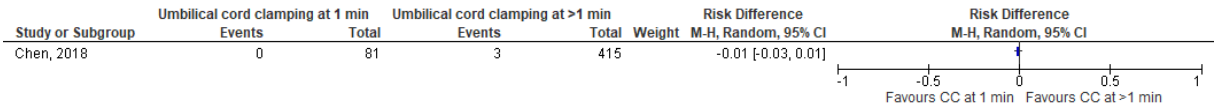


Figure 9b. Frequency of admission to neonatal department, risk ratio for umbilical cord clamping at 1 min compared with clamping at >1 min

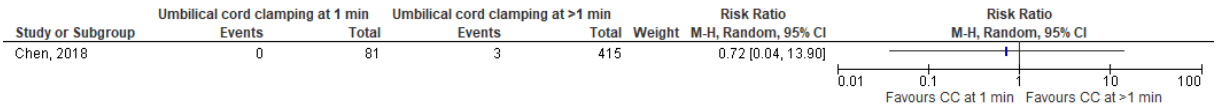
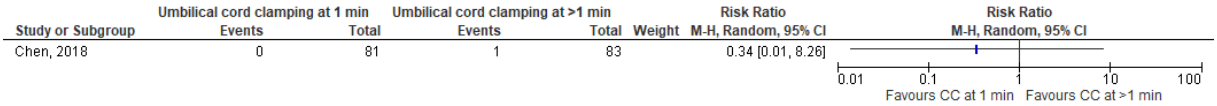


Figure 10. A sensitivity analysis for frequency of admission to neonatal department – risk ratio for umbilical cord clamping at 1 min compared with clamping at no pulsation in the umbilical cord



Conclusion: It is uncertain whether there is a difference in the occurrence of admission to neonatal department when the umbilical cord is clamped at 1 min, compared with umbilical cord clamping at >1 min. Very low certainty of evidence (GRADE ⊕◯◯◯).

Maternal outcomes – important for decision-making

The outcomes: **Manual removal of retained placenta**, and **Blood transfusion**, were not reported. **Maternal blood loss >500 ml** was reported as PPH (see below).

Postpartum haemorrhage >500 ml (Appendix 4:1)

PPH >500 ml, after umbilical cord clamping at 1 min compared with clamping at >1 min, was reported in 2 RCTs (Chaudhary et al., 2023; Chen et al., 2017) with 635 participants. Regarding this outcome there was serious indirectness and imprecision, across the studies.
The difference in PPH >500 ml between the groups was RD: -0.02 (95%CI: -0.07 to 0.04), n.s., and RR: 0.74 (95%CI: 0.19 to 2.98), n.s. (Figures 11a and 11b).
A sensitivity analysis comparing umbilical cord clamping at 1 min with clamping at no pulsation in the umbilical cord, resulted in RR 0.69 (95%CI: 0.19 to 2.44), n.s. (Figure 12).

Figure 11b. Postpartum haemorrhage >500 ml – risk difference after umbilical cord clamping at 1 min compared with clamping at >1 min

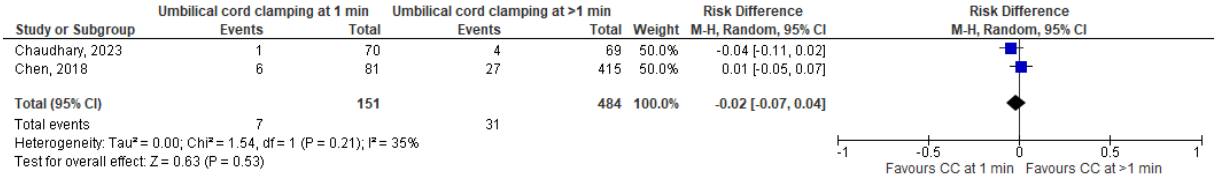


Figure 11b. Postpartum haemorrhage >500 ml – risk ratio after umbilical cord clamping at 1 min compared with clamping at >1 min

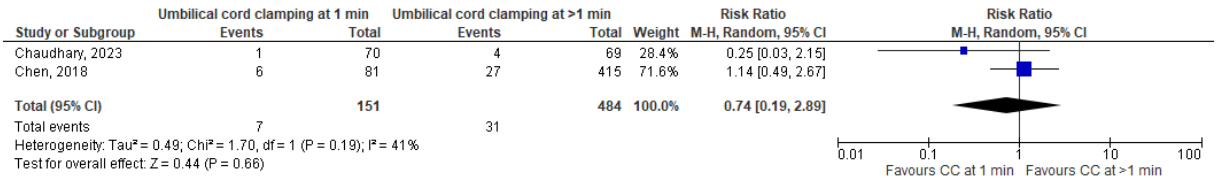
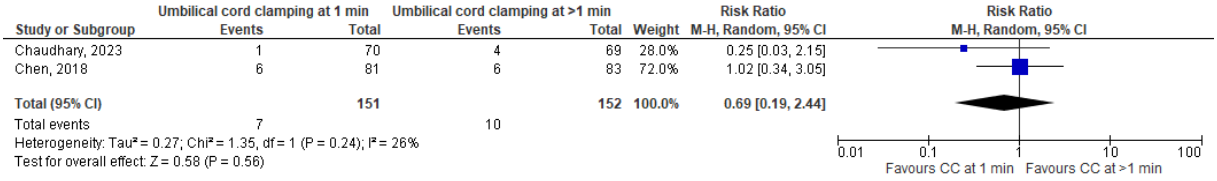


Figure 12. A sensitivity analysis for postpartum haemorrhage >500 ml (Appendix 4:1) – risk ratio for umbilical cord clamping at 1 min compared with clamping at no pulsation in

the umbilical cord



Conclusion: There may be little or no difference in the occurrence of PPH >500 ml if the umbilical cord is clamped at 1 min, compared with at >1 min. Low certainty of evidence (GRADE ⊕⊕◯◯).

Methodological outcomes

Successful stem cell harvest
The outcome was not reported.

10 Organisational aspects

Time frame for the putative introduction of the new health technology

Hypothetically, if umbilical cord clamping was to be performed at 1 min as a new recommendation for children born ≥37+0 weeks of gestational age by healthy mothers delivered by vaginal births, it could be implemented directly.

Present use of the technology in other hospitals in Region Västra Götaland

The technology at issue (umbilical cord clamping at 1 min) is used in the majority of caesarean sections in the Region, but not after vaginal deliveries where the recommendation is delayed umbilical cord clamping.

Consequences of the new health technology for personnel

Hypothetically, if the recommended timing of cord clamping would change to clamping at 1 min at vaginal births, there would probably be some lack of acceptance among personnel, with the current body of evidence.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Except for improved availability of cord blood stem cells for transplantation, the HTA-group could not identify any potential consequences for other clinics or supporting functions.

