

## Timing of umbilical cord clamping for neonatal and maternal outcomes

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[Tidig och sen avnavling- effekter på mor och barn]

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Statement from HTA-centrum 2012-04-25  
Utlåtande från HTA-centrum 2012-04-25

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Appendix 4 Summary of Findings (SoF) table

### Method and patient group

Late versus early clamping of the umbilical cord- maternal and infant effects

### Question at issue

Is early umbilical cord clamping not different from or better than late umbilical cord clamping regarding postpartum infant iron deficiency and iron deficiency anaemia variables, long-term cognitive function, loss of stem cells, maternal postpartum haemorrhage, manual removal of retained placenta and correct sampling for blood gas analysis?

### Studied risks and benefits for patients of the new health technology

Level of evidence: The literature search identified four studies that fulfilled the selection criteria; a systematic review (SR) and three subsequently published randomised controlled trials (RCTs). The definition of early cord clamping varied from within 10 to < 60 sec between studies. The SR was methodologically of high quality but included mainly studies with high risk of bias. One of the RCTs was of high and the others of low quality.

### Infant outcomes O<sup>1</sup>

No studies evaluated cognitive function or loss of stem cells.

Conclusions: There is some support for an increased risk of immediate anaemia (6.3% vs 1.2%) (GRADE ⊕⊕○○) and support for lower immediate Hb (mean difference 18g/l) and haematocrit (GRADE ⊕⊕⊕○) with early as compared with late clamping. There is support for little or no difference regarding these outcomes at long-term (at 2 to 6 months of age) (GRADE ⊕⊕⊕○). There is some support for an increased risk of long-term iron deficiency (5.7% vs. 0.6%) (GRADE ⊕⊕○○) and support for lower long-term ferritin levels (GRADE ⊕⊕⊕○).

There is some support for little or no difference regarding jaundice requiring phototherapy and a low Apgar score (<7 at 5 min) (GRADE ⊕⊕○○) and insufficient support for an effect on the need for admittance to special baby care nursery or neonatal intensive care unit (GRADE ⊕○○○).

### Maternal outcomes O<sup>2</sup>

There is some support for little or no difference regarding severe postpartum bleeding (GRADE ⊕⊕○○) and insufficient support for an effect on the need for manual removal of placenta (GRADE ⊕○○○).

### Methodological outcome O<sup>3</sup>

There is insufficient scientific documentation to evaluate the rate of correct sampling for cord blood acid-base and gas analysis after early versus late clamping.

### Ethical questions

Is early cord clamping of the healthy term neonate ethically acceptable in view of unknown long-term infant risks regarding cognitive function? Presently, late cord clamping does not allow cord blood collection. Future research may identify optimal timing of cord clamping, to resolve these ethical issues.

### Economical aspects

There are no reasons to believe that initial costs are different.

**Which health technology or method will be assessed?**

**1a Who will lead the project?**

Ulla-Britt Wennerholm, MD, PhD, Associate professor, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Göteborg, Sweden

**1b Who posed the question?**

Anders Fasth and Olof Mattson, Clinical Unit Manager, Clinical Unit 4, Sahlgrenska University Hospital

**Additional parties who posed the question?**

No

**1c Co-workers:**

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**1d Other participants, from the HTA centre, Region Västra Götaland, Sweden**

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**1e Are there any conflicts of interest for the proposer or any of the participants in the work group?**

Anders Fasth is the Medical Director of the Swedish National Cord Blood Bank

## Disease/disorder of Interest and Present Treatment

### 2a **Disease/disorder of interest and its degree of severity**

This HTA report concerns mainly infant and maternal effects of timing of umbilical cord clamping during labour after full term pregnancy. Early cord clamping after birth might result in low initial blood volume in the newborn baby which could cause low iron stores in the infant. Iron deficiency during infancy has been associated with a delay in psychomotor and mental development (Thomas et al., 2009)

- Risk of premature death
- Risk of permanent illness or damage, or reduced quality of life
- Risk of disability and reduced health-related quality of life

### 2b **Prevalence and incidence of the disease/disorder**

In Sweden, approximately 90,000 to 120,000 children are born annually corresponding to approximately 15,000 to 20,000 in Region Västra Götaland (VGR). In the Nordic countries the prevalence of iron deficiency anaemia in all infants at 6 months of age has been reported between 3 and 4%. (Domellof et al., 2001, Hay et al., 2004). If these prevalence rates are valid also in the VGR population, iron deficiency anaemia could affect 450 to 800 infants annually in the VGR.

### 2c **Present treatment of the disease/disorder in the outpatient setting/ in-patient setting.**

#### **Procedures for clamping of the umbilical cord and sampling of umbilical cord blood for blood gas measurement at the obstetrical units in VGR.**

##### **SU/Östra Hospital**

The guideline is early cord clamping, which means that the cord is clamped immediately after the baby is born. The baby is put directly on the mother's chest if vital. When the cord is cut blood samples are obtained from both arterial and venous blood for pH measurements. If the mother expresses a wish for late cord clamping, no blood samples are taken.

##### **SU/Mölndal Hospital:**

The routine has changed recently. After birth the baby is placed either between the mother's legs or at her chest. The midwife compresses the umbilical cord, while cord blood samples are taken. After cord blood sampling, the midwife unclamps the cord. Definitive clamping and cutting of the cord is carried out when appropriate.

##### **SÄS (Södra Älvsborg Hospital)**

The routine is no clamping of the umbilical cord. The baby is kept between the mother's legs after birth and sampling of the cord blood for pH measurement is carried out as soon as possible. After the blood sampling, the baby is placed on the mother's chest. The clamping and cutting of the umbilical cord occur when pulsations have ceased.

##### **NÄL (Norra Älvsborg Hospital)**

The present routine is that the baby initially is placed between the mother's legs for about 30 sec. The midwife compresses the umbilical cord temporarily while blood samples are taken. The baby is then placed on the mothers' chest. Clamping and cutting of the cord are carried out when appropriate.

### **SKAS (Skaraborgs Hospital)**

The baby is placed between the mother's legs and the blood sampling is carried out as soon as possible without clamping the cord.

At all clinics oxytocin is administered immediately after birth.

### **Conclusion**

The practice regarding timing (early or delayed) of umbilical cord clamping varies in the VGR.

**2d Number of patients per year who undergo current treatment regimen?**

Late clamping is used in approximately two thirds of all deliveries in the VGR.

**2e The normal pathway of a patient through the health care system**

Following a normal vaginal delivery after a full-term pregnancy the mother and the newborn baby usually stay for one or two days at the maternity ward. There is no screening for iron deficiency or anaemia at the Child welfare centres.

**2f Actual wait time in days for medical assessment /treatment**

Not applicable

## Present Health Technology

### 3a Name/description of the health technology at issue

The technology at issue is early umbilical cord clamping, usually defined as clamping within less than one minute (mostly within 15 seconds) after birth. At the time of birth, the infant is still attached to the mother via the umbilical cord, which is part of the placenta. The infant is usually separated from the placenta by putting two clamps on the umbilical cord, one close to the infant's umbilicus and the other further along the cord; the cord is then cut between these two clamps.

The timing of late clamping is more variable, from one minute to five minutes. Others define late clamping as when the cord stops pulsating or after placental descent.

### 3b The work group's understanding of the potential value of the health technology

The timing of umbilical cord clamping: delayed/late or early (within  $\leq 1$  min) at birth is still a controversial issue and the practice worldwide varies. Studies have shown that, of the total blood volume in the combined foetal-placental circulation at term gestation, approximately 25% to 60% (54-160 ml) is found in the placental circulation and as many as 60% of the foetal red blood cells are found therein. This blood is also known to be rich in stem cells (Harris, 2008).

Studies have shown that early as compared with late clamping of the cord results in a decreased blood volume of the neonate of 20 to 40 ml of blood per kilogram body weight, which would correspond to 30 to 35 mg of iron. The technology at issue, early cord clamping, may thus cause anaemia and iron deficiency in the newborn. Iron deficiency in infancy may cause poor neurodevelopment (Lozoff and Georgieff, 2006). It is thus tempting to supplement iron already in situations where iron deficiency is suspected. Iron cannot, however, be actively secreted and the risk for iron overload must be considered. Too much iron increases the risk for infections and impairs growth. Also, infants with low iron stores increase their iron absorption from the intestine by decreasing hepcidin. (Berglund, 2011)

Delayed clamping on the other hand could be harmful by causing an overload of the neonatal blood volume, which may increase the risk for respiratory problems, neonatal jaundice and polycythemia.

Early clamping also means a loss of hematopoietic stem cells. The consequences for the newborn baby of this are unknown. It has been argued that the loss of stem cells could cause consequences later in life (Sanberg et al., 2010). Strong homeostatic mechanisms do occur within the hematopoietic system (Mikkola and Orkin, 2006) and the stem cells in donated cord blood are sufficient to replace totally the haematopoiesis of even an adult patient transplanted with donated cord blood. This makes negative effects of less stem cells infused into the babies whose cord was clamped early unlikely.

Early clamping allows cord blood collection in benefit for transplantation of stem cells to other individuals and research. This is presently not possible in conjunction with late cord clamping.

The management of the third stage of labour could be either expectant (physiological) or active. Active management of the third stage of labour (AMTSL) has demonstrated to be favourable in preventing post-partum haemorrhage (PPH), in comparison to expectant management. AMTSL includes three steps; early cord clamping (within one minute after birth of the baby), administration of uterotonic and controlled cord

traction. AMTSL was introduced by the World Health Organisation (WHO) in 1989, with the purpose to decrease maternal mortality caused by PPH. The AMTSL was adopted by FIGO (International Federation of Gynecology and Obstetrics) and ICM (International Confederation of Midwives) in “Joint statement: management of the third stage of labour to prevent post-partum haemorrhage” (ICM/FIGO, 2003). However, due to the risk for infant anaemia, the recommendation of early cord clamping by WHO (WHO, 2007) was abandoned in 2006 and changed into delaying cord clamping for three minutes. In Sweden the guideline “*Care program for umbilical cord clamping of newborn children*” recommends a change from early to late clamping. (Wiklund et al 2008). There may be a risk of low success rates regarding correct arterial and venous cord blood samples with delayed clamping. The values of the cord blood acid-base variables are different in delayed clamping as compared with early clamping (Wiberg et al., 2008)

**3c The central question for the current HTA project in one sentence**

Is early umbilical cord clamping not different from or better than late umbilical cord clamping regarding postpartum infant iron deficiency and iron deficiency anaemia variables, long-term cognitive function, loss of stem cells, maternal postpartum haemorrhage, manual removal of retained placenta and correct sampling for blood gas analysis?

**3d PICO P= Patients, I= Intervention, C= Comparison, O=Outcome**

**P=** Newborn infants and mothers with full-term pregnancy ( $\geq 37$ )

**I=** Early umbilical cord clamping ( $< 1$ min)

**C=** Delayed or late umbilical cord clamping ( $\geq 1$  min)

**O<sup>1</sup> (Infant) =**

Primary outcomes:

Iron-deficiency, long-term\*

Ferritin level, long-term

Anaemia, immediate\* and long-term

Haemoglobin level, immediate and long-term

Haematocrit, immediate and long-term

Cognitive function

Loss of stem cells

(\*Immediate defined as within 0-48 h and long-term as after 2-6 months)

Secondary outcomes:

Need for phototherapy

Apgar score  $< 7$  at five min

Admission to neonatal intensive care units (NICU)

**O<sup>2</sup> (Mother)**

Severe postpartum haemorrhage  $\geq 1000$ ml

Manual removal of retained placenta

**O<sup>3</sup> (Methodological)**

Correct sampling of arterial and venous blood from the cord for blood gas analysis

**Eligibility criteria:**

Study design:

Randomized controlled trials – for O<sup>1</sup> and O<sup>2</sup> (Infant and Maternal outcomes)

Cohort studies with  $\geq 100$  patients – for O<sup>3</sup> (Methodological outcomes)

Systematic reviews

**Language:** Swedish, Norwegian, Danish, English, German

**3e**

**Key words**

Umbilical Cord, Fetal Blood, Infant, newborn, Time Factors

Navelsträng, Avnavling, Navelsträngsblod, Nyfödda, Tidsfaktorer

### 4 Search strategy, study selection and references – appendix 3 (Search strategy, Eligibility criteria, Selection process – flow diagram, References)

This report is based on one systematic review (McDonald et al, 2008 Cochrane review) and subsequently published articles.

During November 2011, the library performed searches in PubMed, Embase, the Cochrane Library, CINAHL, PsycINFO, Mosby Nursing Index, CRD and a number of other HTA-databases. Reference lists of relevant articles were also scanned for additional references. A total of 1205 articles were identified after removal of duplicates, of which the library excluded 1077 abstracts. Another 85 articles were excluded by the library after having been read in full text. 43 articles, including McDonald's review, were sent to the work group for assessment.

McDonald's systematic review includes 10 studies and one conference abstract. Data from the 10 studies included in the SR were obtained from the SR and included in meta-analyses in this report. These studies were appraised in the systematic review and are not reappraised in the present HTA report. In addition to the articles from the systematic review, three articles (RCTs) are included in the current report. All of those have been critically appraised. The appraisal of articles is based on checklists from SBU regarding randomized controlled trials and regarding systematic reviews according to AMSTAR.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 3. The literature search and exclusion of abstracts were made by two librarians (ELD, YH) in consultation with the HTA-centre and the work group.