11 Economic aspects

The costs associated with clamping at 1 min, compared to clamping at >1 min are not possible to calculate but are very unlikely to differ, i.e., the medical intervention is identical except for timing of clamping, 1 min vs > 1 min. Thus, there are no expected costs of the health technology at issue and hence no cost advantages or disadvantages.

12 Ethical aspects

With umbilical clamping at 1 min, it is possible to harvest cord blood units for the NSCBB. These stem cells are made available through the Tobias Registry for the treatment of potentially life-threatening diseases. This HTA-review shows that there it is uncertain whether postpartum haemorrhage >1,000 ml is affected by early compared with delayed umbilical cord clamping and that there are no data for infant outcomes critical for decision-making, such as mortality and long-term cognitive function. However, for important infant outcomes, with moderate certainty of evidence, significant differences were seen for infant immediate haematocrit, with a mean difference of -3.09 (95%CI: -3.87 to -2.30) pp., p<0.00001, and short-term haemoglobin with a mean difference of -1.36 g/dl (95%CI: -1.48 to -1.24), p<0.00001, both (<10% difference between the groups) in favour for clamping at >1 min. There may be little or no difference in long-term haematocrit and ferritin levels and in short-term anaemia with early, compared with delayed umbilical cord clamping. As mentioned above this HTA-review did not find data on long-term cognitive function. One of the main ethical dilemmas concerning cord blood donation is that one individual might be exposed to a risk from an intervention that another individual benefits from. Moreover, the individual that might be exposed to the risk (the neonate), is in this case, not a person who can make an informed autonomic decision. The parents make an altruistic decision that might benefit another person.

Unfortunately, this analysis was not able to fully answer the question if there is increased risk of morbidity among children with cord clamping at 1 min compared with >1 min due to low quality of evidence. However, studies included in this HTA did not suggest major differences. As follows, a comprehensive ethical reasoning of risks versus benefits that could facilitate parents´ choice or informed consent to donation was not possible to perform. Therefore, since the evidence of safety concerning cord clamping at 1 min is uncertain, caution should be observed. However, if no donations are available this affects the possibility to offer treatment to patients with severe hereditary and malignant diseases in need of stem cell transplantation at Sahlgrenska University Hospital and worldwide.

13 Discussion

Summary of main results

In summary, of infant or maternal outcomes critical for decision making, only PPH >1,000 ml was reported in one of the studies and may not be affected by umbilical cord clamping at 1 min or at >1 min (few events, n.s.). No other outcomes critical for decision making were reported.

The present results, based on moderate certainty of evidence, show that umbilical cord clamping at 1 min, probably decreases the infant immediate haematocrit and short-term haemoglobin compared with clamping of the umbilical cord at >1 min. Whether these findings are clinically relevant or not was not further investigated in this HTA-analysis.

Also, based on moderate certainty of evidence, there is probably little or no difference in the frequency of phototherapy treatment comparing umbilical cord clamping at 1 min, with umbilical cord clamping at >1 min.
Based on low certainty of evidence, there may be little or no difference in maternal postpartum haemorrhage >500ml, infant long-term haematocrit, long-term ferritin, infant short-term anaemia, and infant long-term haemoglobin. It is uncertain whether long-term infant anaemia and long-term iron deficiency is affected by clamping the umbilical cord at 1 min or at > 1 min (very low certainty of evidence).

Thus, the combination of low certainty of evidence for most outcomes studied and absence of data critical for decision-making reveals important knowledge gaps and hence, the focused question of this HTA cannot be fully answered. Clinical decisions regarding timing of cord clamping are based on recommendations from the Swedish Association of Midwives and SFOG published in 2022 (Rekommendationer om avnavling av det nyfödda barnet, SFOG, 2022) and the results of this HTA-analysis will not affect the recommendations of umbilical cord clamping on a general basis.

Overall completeness and applicability of evidence

The current body of evidence regarding the optimal timing of umbilical cord clamping is far from unambiguous. The available studies do not allow definitive statements about benefits or disadvantages for the mother and the infant of clamping at 1 min versus >1 min. There were also some problems with directness since the RCTs were conducted in countries with a different level of development and/or health care settings than Sweden. Only one cohort study was performed in a country with corresponding socioeconomic level, with no significant differences at long-term (4 months) in haematocrit levels, haemoglobin levels, iron deficiency, or anaemia (Askelöf et al., 2017). Furthermore, the population where the RCTs where conducted are likely to vary from the Swedish population e.g. factors concerning the mothers' haemoglobin, ferritin-value and daily intake of iron are likely to vary and could affect the outcomes.

More extensive and rigorous research is needed to establish clear guidelines and ensure that clinical decisions on timing of clamping are based on solid evidence. Until then, uncertainty remains, highlighting the need for further investigation in this area of neonatal care.

The current incomplete evidence on the timing of umbilical cord clamping underscores the importance of further research. This research should aim to provide clear guidance to clinicians and expecting parents, ensuring that ethical principles are upheld in clinical practice.

Agreements and disagreements with other studies and reviews

There is no established definition for early cord clamping, nor delayed cord clamping, hence there is a broad spectrum of timing of cord clamping in different studies. Most studies compare early cord clamping (direct cord clamping, within 60 seconds) with delayed cord clamping, >1 min to 5 min (McDonald et al., 2013, Hutton and Hassan, 2007, Chapparo et al., 2006).

In a Cochrane review (McDonald et al., 2013) including 3,911 full term infants, comparing umbilical cord clamping at <1 min with >1 min, there was no significant increased risk of PPH or neonatal mortality. There were fewer infants requiring phototherapy, significantly lower haemoglobin at 24-48 hours and an increased risk of iron deficiency at 3-6 months of age in the group with umbilical cord clamping at <1 min.

According to the current Swedish recommendations the umbilical cord should be clamped when 'pale and limp' and at the latest concurrent with the expulsion of the placenta (SFOG, 2022). The recommendation refers to studies showing "good effects" e.g. increased ferritin levels, decreased risk of anaemia and better outcomes regarding fine motor skills and social domains when the umbilical cord is clamped at least 3 min after birth. However, the studies which the recommendation refers to, include studies where both early cord clamping, and delayed cord clamping have different definitions. In one study delayed cord clamping is defined as umbilical cord clamping at 1 min or more, early cord clamping is mostly defined as <1 min, but often <30 seconds (Mercer et al., 2020, Mercer et al., 2018, Andersson et al., 2015, McDonald et al., 2013).