### 5a Describe briefly the present knowledge of the health technology

The systematic literature search identified four studies that fulfilled the selection criteria; the latest systematic review (SR) and three subsequently published randomised controlled trials (RCT). The methodology of the SR was of high quality but included mainly studies with high risk of bias (Table 1). One of the RCTs was of high (Andersson et al., 2011), the others of low quality (Jahazi et al., 2008, De Paco et al., 2011). No RCTs evaluated cognitive function or loss of stem cells.

#### *Participants, intervention and uterotonics*

Participants were mainly healthy pregnant women expected to give birth vaginally. In the SR, one trial included anaemic women, one was conducted in a malaria-endemic area and one included some women who gave birth by caesarean section (McDonald and Middleton 2008).

In the SR the timing of early clamping was relatively consistent between studies at less than one minute (mostly within 15 seconds of birth). The timing of late clamping was quite variable from >60 seconds up to 5 minutes, after pulsation in the cord had stopped or after placental descent in the vagina. In the three RCTs early clamping was defined as  $\leq 10$  to 30 seconds and late clamping as  $> 120$  to 180 seconds.

In the SR, administration of uterotonics, either before or after cord clamping, were recorded in five trials. In the study by Andersson et al., (2011) oxytocin (10 IU) was administered intravenously immediately after clamping of the cord. The other trials (Jahazi et al., 2008, De Paco et al., 2011) did not specify use or timing of any uterotonics.

## Primary infant outcomes O<sup>1</sup>

### *Iron deficiency, long-term*

One RCT (high quality) evaluated long-term iron deficiency (Table 2). Iron deficiency after four months was found in 5.7% in the early and in 0.6% in the late clamping group.

Conclusion: There is some support for an increased risk of long-term (at four months of age) iron deficiency (5.7% vs. 0.6%) (GRADE ⊕⊕○○) with early as compared with late clamping.

### *Ferritin level, long-term*

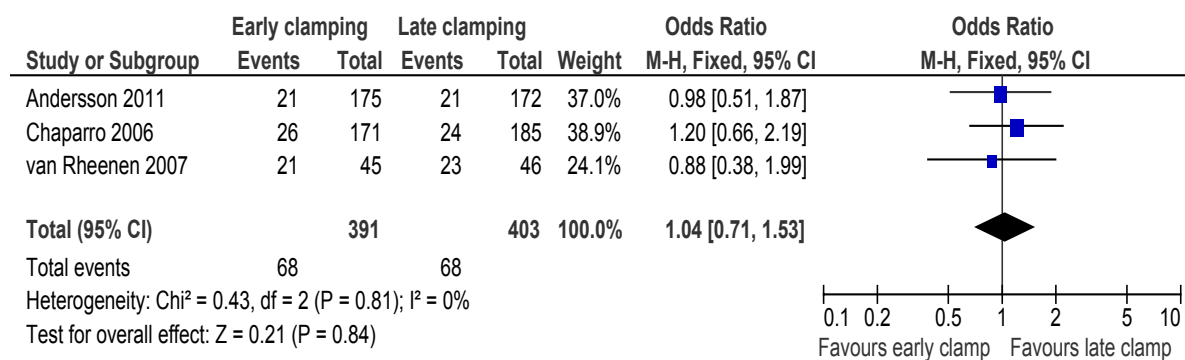
One SR and one RCT (high quality) evaluated long-term infant ferritin levels (Table 3). At three, four and six months infant ferritin levels were significantly lower in the early as compared with the late clamping group.

Conclusion: There is support for lower mean long-term ferritin levels with early as compared with late clamping (GRADE ⊕⊕⊕○).

### *Anaemia, immediate and long-term*

One SR and one RCT (high quality) evaluated immediate and long-term infant anaemia (Table 4). At two days of age, infants with early clamping had anaemia significantly more often (6.3% vs. 1.2%) as compared with infants with late clamping whereas there was no difference (Figure 1) at four to six months of age (long-term anaemia).

Figure 1. Anaemia, long-term



Conclusions: There is some support for an increased risk of immediate anaemia (GRADE ⊕⊕○○) with early as compared with late clamping. There is support for little or no difference in anaemia at long-term (at 2 to 6 months of age) (GRADE ⊕⊕⊕○).

### *Haemoglobin level, immediate and long-term*

One SR and one RCT (high quality) evaluated immediate and long-term haemoglobin (Hb) levels (Table 5). At 0-48 h of age, infants with early cord clamping had significantly lower mean Hb (Figure 2). At two to six months there was no significant difference in mean Hb between the groups (Figure 3).

Figure 2. Haemoglobin level, immediate

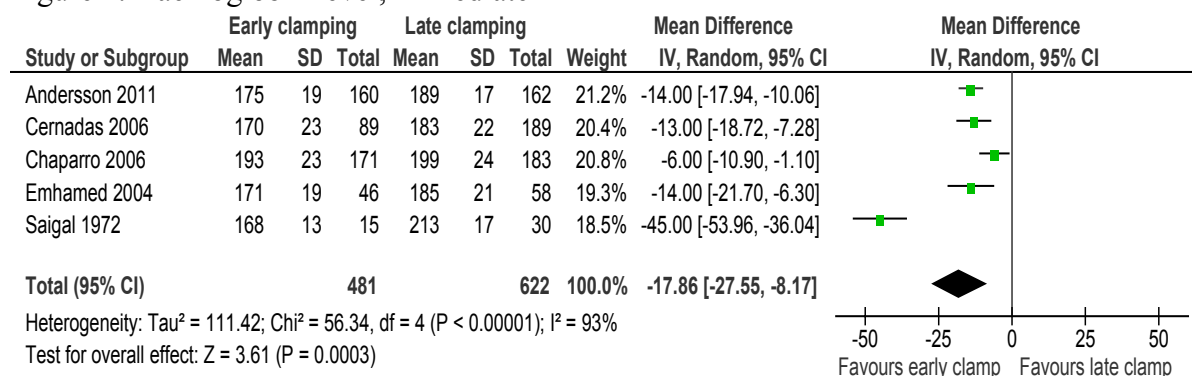
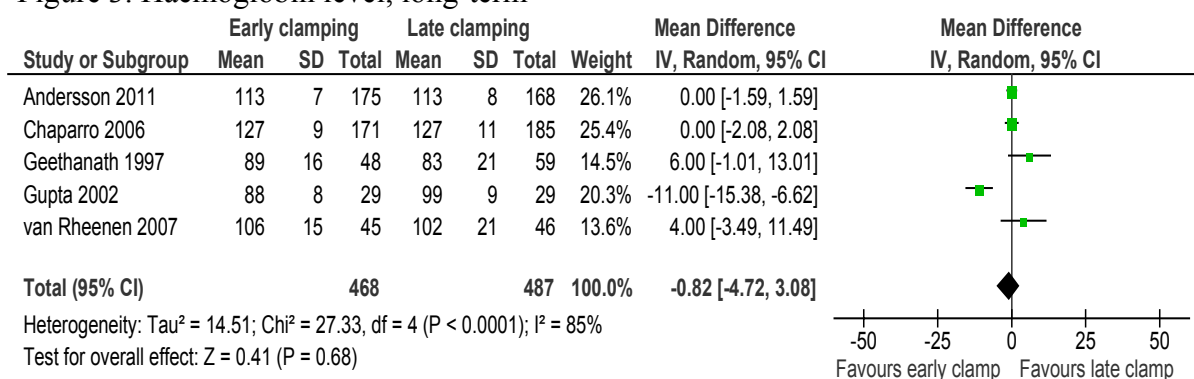


Figure 3. Haemoglobin level, long-term



Conclusions: There is support for lower immediate Hb (mean difference 18g/l) with early as compared with late clamping (GRADE ⊕⊕⊕○). There is support for little or no difference regarding Hb at long-term (at 2 to 6 months of age) (GRADE ⊕⊕⊕○).

### Haematocrit level, immediate and long-term

One SR and two RCTs (high quality and low quality, respectively) evaluated immediate and long-term infant haematocrit levels (Table 6). At 6-48 h of age, more infants in the early cord clamping group had a low haematocrit. One RCT (high quality) showed a slightly lower mean haematocrit at 48 h. One RCT (low quality) showed no difference in mean haematocrit at 2 and 18 h. At 4 months of age, there was no difference in mean haematocrit between the groups.

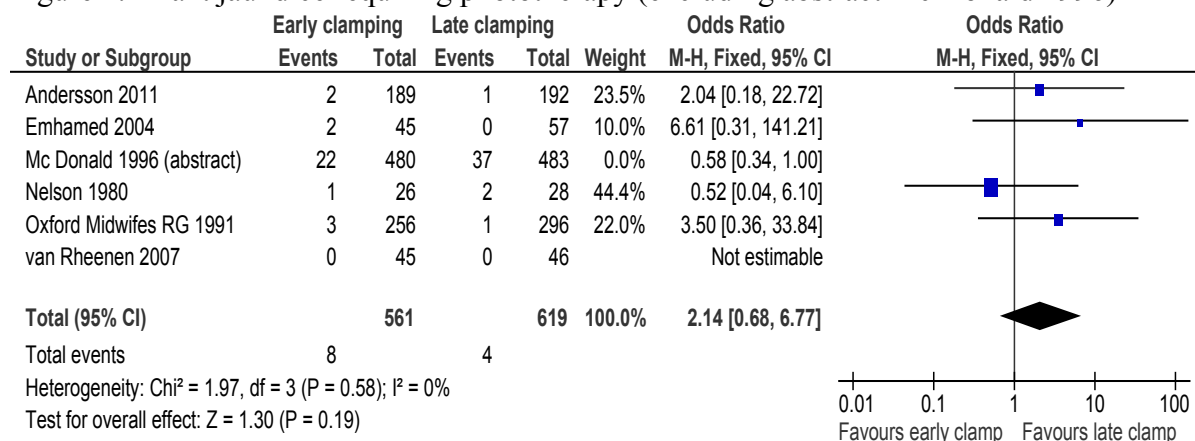
Conclusions: There is support for lower immediate haematocrit with early as compared with late clamping (GRADE ⊕⊕⊕○). There is support for little or no difference regarding haematocrit at long-term (at 2 to 6 months of age) (GRADE ⊕⊕⊕○).

### Secondary infant outcomes O<sup>1</sup>

#### Jaundice requiring phototherapy

One SR and one RCT (high quality) evaluated the need for phototherapy (Table 7). In the SR, a meta-analysis showed that fewer infants in the early clamping group were reported to require phototherapy. The largest study included in the SR is published only as a conference abstract (McDonald, 1996). This study is not included in the present meta-analysis in Figure 4 that shows no difference between the early and late clamping groups. The results in the SR are divergent mainly due to unpublished study included in the meta-analysis in the SR.

Figure 4. Infant jaundice requiring phototherapy (excluding abstract Mc Donald 1996)

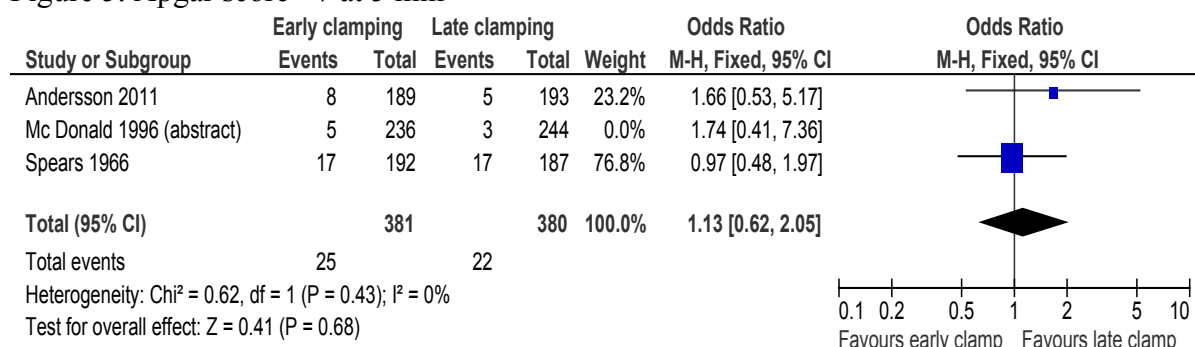


Conclusion: There is some support for little or no difference regarding jaundice requiring phototherapy with early as compared with late clamping (GRADE ⊕⊕○○).

#### Apgar score <7 at 5 minutes

One SR and one RCT (high quality) evaluated the rate of low Apgar score (Table 8). No difference between early and late cord clamping was found for this outcome (Figure 5).

Figure 5. Apgar score <7 at 5 min



Conclusion: There is some support for little or no difference regarding Apgar score < 7 at 5 minutes with early as compared with late clamping (GRADE ⊕⊕○○).

#### Admission to special baby care nursery (SCN) or neonatal intensive care unit (NICU)

One SR evaluated the need for admittance to SCN or NICU (Table 9). No difference between early (2.5%) and late (3.5%) cord clamping was found for this outcome.

Conclusion: There is insufficient support for an effect on the need for admittance to special baby care nursery or neonatal intensive care unit (GRADE ⊕○○○).

#### Maternal outcomes O<sup>2</sup>

##### Severe postpartum haemorrhage

One SR evaluated severe postpartum haemorrhage (≥1000 ml) (Table 10). No difference between early (2.5%) and late (3.1%) cord clamping was seen for this outcome.

Conclusion: There is some support for little or no difference regarding severe postpartum bleeding with early as compared with late clamping (GRADE ⊕⊕○○).

### *Need for manual removal of the placenta*

One SR evaluated the need for manual removal of the placenta (Table 11). No difference was seen between early (2.4 %) and late (1.5%) cord clamping for this outcome.

Conclusion: There is insufficient support for an effect on the need for manual removal of placenta with early as compared with late clamping (GRADE ⊕○○○).