Studies where early cord clamping was defined as <20 and <10 seconds and delayed cord clamping as 3-5 minutes , timeframes which are thus not included in this report, have shown that late cord clamping is associated with higher ferritin levels, greater myelin content and improved scores in fine-motor and social domains when newborn are followed up after 4 months and 4 years (Mercer et al., 2018, Andersson et al., 2015, Andersson et al., 2013). In another study by Andersson et al. (2014) where newborn with early or late cord clamping were followed up at 12 months, delayed clamping did not affect iron status or neurodevelopment. Another RCT by Mercer et al., 2022, comparing cord clamping at $\leq$ 20 seconds with cord clamping at $\geq$ 5 minutes, with a follow up at 12 months, showed increased white matter cell growth on magnetic resonance imaging (MRI) in the group with late cord clamping, but no difference in development tests between the two groups. However, only 56% of the children had a usable MRI and those who did were more likely to be from families who had private insurance and listed race as white. We have neither critically appraised nor defined the certainty of evidence of the conclusions in these studies.

Implications for research

During the last years, results from studies investigating long term effects of cord clamping indicate that there are several benefits of delayed compared clamping with early cord clamping (Bayer 2016, Andersson and Mercer, 2021, Mercer et al., 2022, Mercer et al., 2018, Andersson et al., 2015, McDonald et al., 2013). As mentioned above these studies mostly compare cord clamping <1 min with >1 min, e.g., direct cord clamping vs. cord clamping at 3 min. Hence, there is not yet enough research to

conclude at which time after delivery the cord can be clamped to secure enough blood volume and iron stores necessary for normal development for the child.

However, it is also known, from previous studies on perinatal physiology that most of the remaining blood in the placenta is transferred to the child during the first min after birth. Taken together, it is clear that the answer is multifactorial and further research on perinatal physiology and optimal timing of clamping might bring further knowledge. Current research on cord blood collection concludes that successful collection is possible with clamping at 1 min but further research on perinatal physiology, collection efficiency and collection techniques might have implications on timing of collection.

As none of the infant or maternal outcomes critical for decision making were reported in the present included studies, further research is necessary concerning these aspects.

None of the included studies reported data regarding stem cell harvesting. More effective techniques for stem cell collection might increase collection yields at later clamping timepoints.

14 Future perspectives

Scientific knowledge gaps

The critical infant outcomes: Mortality, long-term cognitive function, neonatal intensive care unit care >4 days, and Apgar score <5 at 5 minute, and the critical maternal outcomes: Mortality, severe morbidity, organ failure, and ICU admission were not reported in any of the present studies.

Ongoing research

A search in Clinicaltrials.gov (07 April 2024) identified 396 trial records of which two was matching the current PICO.

NCT05492214: An RCT, with study completion estimated in December 2024, studying the effects of time window for umbilical cord clamping during caesarean section on the health outcomes of offspring haemoglobin, maternal blood loss, and children's growth and development. Two of the four study groups were according to the current PICO with umbilical cord clamping at 60 seconds, and at 90 seconds.
Last update on 2023-05-06, status: Active, not recruiting. No results posted.

NCT04351997: An RCT with the aim to evaluate the effect of umbilical cord clamping at 60 seconds and at 180 seconds, on placental transfusion in two-step delivery, by change in haematocrit from arterial cord blood at birth and capillary blood at 48 hours of age. Last update on 2020-04-17, status, actual study completion date, 2018-09-01. No references filed.

In addition, recently, additional uses of cord blood have been investigated, such as cord blood erythrocyte transfusions to very premature infants, with clinical studies ongoing in Europe (e.g., ClinicalTrials.gov: NCT05100212, Registered 29 October 2021).

15 Participants in the project

The question was nominated by

Kerstin Åmark, MD, PhD, MSc. Verksamhetschef. Region Västra Götaland, Sahlgrenska University Hospital, Dept of Clinical Immunology and Transfusion Medicine, Gothenburg, Sweden

Participating healthcare professionals

Elin Bergdahl, Registrar, Region Västra Götaland, Sahlgrenska University Hospital, Dep of Gynaecology and Obstetrics, Gothenburg, Sweden

Hanna Friberg, MD, Consultant obstetrican, Region Västra Götaland, Sahlgrenska University Hospital, Department of Gynaecology and Obstetrics, Gothenburg, Sweden

Sofia Frändberg, MD, PhD, Region Västra Götaland, Sahlgrenska University Hospital, Dept of Clinical Immunology and Transfusion Medicine, Gothenburg, Sweden

Vesta Seyed Alikhani, MD, Consultant neonatologist, Region Västra Götaland, Sahlgrenska University Hospital, Department of neonatology, Gothenburg, Sweden

Anna Wessberg, RNRM, PhD, senior midwife, Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital, Gothenburg, Sweden and Department of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden

Participants from the HTA-centrum

Lennart Jivegård, MD, consultant vascular surgeon; PhD, associate professor, Region Västra Götaland, Sahlgrenska University Hospital, HTA-centrum, Gothenburg, Sweden

Petteri Sjögren, DDS, PhD, Region Västra Götaland, Sahlgrenska University Hospital, HTA-centrum, Gothenburg, Sweden

Participants Medical Library

Agnes Holmberg, Librarian, Region Västra Götaland, Sahlgrenska University Hospital, Medical Library, Gothenburg, Sweden

Therese Svanberg, HTA-librarian, Region Västra Götaland, Sahlgrenska University Hospital, Medical Library, Gothenburg, Sweden

External reviewers

Maria Skogby, CCNS, PhD, Region Västra Götaland, Sahlgrenska University Hospital, Department of Neonatology, Gothenburg, Sweden

Margareta Hellgren Wångdahl, MD, PhD, Professor emerita, Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

Declaration of interests

The authors report that they have no conflicts of interest related to the content of this HTA.

Project time

The HTA was accomplished during the period of 2023-12-07 to 2024-09-25. Literature searches were done 2023-12-15.