### Methodological outcomes O<sup>3</sup>

One RCT (low quality) evaluated the cord blood acid-base and gas analysis in early and delayed cord clamping (Table 12). There was no significant difference in the number of samples taken from both artery and vein after early (79.7 %) and late (65.7 %) clamping respectively. It was not specified if the samples were correctly taken from both artery and vein.

Conclusion: There is insufficient scientific documentation to evaluate the rate of correct sampling for cord blood acid-base and gas analysis after early versus late clamping.

## **5b Outcome tables – appendix 1**

## **5c Excluded articles – appendix 2**

## **5d Ongoing research**

A search in Clinicaltrials.gov (2011-12-28) using the search terms (*cord AND (clamp OR clamping OR cut OR cutting)*) identified 50 trials. Three were relevant for our question (<http://ClinicalTrials.gov/show/NCT01029496>; <http://clinicaltrials.gov/show/NCT01081977>; <http://clinicaltrials.gov/show/NCT00298051>). The recruitment in these trials is unknown because the information has not been verified recently according to the Clinical trials document. The trials were planned in China, Pakistan and Mexico.

## **6 Which medical societies or health authorities recommend the new health technology (=late clamping)?**

- The National Board of Health and Welfare**
- Medical societies**
- Other health authority**

### **Which medical society or health authority?**

The Swedish Association of Midwives, The Swedish Society of Obstetrics and Gynecology (SFOG) and the Swedish Paediatric Society (BLF) (Wiklund et al., 2008)

## Ethical aspects

### 7 Ethical consequences

Using the early clamping technique, the children may suffer a risk of lower iron stores and some children might not have enough iron to support the fast growing central nervous system. This might lead to cognitive and/or behavioural problems. Importantly, there is no evidence for such damage in full term healthy newborns, but circumstantial evidence from animal studies as well as from human studies of preterm and low birth infants suggests that this might be a possibility (Domellof, 2011).

A change to late clamping at 3 minutes or more is incompatible with collection of placenta blood for donation to the National Cord Blood Bank. Cord blood transplantation is a life-saving procedure for 25 - 50% of those in need of hematopoietic stem cell transplantation who lack a sibling donor or a donor from a registry. The unknown risk for the donating newborn is not compensated for by any positive effects for the donor, but the donation has important positive life saving effects for the recipient.

Whether or not a compromise between the two routines is possible by delaying the clamping to 30 or 60 seconds is unknown, but such a compromise could be a solution to the ethical conflict not to harm the child and to do good to patients in need of a transplant.

## Organisation

### 8a When can this new health technology be put into practice?

Late cord clamping can be put into practice immediately.

### 8b Is this technology used in other hospitals in Western Region of Sweden?

In the VGR, all hospitals practice blood sampling for blood gas analysis immediately without clamping or by compressing the cord until blood sampling is done (Södra Älvsborgs Hospital (Södra Älvsborgs Sjukhus), Norra Älvsborg County Hospital (Norra Älvsborgs Länssjukhus) and Skaraborg hospital (Kärnsjukhuset i Skövde). Sahlgrenska University Hospital/ Mölndal (SU/ Mölndal) has also recently changed to late clamping. (See 2 c)

### 8c According to the work group, will there be any consequences of the new health technology for personnel?

Midwives and nursing assistants need a period of training to do blood sampling without clamping. The consequences of a change in practice for correct blood gas analysis are unknown.

### 8d Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

No

## Economy

- 9a Present costs of currently used technologies**  
The initial costs associated with late (and early) cord clamping per se are not possible to calculate but there are no reasons to believe that initial costs should be different.
- 9b Expected costs of the new health technology?**  
See 9a.
- 9c Total change of cost**  
See 9a.
- 9d Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?**  
Yes
- 9e Are there any available analyses of health economy? Cost advantages or disadvantages?**  
No

## Unanswered Questions

### 10a **Important gaps in scientific knowledge?**

This HTA has shown that early clamping of the umbilical cord in healthy full term infants results in lower serum ferritin at 4- 6 months. (Andersson et al.) 2011) also found that more infants had low ferritin levels, defined as <20 ug/L. This cut-off level is controversial; others have set the limit at 12 ug/L (Lönnerdal and Hernell 2010, Domellof, 2011). The definition of iron deficiency is controversial as no direct measures of iron stores can be done. Ferritin is commonly used, but also the combination of different serum proteins such as ferritin, transferrin saturation and transferrin receptor.

Thus, we need better definition of iron deficiency in infants; regarding which analysis to use as well as appropriate cut-off levels.

The consequences, if any, of lower ferritin for full term healthy infants born after uncomplicated birth and early clamping vs. those whose cord was clamped late are unknown. The association between iron deficiency and poor cognitive and behavioural performance is reviewed in Domellof, 2011, suggesting it is important to prevent iron deficiency in infants.

Thus we need more knowledge whether or not children born after early clamping are at risk for severe iron deficiency with potential consequences for the developing brain.

Early clamping also means a loss of hematopoietic stem cells. The consequences of this are unknown.

### 10b **Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?**

A research group associated to the Swedish National Cord Blood bank and to the team of Ola Andersson is performing a project where an intermediate clamping time (1 minute) and its effect on the child will be studied using the same outcomes as in the published article (Andersson et al, 2011).

Using qualitative methods, the experience of parents who had donated the child's cord blood will be studied in the same project.

A study is planned by Andersson and coworkers where the newborns with early clamping are randomized to iron supplementation or placebo.

## Statement from the Regional HTA Centre of Region Västra Götaland, Sweden

### Timing of umbilical cord clamping for neonatal and maternal outcomes

#### Method and patient category:

This HTA report concerns effects of timing of clamping the umbilical cord after delivery in term pregnancy. Of the total blood volume in the combined fetal-placental circulation, approximately 25% to 60% is found in the placental circulation and 60% of the fetal red blood cells are found therein. This blood is also rich in stem cells. Early cord clamping might result in low initial blood volume in the infant which could cause low iron stores and anaemia. Iron deficiency during infancy has been associated with a delay in psychomotor and mental development. The loss of stem cells could potentially cause blood disorders and diabetes later in life. Early cord clamping is an integrated part of active management in the third stage of labour, with the intention to reduce the risk of maternal postpartum hemorrhage. Delayed clamping on the other hand could be harmful by causing an overload of the neonatal blood volume which may increase the risk for respiratory disorders, neonatal jaundice and polycythemia. A subsequent question is stem cell banking possibilities, since early cord clamping at present, is a prerequisite for cord blood donation.