Components of this Health Technology Assessment

- ✓ Description of methods
- ✓ PICO
- ✓ Full literature search
- ✓ Flowchart
- ✓ Quality assessment
- ✓ Data tabulation
- ✓ Evidence synthesis
- ✓ Meta-analysis
- ✓ Certainty of evidence by GRADE
- ✓ Summary
- ✓ Economical aspects
- ✓ Organisational aspects
- ✓ Ethical aspects
- ✓ Ongoing studies
- ✓ Excluded articles
- ✓ Participation of experts
- ✓ External review
- ✓ Knowledge gaps identified
- ✓ Conflict of interest reported

Appendix 1: PICO, study selection, search strategies, and references

Question at issue: Effects of umbilical cord clamping in newborn infants and mothers with term pregnancy (≥37+0) at 1 min, compared with clamping at >1 min concerning infant and maternal morbidity and mortality?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO	
P	Newborn infants not in need of stabilisation, and mothers with uncomplicated term pregnancy (≥37+0).
I	Umbilical cord clamping at 1 min
C	Umbilical cord clamping at >1 min
O	Outcomes critical for decision-making Infant Mortality Long-term cognitive function NICU care ≥4 days Apgar score <5 at five min Mother Mortality Severe morbidity, organ failure, ICU admission Severe postpartum haemorrhage ≥1000ml Outcomes important for decision-making Infant • Haematocrit – immediate and long-term • Ferritin – immediate and long-term • Iron-deficiency, anaemia: immediate and long-term* and haemoglobin level, immediate and long-term (*Immediate defined as within 0-48 hours and long-term as after 2-6 months) Phototherapy Admission to neonatal units Apgar score <7 at five min Neurodevelopment, long term Mother Manual removal of retained placenta Blood transfusion Maternal blood loss >500 ml Methodological outcomes Successful stem cell harvest

Eligibility criteria

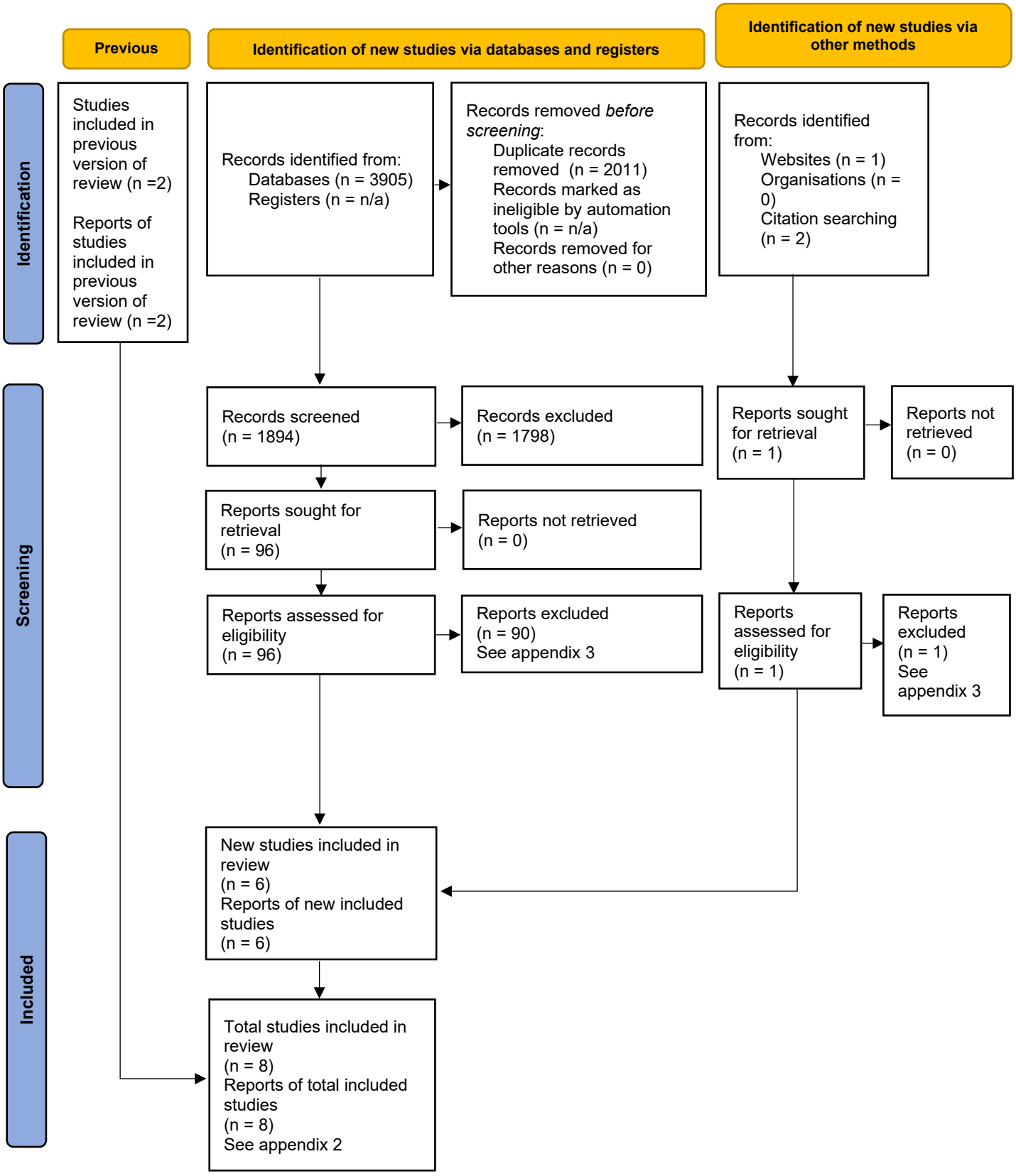
Study design:
Randomised controlled trials – (All outcomes)
Cohort studies with ≥100 patients

Language:
Swedish, Norwegian, Danish, English

Publication date: 2011-

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



From: Page et al., 2021

Search strategies

Database: Ovid MEDLINE(R) ALL (OvidSP)
Date: 15 Dec 2023
No. of results: 1,130

#	Searches	Results
1	exp Umbilical Cord/	29461
2	(clamping or clamp or cutting or cut or detachment or separation).ab,kf,ti.	615327
3	1 and 2	1402
4	cord.ab,kf,ti.	246731
5	(cord adj4 (clamping or clamp or cutting or cut or detachment or separation)).ab,kf,ti.	2450
6	3 or 5	2956
7	Time Factors/	1230974
8	(immediate or prompt or early or late or delay or delayed or time or timing or deferred).ab,kf,ti.	6288335
9	7 or 8	7028516
10	6 and 9	1839
11	Umbilical Cord Clamping/	104
12	cord management.ab,kf,ti.	91
13	10 or 11 or 12	1892
14	animals/ not (animals/ and humans/)	5143714
15	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or murine or porcine or horses or horse).ti.	2125521
16	14 or 15	5566020
17	13 not 16	1751
18	limit 17 to (danish or english or norwegian or swedish)	1635
19	**limit 18 to yr="2011 -Current"**	**1130**

Database: Embase 1974 to 2023 December 13 (OvidSP)
Date: 15 Dec 2023
No. of results: 1,541

#	Searches	Results
1	exp umbilical cord/	75886
2	(clamping or clamp or cutting or cut or detachment or separation).ab,kf,ti.	809494
3	1 and 2	2901
4	cord.ab,kf,ti.	322788
5	(cord adj4 (clamping or clamp or cutting or cut or detachment or separation)).ab,kf,ti.	3330
6	3 or 5	4983
7	time factor/	47113
8	(immediate or prompt or early or late or delay or delayed or time or timing or deferred).ab,kf,ti.	8438788
9	7 or 8	8458259
10	6 and 9	2873

11	exp umbilical cord clamping/	914
12	cord management.ab,kf,ti.	107
13	10 or 11 or 12	3208
14	animal/ not (animal/ and human/)	1204983
15	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or murine or porcine or horses or horse).ti.	2292934
16	14 or 15	3220233
17	13 not 16	3115
18	limit 17 to (embase or medline)	2329
19	limit 18 to (danish or english or norwegian or swedish)	2128
20	**limit 19 to yr="2011 -Current"**	**1541**

Database: The Cochrane Library
Date: 15 Dec 2023
No of results: 410 ref
Cochrane reviews: 16
Cochrane protocols: 0
Trials: 394
Editorials: 0
Special collections: 0
Clinical answers: 0

ID	Search	Hits
#1	MeSH descriptor: [Umbilical Cord] explode all trees	802
#2	(clamping or clamp or cutting or cut or detachment or separation):ti,ab,kw (Word variations have been searched)	79008
#3	#1 AND #2	297
#4	((cord near/3 (clamping or clamp or cutting or cut or detachment or separation))):ti,ab,kw (Word variations have been searched)	1264
#5	#3 OR #4	1299
#6	MeSH descriptor: [Time Factors] this term only	73054
#7	(immediate or prompt or early or late or delay or delayed or time or timing or deferred):ti,ab,kw (Word variations have been searched)	751073
#8	#6 OR #7	751073
#9	#5 AND #8	1058
#10	MeSH descriptor: [Umbilical Cord Clamping] this term only	34
#11	("cord management"):ti,ab,kw (Word variations have been searched)	23
#12	#9 OR #10 OR #11	1070
#13	(clinicaltrials OR trialsearch):so	490964
#14	#12 NOT #13	691
#15	(conference proceeding):pt	232480
#16	#14 NOT #15	608
Limit search to publication year 2011-2023		**410**

Database: CINAHL (EBSCOhost)
Date: 15 Dec 2023
No. of results: 824

#	Query	Results
S19	**S13 NOT S16 Limiters - Publication Date: 20110101-20231231**	**824**
S18	S13 NOT S16 Limiters - Language: Danish, English, Norwegian, Swedish	992
S17	S13 NOT S16	1,016
S16	S14 OR S15	126,930
S15	TI animal OR animals OR rat OR rats OR mouse OR mice OR rodent OR rodents OR dog OR dogs OR cat OR cats OR hamster OR hamsters OR rabbit OR rabbits OR swine OR murine OR porcine OR horses or horse	86,768
S14	(MH "animals") NOT ((MH "animals") AND (MH "human"))	51,365
S13	S10 OR S11 OR S12	1,019
S12	TI "cord management" OR AB "cord management"	53
S11	(MH "Umbilical Cord Clamping")	295
S10	S6 AND S9	904
S9	S7 OR S8	1,368,745
S8	TI (immediate or prompt or early or late or delay or delayed or time or timing or deferred) OR AB (immediate or prompt or early or late or delay or delayed or time or timing or deferred)	1,271,254
S7	(MH "Time Factors")	186,249
S6	S3 OR S5	1,178
S5	S4 N3 S2	1,108
S4	TI cord OR AB cord	46,697
S3	S1 AND S2	488
S2	TI (clamping or clamp or cutting or cut or detachment or separation) OR AB (clamping or clamp or cutting or cut or detachment or separation)	78,760
S1	(MH "Umbilical Cord+")	4,409

The web-sites listed below were visited 27 Feb 2024.
One report relevant to the question at issue was found.

Sökkällor	Sökord/ Browsa	Antal träffar	Antal relevanta träffar
SBU www.sbu.se ”Visa även träffar äldre än 5 år”	Avnavling Avnavla Navelsträng Förlossning	1 0 0 134	1 0 0 0
Folkehelseinstituttet (Norge) https://www.fhi.no/ku/metodevurdering/	Browsat kategori Metodevurdering – Rapporter		0
Behandlingsrådet (Danmark) https://behandlingsraadet.dk/	Browsat		0
Nationale Kliniske Anbefalinger og Retningslinjer (Danmark) https://www.sst.dk/da/Fagperson/Retningslinjer-og-procedurer/NKA-og-NKR/NKR-og-NKA-efter-omraade	Browsat kategori Ovrige emner		0
CAMTÖ	Browsat		0

https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/			
HTA Region Stockholm https://www.chis.regionstockholm.se/hta/rapporter/	Browsat		0
Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/	Browsat		0
HTA Syd https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365	Browsat		0
Medicinska rådet, Region Dalarna https://www.regiondalarna.se/plus/vard/ovrig-halso--och-sjukvard/medicinska-radet/	Browsat		0

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Reference lists
A comprehensive review of reference lists brought 2 new records.

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Project: Cord Clamping
Appendix 2 – Characteristics of included studies

Author, year country	Study Design	Length of follow-up	Study groups Intervention vs. Control	Patients (n)	Mean Gestational Age (years)	Mean (%)	Outcome variables
Askelöf, 2017 Sweden	Cohort	4 months	I=UCC at 60s C=UCC at 180s	400	GA (wk), Mean (SD) I=40.0 (1.0) C=40.0 (1.1)	I=51% C=43%	Ferritin Haematocrit Iron deficiency Anaemia at 4 months of age
Ceriani, 2006 Argentina	RCT	4 months	I=UCC at 60 C=UCC at 180 s	183	GA (wk), Mean (SD) I=39.1 C=39.3	Not reported	Anemia at 6 hours of life, Haematocrit at 24-48h Anaemia at 24-48h
Chaudhary, 2023 India	RCT	12±2 wk	I=UCC at 60s vs C=UCC at 120s	I=70 C=69	GA (wk), Mean (SD) I =37.8 (1.8) C=37.8 (1.7)	I=41.4% C=46.4%	PPH Infant haematocrit, immediate Infant serum ferritin level, long term Infant iron deficiency, long term Phototherapy
Chen, 2017 China	RCT	72h	I=UCC at 60s vs C=UCC at 90s, 120s, 150s, 180s and at “no pulsation”	I=90 C=450	GA (wk), Mean (SD) I=40 (1) C=40 (1) (for all subgroups)	I=46.7% C=45.6%, 52.2%, 48.9%, 46.7%, 47.8 %,	PPH Infant haematocrit, immediate Phototherapy Admission to neonatal department
Katariya, 2021 India	RCT	24-48h	I=UCC at 1 min Vs C= UCC at 2 min and 3 min	I=49 C=98	GA Between 37-42 weeks included in study	I=54.5 % C=50%, 56.8%	Infant haemoglobin, short term Phototherapy
Rao, 2018 Pakistan	RCT	6h	I=UCC at 1 min C=UCC at 2 min	I=109 C=109	“Full term newborn”	I=56% C=38.5%	Infant haemoglobin, short term Infant haematocrit, immediate
Saigal, 1972 Canada	RCT	72h	I=UCC at 1 min C=UCC at 5 min	I=15 C=15	GA (wk), Mean (range) I=40.0 (38-41) C=40.1 (38-42)	Not reported	Infant haematocrit, immediate
Songthamwat, 2020 Thailand	RCT	48-72h	I=UCC at 1 min C=UCC at 2 min	I=80 C=80	GA (wk), Mean (SD) I=38.8 (1.2) C=38.6 (1.1)	Not reported	Phototherapy

Wk=Week; RCT=randomized controlled trial; GA=gestational age; UCC=Umbilical cord clamping; PPH=Post partum haemorrhage.