#### Question at issue:

Is early umbilical cord clamping not different from or better than late umbilical cord clamping regarding postpartum infant iron deficiency and iron deficiency anaemia variables, long-term cognitive function, loss of stem cells, maternal postpartum haemorrhage, manual removal of retained placenta and correct sampling for blood gas analysis

#### PICO 1 ( Patient, Intervention, Comparison, Outcome)

P = Newborn infants and mothers with term pregnancy ( $\geq 37$  weeks)

I = Early umbilical cord clamping (<1min)

C = Delayed or late umbilical cord clamping ( $\geq 1$  min)

O = **O<sup>1</sup> (Infant) Primary outcomes:** Iron-deficiency; long term\*, ferritin level; long term, anaemia; immediate\* and long term, haemoglobin level; immediate and long term, haematocrit; immediate and long term, cognitive function; loss of stem cells  
(\*Immediate defined as within 0-48 h and long term as after 2-6 months)

**Secondary outcomes:** Need for phototherapy, Apgar score <7 at five min, admission to neonatal intensive care units (NICU)

**O<sup>2</sup> (Mother):** Postpartum hemorrhage  $\geq 1000$ ml, manual removal of retained placenta

**O<sup>3</sup> (Methodological):** Correct sampling of arterial and venous blood from the cord for blood gas analysis

#### Level of evidence:

The literature search identified four articles fulfilling the selection criteria: a systematic review (SR) and three subsequently published randomised controlled trials (RCT). The definition of early cord clamping varied from within  $\leq 10$  to < 60 sec between studies. The SR was methodologically of high quality but included mainly studies with high risk of bias. One of the RCTs was of high and the others of low quality.

Infant outcomes

No studies evaluated cognitive function or loss of stem cells.

Conclusions: There is some support for an increased risk of immediate anaemia (6.3% vs 1.2%) (GRADE ⊕⊕○○) and support for lower immediate Hb (mean difference 18g/l) and haematocrit (GRADE ⊕⊕⊕○) with early as compared with late clamping. There is support for little or no difference regarding these outcomes at long term (GRADE ⊕⊕⊕○). There is some support for an increased risk of long term iron deficiency (5.7% vs. 0.6%) (GRADE ⊕⊕○○) and support for lower long term ferritin levels (GRADE ⊕⊕⊕○)

There is some support for little or no difference regarding jaundice requiring phototherapy and a low Apgar score (<7 at 5 min) (GRADE ⊕⊕○○) and insufficient support for an effect on the need for admittance to special baby care nursery or neonatal intensive care unit (GRADE ⊕○○○).

Maternal outcomes O<sup>2</sup>

There is some support for little or no difference regarding severe postpartum bleeding (GRADE ⊕⊕○○) and insufficient support for an effect on the need for manual removal of placenta (GRADE ⊕○○○)

Methodological outcome O<sup>3</sup>

There is insufficient scientific documentation to evaluate the rate of correct sampling for cord blood acid-base and gas analysis after early versus late clamping.

Ethical aspects:

Using the early clamping technique, the children may suffer a risk of lower iron stores and some children might not have enough iron to support the fast growing central nervous system. This might lead to cognitive and/or behavioural problems. Late clamping is incompatible with collection of placenta blood for donation to the National Cord Blood Bank. Cord blood transplantation is life-saving for 25 - 50% of those in need of hematopoietic stem cell transplantation who lack a sibling donor or a donor from a registry. The (unknown) risk for the donating newborn is not compensated for by any positive effects for that child, but the donation has important positive life saving effects for other patient groups.

Economical aspects:

There are no reasons to believe that the early cost, associated with the delivery, are different with early as compared to late clamping. The late effects (cognitive function) are not studied and no long-term economical conclusions can be made.

Concluding remarks:

No studies evaluated effects of early versus delayed clamping on cognitive function. Early as compared with late clamping is related with immediate but not long term infant anemia and anemia-related variables (low to moderate quality of evidence) but there is no support for an effect on infant jaundice and early Apgar score (very low to low quality of evidence). There is no support for a difference regarding maternal severe postpartum bleeding and need for manual removal of placenta (low and very low quality of evidence). Late clamping is incompatible with collection of cord blood to be used for stem cell transplantation. A possible long-term risk with early clamping is an unstudied, theoretical risk that early iron deficiency related to early cord clamping might lead to cognitive and/or behavioural problems. The balance between this unknown risk for the infant versus the benefit for recipients of stem cells is uncertain due to gaps of knowledge mainly regarding long term infant cognitive function and effects of loss of stem cells.

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

The HTA was accomplished during the period of 2011-11-16—2012-04-25.

Last search updated in November 2011.

On behalf of the HTA quality assurance group, in Region Västra Götaland, Sweden  
Göteborg, Sweden, 2012-04-25

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## Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen.

### Betydelsen av tidig jämfört med sen avnavling för barnet och modern

Frågeställning: Är tidig avnavling lika bra eller bättre än sen avnavling vad gäller hos barnet järnbrist och järnbristanemirelaterade variabler, långsiktig kognitiv funktion, förlust av stamceller, hos modern postpartum blödning och manuell placentalösning samt möjligheten för korrekt provtagning för blodgasanalys.

#### PICO 1 ( Patient, Intervention, Comparison, Outcome)

P = Nyfödda och mödrar efter fullgången graviditet ( $\geq 37$  veckor)

I = Tidig avnavling ( $<1$  min)

C = Fördröjd eller sen avnavling ( $\geq 1$  min)

O = **O<sup>1</sup> (Nyfödd)** Primära utfall: Järnbrist; långsiktig\*, ferritin nivåer; långsiktigt, anaemi omedelbar\* and långsiktig, haemoglobin; omedelbar and långsiktig, hematokrit; omedelbar and långsiktig, kognitiv funktion; förlust av stamceller (\*Omedelbar definierad som inom 0-48 h och långsiktig som efter 2-6 månader)

Sekundära utfall: behov av ljusterapi för gulsot, Apgar score  $<7$  vid 5 min, vård på neonatal intensivvårdsavdelning (NICU)

**O<sup>2</sup> (Moder)**: Postpartum blödning  $\geq 1000$ ml, manuell placentalösning

**O<sup>3</sup> (Metodologisk)**: korrekt provtagning för blodgasanalys från arteriellt och venöst blod

### Sammanfattning:

#### Metod och patienter:

Denna HTA avser effekter för barn och moder av tidpunkten för avnavling vid födsel efter fullgången graviditet. 25% - 60% av den totala blodvolymen hos nyfödd och moderkaka finns i moderkaka och navelsträng och 60% av de foetala röda blodkropparna finns där. Detta blod är också rikt på stamceller. Tidig avnavling ökar möjligheterna att spara stamceller i en stamcellsbank men skulle kunna resultera i minskad initial blodvolym hos den nyfödde vilket skulle kunna ge låga järnförråd och anemi. Järnbrist under spädbarnsåldern har förknippats med försenad psykomotorisk och mental utveckling. Förlust av stamceller kan potentiellt orsaka blodsjukdomar och diabetes senare under livet. Tidig avnavling är en integrerad del av aktivt efterbördsskede under förlossningen med avsikt att minska risken för postpartumblödning hos modern. Sen avnavling å andra sidan skulle kunna innebära överbelastning av den nyföddes blodvolym vilket kan öka risken för lungsjukdomar, gulsot och polycytemi. En associerad metodologisk fråga är möjligheter till en stamcellsbank, eftersom tidig avnavling för närvarande är en förutsättning för att donera navelsträngsblod.

#### Evidensläge:

Vid sökningen identifierades fyra artiklar som uppfyllde selektionskriterierna: en systematisk översikt (SR) och tre därefter publicerade randomiserade kontrollerade studier (RCT). Den systematiska översikten var metodologiskt av hög kvalitet men inkluderade främst studier med hög risk för bias. En RCT hade hög och resterande låg kvalitet.

### Utfall hos barnet:

Ingen studie utvärderade kognitiv funktion eller förlust av stamceller. Slutsatser: Tidig jämfört med sen avnavling kan leda till ökad risk för omedelbar anemi (6.3% vs 1.2%) (GRADE ⊕⊕○○) och leder troligen till lägre Hb (medelskillnad 18g/l) och hematokrit (GRADE ⊕⊕⊕○), men leder troligen till liten eller ingen skillnad för dessa utfall långsiktigt (GRADE ⊕⊕⊕○). Tidig jämfört med sen avnavling ger troligen en ökad risk för järnbrist långsiktigt (5.7% vs. 0.6%) (GRADE ⊕⊕○○) och ger troligen lägre ferritinnivåer långsiktigt (GRADE ⊕⊕⊕○).

Tidig jämfört med sen avnavling kan resultera i liten eller ingen skillnad vad gäller behov av ljusbehandling för gulsot och frekvens av låg Apgar score (<7 vid 5 min) (GRADE ⊕⊕○○) medan det är osäkert huruvida behovet av neonatal intensiv- eller specialvård påverkas (GRADE ⊕○○○).

### Maternella utfall O<sup>2</sup>

Tidig jämfört med sen avnavling kan resultera i liten eller ingen skillnad vad gäller svår postpartumblödning (GRADE ⊕⊕○○) medan det är osäkert huruvida behovet av manuell placentalsöning påverkas (GRADE ⊕○○○).

### Metodologiskt utfall O<sup>3</sup>

Det vetenskapliga underlaget är otillräckligt för att bedöma om korrekt provtagning för blodgasanalys från navelblod påverkas av tidig jämfört med sen avnavling.

### Etiska aspekter:

Vid tidig avnavling kan barnet riskera lägre järnförråd och några barn skulle kunna tänkas ha för lite järn för det snabbväxande centrala nervsystemets behov. Detta skulle kunna ge kognitiva och/eller beteendestörningar. Sen avnavling är oförenligt med insamling av moderkaksblod för donation till den nationella navelsträngsblodbanken. Transplantation av navelsträngsblod är livräddande för 25 – 50% av de som behöver blodbildande stamcellstransplantation och som saknar en anhörig eller annan donator. Den (okända) risken för den donerande nyfödde kompenseras inte av några positiva effekter för det barnet men donationen har viktiga och livräddande effekter för andra patientgrupper.

### Ekonomiska aspekter:

Det finns ingen anledning att tro att den initiala kostnaden, i samband med förlossningen, skulle skilja mellan tidig och sen avnavling. Eventuella sena effekter (kognitiv funktion) är ej studerade och långsiktiga ekonomiska slutsatser kan ej dras

### Sammanfattande slutsatser:

Definitionen av tidig avnavling varierar mellan ≤ 10 sek till < 60 sek. Ingen studie utvärderade effekter av tidig jämfört med sen avnavling på kognitiv funktion. Tidig jämfört med sen avnavling kan vara relaterat till omedelbar men inte långsiktig anemi och anemirelaterade tillstånd (låg till medelhög evidensstyrka) men har liten eller ingen effekt på gulsot eller Apgar score (mycket låg till låg evidensstyrka). Tidig jämfört med sen avnavling kan resultera i liten eller ingen skillnad vad gäller maternell postpartum-blödning och behov av manuell placentalsöning (låg och mycket låg evidensstyrka). Sen avnavling är oförenligt med insamlande av moderkaksblod för navelsträngsblodstransplantation, vilket kan vara livräddande för andra individer. En möjlig långsiktig risk med tidig avnavling är en ostuderad, teoretisk risk att tidig järnbrist till följd av tidig avnavling skulle kunna leda till kognitiva och/eller beteendestörningar. Balansen mellan denna teoretiska risk för barnet versus nyttan för mottagare av stamceller är osäker beroende på kunskapsluckor främst avseende långsiktiga effekter på barnets kognitiva funktion och av förlusten av stamceller.

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerade teknologin.

Slutsatser har diskuterats vid möten mellan HTA-centrum och HTA-projektgruppen. Ett utlåtande har tagits fram, diskuterats och fastställts vid HTA-kvalitetssäkringsgruppens möte 2012-04-25.

Projektet har pågått under perioden 2011-11-16—2012-04-25.

Sista uppdatering av artikelsökning november 2011

För HTA-kvalitetssäkringsgruppen 2012-04-25

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Table 1 Summary of risk of bias as described by McDonald and Middleton, in studies included in the systematic review by McDonald and Middleton, 2008

Author, year	Allocation concealment	Blinding	Losses to follow up
Ceriani-Cernadas, 2006	Yes	Partially	
Chaparro, 2006	Yes	Not reported	29% at 6 months
Emhamed, 2004	Unclear	Not reported	
Geethanath, 1997	Unclear	Not reported	
Gupta, 2002	Unclear	Not reported	
McDonald, 1996	Yes	Partially	
Nelson, 1980	Not specified	Not reported	
Oxford Midwives, 1991	Yes	Not reported	
Saigal, 1972	Not specified	Not reported	
Spears, 1966	Not specified	Not reported	
van Rheenen, 2007	Yes	Partially	33% at 6 months

Appendix 1

Table 2. Outcome variable: Infant iron deficiency, long-term

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
Andersson, 2011	Sweden	RCT	400 infants	59 (EC 25 DC 34)	At 4 months: 10*/175 (5.7%)	At 4 months: 1*/166 (0.6%)	RR reduction (95% CI) DC vs EC: 0.90 (0.38, 0.98), p=0.01 NNT (95 % CI) 20 (17 to 67)	High

RCT randomised controlled trial, EC early clamping, DC delayed clamping, RR relative risk, CI confidence interval, NNT number needed to treat  
 \*Iron deficiency defined as  $\geq 2$  iron indicators (low ferritin, low mean cell volume, low transferrin saturation, high transferrin receptors) outside reference range