Project: Umbilical cord clamping
Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Aboulshady, 2023	Wrong I not clamping at 1 min
Aithal, 2023	Cohort study with <100 patients/arm
Alfartosy, 2023	Wrong I not clamping at 1 min
Allan, 2016	Wrong I not clamping at 1 min
Alzaree, 2018	Wrong intervention, wrong comparison (cord milking)
Andersson, 2019	Wrong P – resuscitation
Andersson, 2021	Wrong publication type: review
Andersson, 2023	Wrong publication type, review
Anonymous, 2020 ACOG Committee	Wrong publication type, ACOG guidelines
Ashish, 2017	Duplicate publication Kc 2017
Avinash B, 2023	Wrong P – resuscitation
Badurdeen, 2022	Wrong intervention
Badurdeen, 2021	Wrong intervention
Berg, 2021	Wrong I not clamping at 1 min
Blouin, 2013	Wrong I not clamping at 1 min
Carvalho, 2019	Wrong I not clamping at 1 min
Cavallin, 2019	Wrong intervention, wrong comparison (wrong clamping time)
Celen, 2021	Wrong P – resuscitation
Ceriani Cernadas, 2012	Wrong publication type: summary
Chatha, 2021	Wrong I – clamping times not specified
Chetan, 2021	Wrong I not clamping at 1 min
Chien, 2015	Wrong language: Chinese
Consonni, 2020	Wrong intervention, wrong comparison (wrong clamping time)
Cuibotario, 2018	Wrong I not clamping at 1 min
Dinc, 2023	Wrong intervention, wrong comparison (wrong clamping time)
Ersdal, 2016	Wrong comparison

Project: Umbilical cord clamping
Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Ersdal, 2014	Wrong comparison
Fawzy, 2015	Wrong intervention (wrong clamping time)
Frändberg, 2016	Wrong intervention (wrong clamping time)
Fu, 2020	Wrong publication type, meta-analysis
Ghirardello, 2018	Wrong comparison (wrong clamping time)
Gomersall, 2021	Wrong I not clamping at 1 min
Gupta, 2022	Wrong study design: case series
Gyorkos, 2021	Wrong I not clamping at 1 min
Herold, 2023	Wrong publication type, review
Isacson, 2021	Wrong P – resuscitation
Ishaq, 2016	Wrong I – clamping times not specified
Jenusaitis, 2022	Wrong intervention (wrong clamping time)
Kartal, 2022	Wrong intervention (wrong clamping time)
Katageri, 2018	Wrong intervention, wrong comparison, <100 patients/arm
Katheria, 2017	Wrong P – resuscitation
Kc, 2017	Wrong I not clamping at 1 min
Kc, 2019	Wrong I not clamping at 1 min
Kc, 2023	Wrong I not clamping at 1 min
Khalid, 2013	Wrong intervention (wrong clamping time)
Koo, 2022	Wrong publication type, review
Kosinska-Kaczynska, 2022	Wrong intervention, <100 patients/arm
Kuo, 2018	Wrong population (preterm)
Lara-Canton, 2022	Wrong publication type: review
Li, 2020	Wrong intervention
Liyanage, 2020	Wrong publication type, review
Malhi, 2015	Wrong I – clamping times not specified

Project: Umbilical cord clamping
Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Marrs, 2022	Wrong publication type: review
McDonald , 2022	Wrong publication type, review.
McDonald, 2023	Wrong publication type
Mercer, 2018	Wrong I not clamping at 1 min
Mercer, 2022	Wrong I not clamping at 1 min
Mejía Jiménez, 2021	Wrong intervention, wrong comparison (wrong clamping time)
Mina, 2023	Wrong I not clamping at 1 min
Mukherjee, 2020	Wrong intervention, wrong comparison (wrong clamping time)
Nesheli, 2014	Wrong intervention, wrong comparison (wrong clamping time)
Nouraie, 2019	Wrong I not clamping at 1 min
Nudelman, 2020	SR, included studies wrong intervention and/or wrong publication year
Okulu, 2022	Wrong intervention (wrong clamping time)
Orenga–Orenga, 2022	Wrong I not clamping at 1 min
Pakkan, 2018	Wrong intervention, wrong comparison, wrong study design
Pan, 2022	Wrong intervention, wrong comparison (wrong clamping time)
Pilania, 2023	Wrong P for the study
Qian, 2020	Wrong I not clamping at 1 min
Rana, 2020	Wrong I not clamping at 1 min
Rana, 2019	Wrong I not clamping at 1 min
Rhoades, 2019	Wrong intervention
Sahoo, 2020	Wrong intervention, wrong comparison (wrong clamping time)
Schwaberger, 2022	Wrong I and O for the study
Shao, 2021	Wrong I not clamping at 1 min
Shao, 2022	Wrong I not clamping at 1 min
Singh, 2022	Wrong study design: cohort study with <100 patients/arm
Sun, 2017	Wrong I not clamping at 1 min

Project: Umbilical cord clamping
Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Taskin, 2022	Wrong I not clamping at 1 min
Vatansever, 2018	Wrong intervention (wrong clamping time)
Verbeek, 2017	Wrong intervention, wrong comparison
Vimalshika, 2019	Wrong I not clamping at 1 min
Wennerholm, 2012	Wrong publication type
Wilander, 2023	Wrong study design: cohort study with <100 patients/arm
Winkler, 2022	Wrong intervention, wrong comparison (wrong clamping time)
Withanathanrig, 2017	Wrong I not clamping at 1 min
Xodo, 2021	Wrong I not clamping at 1 min, and study design
Yasartekin, 2020	Wrong intervention
Yoon, 2023	Wrong intervention, wrong comparison (wrong clamping time)
Zhang, 2020	Wrong C too wide time interval
Zhao, 2019	SR, included studies wrong intervention and/or wrong comparison (wrong clamping time)

Project: Cord clamping
Appendix 4.1
Outcome variable: PPH, Post partum haemorrhage

* + No or minor problems
? Some problems
- Major problems

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 min	Control Clamping at >1 min				
Chaudhary, 2023 India	RCT	I=70 C=69	I=0 C=0	PPH>500 ml, n (%): 1/70 (2.82%)	PPH >500 m, n (%): 4/69 (5.8), n.s.		?	?	?
Chen, 2017 China	RCT	I=90 C=90 (90s) C=90 (120s) C=90 (150s) C=90 (180s) C=90 (No pulsation)	I=9 C=7 (90s) C=10 (120s) C=1 (150s) C=10 (180s) C=7 (No pulsation)	PPH>500 ml (%): 6/81 (6.7) PPH>1000 ml (%): 2/81 (2.2)	PPH>500 ml (%): 27/415, n.s.* Clamping at 90s PPH>500 ml: 6 (6.7), n.s.* PPH>1000 ml: 2 (2.2), n.s.* Clamping at 120s PPH>500 ml: 7 (7.8), n.s.* PPH>1000 ml 0 (0), n.s.* Clamping at 150s PPH>500 ml: 5 (5.6), n.s.* PPH>1000 ml: 0 (0), n.s.* Clamping at 180s PPH>500 ml: 3 (3.3), n.s.* PPH>1000 ml: 0 (0), n.s.* Clamping at no pulsation: PPH>500 ml: 6 (6.7), n.s.* PPH>1000 ml: 0 (0), n.s.*	* p-value calculated from data (Fisher's exact test) Five different control groups with clamping at 90, 120, 150, 180 s, and at no pulsation	?	+	?

N.s.=not statistically significant; PPH=Post partum haemeorrhage; RCT=randomized controlled trial

Project: Umbilical cord clamping
Appendix 4.2
Outcome variable: Haematocrit - immediate

* + No or minor problems
? Some problems
- Major problems

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping at > 1minute				
Ceriani Cernadas, 2006 Argentina	RCT	I=91 C=92	n=1 n=0	Venous haematocrit (%), mean (SD), at 6 h: 57.0 (5.8), range 43.5-71.0 Mean (SD), at 24-48h: 59.4 (6.1)	Neonatal haematocrit (%), mean (SD), at 6 h: 59.4 (6.1), range 45.0-75.0, n.s* Mean (SD), at 24-48h: 56.4 (7.4)#	C=clamping at 3 min * Statistical equivalence between the groups (less than 8 points higher in C) # p-value not reported	+	+	+
Chaudhary, 2023 India	RCT	I=70 C=69	I=20 C=18	Venous haematocrit (%), mean (SD); 57.3 (5.2)	Venous haematocrit (%), mean (SD); 59.9 (5.0), p=0.056	* Data from subgroup full-term ≥ 37 wk. C=clamping at 120 s	?	+	?
Chen, 2017 China	RCT	I=90 C 90s=90 C 120s=90 C 150s=90 C 180s=90 C no pulsation=90	I=9 C 90s=7 C 120s=10 C 150s=1 C 180s=10 C no pulsation=7	Venous heamatocrit (%) mean (SD), at 24 h: 58.8 (5.9)	Venous heamatocrit (%) mean (SD), at 24 h: C 90s: 59.7 (8.7), n.s. C 120s: 59.5 (6.6), n.s. C 150s: 59.7 (6.8), n.s. C 180s: 60.3 (5.4), n.s. C no pulsation: 61.0 (6.0), p<0.05	For C no pulsation, cord clamping time was mean (SD) 172.0 (92.9) s	?	+	?
Rao, 2018 Pakistan	RCT	I=109 C=109	Not reported	Neonatal haematocrit (%), mean (SD), at 6 h: 46.57 (0.49)	Neonatal haematocrit (%), mean (SD), at 6 h: 50.24 (0.81), 95% CI: -3.843 to -3.483, p=0.000	C=clamping at 2 min	?	-	-
Saigal et al 1972 Canada	RCT	I=15 C=15	I=0 C=0	Neonatal haematocrit (%), mean (SD), at 4 h: 62.6 (SD 4.6)	Neonatal haematocrit (%), mean (SD), at 4 h: 64.9 (SD 5.4)	C=clamping at 5 min	?	?/-	-

95%CI=95% confidence interval; N.s.=not statistically significant; RCT=randomized controlled trial

Project: Cord clamping
Appendix 4.3
Outcome variable: Infant haematocrit, long term

* + No or minor problems
? Some problems
- Major problems

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Askelöf et al 2017 Sweden	Cohort study	I=191 C=168	I=56 C=20	Venous haematocrit (%), mean (95% CI); 33.1% (32.8 to 33.5)	Venous haematocrit (%), mean (95% CI); 32.7% (32.4 to 33.1), n.s.	*Data at 4 months, adjusted for infant age C=clamping at 180s, data from historical controls (Andersson et al., 2011)	+	+	+

95% CI=95% confidence interval; N.s.=not statistically significant; RCT=randomized controlled trial; Wk=week

Project: Cord clamping

* + No or minor problems
? Some problems
- Major problems

Appendix 4.4
Outcome variable: Infant serum ferritin level, long term

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Askelöf, 2017 Sweden	Cohort	I=200 C=200	I=53 C=52	Geometric mean (range), at 4 months*: 96 (44-208) µg/l Ferritin <20µg/l: 4/147 (2.7%)	Geometric mean (range), at 4 months*: 117 (58-232) µg/l, p=0.02 Ferritin <20µg/l: 0/148 (0%), n.s. Geometric mean difference (95% CI): 1.21 (1.03-1.44) µg/l p=0.02	C=historical controls (180 s) from Andersson et al., 2011 *Data at 4 months, adjusted for infant age.	+	+	+
Chaudhary, 2023 India	RCT	I=50 C=51	I=23 C=23	Median (IQR), at 12±2 weeks: 101.0 (67.4-211.5) µg/l Ferritin <50 µg/l: 5/27 (18.5%)	Median (IQR), at 12±2 weeks: 101.7 (52.2-173.8) µg/l, n.s. Ferritin <50 µg/l: 5/28 (17.8%), n.s.	I and C= Subgroup with full-term (≥37 week) infants C=Clamping at 120 s	?	?	?

N.s.=not statistically significant; RCT=randomized controlled trial; Wk=week.

Project: Cord clamping

* + No or minor problems
? Some problems
- Major problems

Appendix 4.5
Outcome variable: Infant iron deficiency, long term

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Chaudhary, 2023 India	RCT	I=50 C=51	I=23 C=23	Ferritin <50 µg/l (%): 5/27 (18.5%)	Ferritin <50 µg/l (%): 5/28 (17.8%), n.s.	I and C=Subgroup with full-term (≥37 week) infants C=Clamping at 120 s Iron deficiency defined as: serum ferritin <50 µg/l	?	?	?
Askelöf, 2017 Sweden	Cohort	I=200 C=200	I=53 C=52	Unadjusted numbers (%), at 4 months: 7/147 (4.8%)	Unadjusted numbers (%), at 4 months: 1/147 (0.7%), p=0.04*	C=Historical controls (180 s) from Andersson et al., 2011 Iron deficiency defined as: ≥2 iron indicators (serum ferritin <20µg/l, MCV <73fl, low transferrin saturation <10% and transferrin receptor >7 mg/l) *After statistical adjustment for sex and age at the time of follow-up, not significant between the groups	+	+	+

N.s.=not statistically significant; RCT=randomized controlled trial; Wk=week.

Project: Cord clamping

* + No or minor problems
? Some problems
- Major problems

Appendix 4.6
Outcome variable: Infant anaemia, short term

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Ceriani Cernadas, 2006 Argentina	RCT	I=91 C=92	I=1 at 6h C=0 at 6h I=2 at 24–48 h C=2 at 24–48 h	Anaemia at 6h (%): 1/90 (1.1) Anaemia at 24-48 h (%): 2/89 (2.3)	Anaemia at 6h, n/n (%): 0/92 (0.0), n.s.* Anaemia at 24-48h: 3/90 (3.3), n.s.*	Anaemia defined as haematocrit <45%. *p-values calculated from data (Fisher's exact test).	?	?	?

N.s.=not statistically significant; RCT=randomized controlled trial

Project: Cord clamping

Appendix 4.7
Outcome variable: Infant anaemia, long term

* + No or minor problems
? Some problems
- Major problems

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Askelöf, 2017 Sweden	Cohort	I=200 C=200	I= 60 C=54	Anaemia at 4 months (%): 16/140 (11.4)	Anaemia at 4 months (%): 20/144 (13.9), ns.	C=historical controls (180 s) from Andersson et al., 2011 Anaemia (haemoglobin <10.5g/dl), unadjusted numbers Anemia did not differ significantly between boys and girls	+	+	+

N.s.=not statistically significant; RCT=randomized controlled trial.

Project: Cord clamping

* + No or minor problems
? Some problems
- Major problems

Appendix 4.8
Outcome variable: Infant haemoglobin, short term

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Katariya, 2021 India	RCT	I=49 C 2 min=49 C 3 min=49	I=5 C 2 min=5 C 3 min=5	Haemoglobin (g/dl), at 24-48h, mean (SD): 15.30 (1.93)	Haemoglobin (g/dl), at 24-48h, mean (SD): C 2 min: 16.26 (2.03) C 3 min: 16.63 (1.33) p=0.00*	*p-value significant for clamping at 3 min, versus 2 min or 1 min For other comparisons, p-values not reported	?	-	-
Rao, 2018 Pakistan	RCT	I=109 C=109	Not reported	Haemoglobin (g/dl), at 6h, mean (SD): 15.82 (0.34)	Haemoglobin (g/dl), at 6h, mean (SD), [95%CI]: 17.18 (0.53), [-1.477 to -1.238]*, p=0.000	C=clamping at 2 min * 95%CI as reported in the article for between groups difference	?	-	-

95%CI=95% confidence interval; N.s.=not statistically significant; RCT=randomized controlled trial

Project: Cord clamping

* + No or minor problems
? Some problems
- Major problems

Appendix 4.9
Outcome variable: Infant haemoglobin, long term

Author, year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Askelöf, 2017 Sweden	Cohort	I=200 C=200	I=53 C=52	Haemoglobin (g/dl) at 4 months, mean (SD): 11.5 (8) Haemoglobin (g/dl) at 4 months, adjusted for infant age, mean (95% CI): 11.4 (11.3 to 11.6)	Haemoglobin (g/dl) at 4 months, mean (SD): 11.3 (8), n.s. Mean difference (95% CI) 2 (0 to 4), p=0.03 Haemoglobin (g/dl) at 4 months, adjusted for infant age, mean (95% CI): 11.3 (11.2 to 11.4), n.s.	C=historical controls (180 s) from Andersson et al., 2011 Haemoglobin levels did not differ significantly between boys and girls	+	+	+

Project: Cord clamping

* + No or minor problems
? Some problems
- Major problems

Appendix 4.10
Outcome variable: Need for phototherapy

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Chaudhary, 2023 India	RCT	I=50 C=51	I=0 C=0	Need for phototherapy (%): 11/50 (22%)	Need for phototherapy (%): 16/51 (31.4%), n.s.	I and C=Subgroup with full-term (≥ 37 week) infants C=clamping at 120 s Duration of phototherapy, hours, median (IQR): I=12 (12-14), C=19 (12-24)	?	?	-
Chen, 2018 China	RCT	I=90 C=450	I=9 C=35	Need for phototherapy (%): 1/81 (1.2%)	Need for phototherapy (%): 12/415 (2.9%), n.s.*	*p-value calculated from data (Fisher's exact test) C group divided into subgroups: Clamping at 90s: 1/83 (1.2%) Clamping at 120s: 3/80 (3.8%) Clamping at 150s: 3/89 (3.4%) Clamping at 180s: 1/80 (1.3%) Clamping at no pulsation: 4/83 (4.8%)	?	+	?
Katariya, 2021 India	RCT	I=49 C=98	I=5 C=10	Need for phototherapy (%): 1/44 (2.3%)	Need for phototherapy (%): 6/88 (6.8%), n.s.	C group divided into subgoups: In Clamping at 2 min: 2/44 (4.5%) Clamping at 3 min 4/44 (9.1%)	?	-	-
Songthamwat, 2020 Thailand	RCT	I=80 C=80	I=4 C=3	Need for phototherapy (%): 21/76 (27.6%)	Need for phototherapy (%): 22/77 (28.6%), n.s. RR 1.07 * (95%CI: 0.53 to 2.14), n.s.	* RR between C-I	+	+	?

95%CI=95% confidence interval; N.s.=not statistically significant; RCT=randomized controlled trial

Project: Cord clamping
Appendix 4.11
Outcome variable: Admission to neonatal department

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Clamping at 1 minute	Control Clamping > 1 minute				
Chen, 2018 China	RCT	I = 90 C = 450	I = 9 C = 35	0/81 (0%)	3/415 (0.7%), n.s. *	Admission to neonatal department * Calculated from data (Fisher's exact test).	?	+	?

N.s.=not statistically significant; RCT=randomized controlled trial