## Appendix 1

Table 3. Outcome variable: Infant serum ferritin level, long-term

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	India	SR	1 RCT (Geethanath) 107 infants	0	Mean (SD) At 3 months: 55.7 (3.7) µg/L	Mean (SD) At 3 months: 73.6 (3.1) µg/L	Mean difference (IV, Fixed, 95% CI): At 3 months: -17.90 (-19.2, -16.59) µg/L	See Table 1 for risk of bias according to McDonald and Middleton
Mc Donald and Middleton, 2008	Mexico	SR	1 RCT (Chaparro) 476 infants	161 (EC 85 DC 76)	Mean (SD) At 6 months: 34.9 (32.2) µg/L	Mean (SD) At 6 months: 46.7 (37.7) µg/L	Mean difference (IV, Fixed, 95% CI): At 6 months: -11.80 (-19.53, -4.07) µg/L	See Table 1 for risk of bias according to McDonald and Middleton
Andersson, 2011	Sweden	RCT	400 infants	53 (EC 25 DC 28)	At 4 months: 81 (6-760) µg/L Ferritin < 20 µg/L: 13/175 (7.4%)	At 4 months: 117 (20-880) µg/L Ferritin < 20 µg/L: 0/172 (0)	Difference (95% CI) At 4 months (geometric mean ratio in percentage): 45% (23%, 71%), p<0.001 At 4 months: Ferritin < 20 µg/L: DC vs EC: RR reduction (95% CI): -25.7 (-441.8, -0.6)* NNT (95% CI): 14 (8 to 29)*	High

SR systematic review, RCT randomised controlled trial, SD standard deviation, IV inverse variance, CI confidence interval, EC early clamping, DC delayed clamping, RR relative risk, NNT number needed to treat, \* recalculated in Stat Calc, wrong figures (1.0 (0.71-1.00), NNT 14 (14-25)) in paper

## Appendix 1

Table 4. Outcome variable: Immediate (at 2 days) and long-term (at 4 or 6 months) infant anaemia

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	Zambia	SR	At 4 months 1 RCT (van Rheenen)  91 infants	13 (EC 7 DC 6)	At 4 months Hb <10.3 g/dL: 18/45	At 4 months Hb<10.3 g/dL: 10/46	RR (M-H, Fixed, 95% CI) 1.84 (0.96, 3.54)	See Table 1 for risk of bias according to McDonald and Middleton
Mc Donald and Middleton, 2008	Zambia Mexico	SR	At 6 months 2 RCTs 44 7 infants (van Rheenen, Chaparro)	135 (EC 8+ 68 DC 11+ 50)	At 6 months Hb<10.5 g/dL (one RCT) or Hb<12.2 g/dL (one RCT) 47/216	At 6 months Hb<10.5 g/dL (one RCT) or Hb<12.2 g/dL (one RCT)  47/231	RR (M-H, Fixed, 95% CI) 1.05 (0.75, 1.48)	See Table 1 for risk of bias according to McDonald and Middleton
Andersson, 2011	Sweden	RCT	400 infants	At 2 days: 78 (EC 40 DC 38)  At 4 months: 53 (EC 25 DC 28)	At 2 days Hb<145 g/L: 10/160 (6.3%)  At 4 months Hb< 105 g/L: 21/175 (12%)	At 2 days Hb<145 g/L: 2/162 (1.2%)  At 4 months Hb< 105 g/L: 21/168 (12%)	At 2 days: RR reduction (95 % CI): 0.80 (0.22, 0.95), p=0.02, NNT (95% CI): 20 (15-111)  At 4 months: RR reduction (95 % CI): -0.04 (-0.83, 0.41), p=1.0, NNT: NA	High

SR systematic review, RCT randomised controlled trial, SD standard deviation, RR risk ratio, M-H Mantel-Haenszel, IV inverse variance, CI confidence interval, EC early clamping, DC delayed clamping, NNT number needed to treat, NA not applicable

Appendix 1

Table 5. Outcome variable: Immediate (0-48 h) and long-term (2-6 months) infant haemoglobin level

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	Canada Argentina Mexico	SR	Newborn: 3 RCTs (Saigal, Ceriani-Cernadas, Chaparro) 671 infants				Newborn: Mean difference (IV, Random, 95% CI): -2.17 g/dL (-4.06, -0.28)	See Table 1 for risk of bias according to McDonald and Middleton
McDonald and Middleton, 2008	Libya Argentina	SR	24-48 h: 2 RCTs (Emhamed, Ceriani-Cernadas) 382 infants				24-48 h: Mean difference (IV, Fixed, 95% CI): -1.34 g/dL (-1.80, -0.88)	See Table 1 for risk of bias according to McDonald and Middleton
McDonald and Middleton, 2008	Zambia India India	SR	2-4 months: 3 RCTs (van Rheenen, Geethanath, Gupta) 256 infants				2-4 months: Mean difference (IV, Random, 95% CI): -0.30 g/dL (-1.25, 0.65)	See Table 1 for risk of bias according to McDonald and Middleton
McDonald and Middleton, 2008	Zambia Mexico	SR	6 months: 2 RCTs (van Rheenen, Chaparro) 447 infants				6 months: Mean difference (IV, Fixed, 95% CI): 0.03 g/dL (-0.17, 0.23)	See Table 1 for risk of bias according to McDonald and Middleton
Andersson, 2011	Sweden	RCT	400 infants	78 (EC 40 DC 38)	48 h, mean (SD): 175 (19) g/L	48 h, mean (SD): 189 (17) g/L	Mean difference (95% CI): 13.5 g/L (9.6, 17.5) g/L, p<0.001	High
Andersson, 2011	Sweden	RCT	400 infants	57 (EC 25 DC 32)	4 months, mean (SD): 113 (7) g/L	4 months, mean (SD): 113 (8) g/L	Mean difference (95% CI) 0.0 g/L (-1.6, 1.6), p=0.98	High

SR systematic review, RCT randomised controlled trial, IV inverse variance, CI confidence interval, EC early clamping, DC delayed clamping, SD standard deviation,

## Appendix 1

Table 6. Outcome variable: Immediate (0-48 h) and long-term (2-6 months) infant haematocrit (hct) level

Author, year	Country	Study design	Number of patients n=	With draws - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Late clamping		
McDonald and Middleton, 2008	Argentina	SR	6 h: 1 RCT (Ceriani-Cernadas) 272 infants	4 (EC 3 DC 1)	Hct <45% 8/90	Hct <45% 1/182	RR (M-H, Fixed, 95% CI) 16.18 (2.05,127.37)	See Table 1 for risk of bias according to McDonald and Middleton
McDonald and Middleton, 2008	Argentina	SR	24-48 h: 1 RCT (Ceriani-Cernadas) 268 infants	NA	Hct <45% 15/89 (	Hct <45% 5/179	RR (M-H, Fixed, 95% CI) 6.03 (2.27, 16.07)	See Table 1 for risk of bias according to McDonald and Middleton
Jahazi, 2008	Iran	RCT	64	0	2 h, mean (SD) 61 (4.9) 18 h, mean (SD) 56.9 (4.1)	2 h, mean (SD) 61.6 (4.5) 18 h, mean (SD) 56.2 (3.9)	2 h: p=0.618 18 h: p=0.532	Low
Andersson, 2011	Sweden	RCT	400 infants	78 (EC 40 DC 38)	48 h , mean (SD): 50 (5)	48 h , mean (SD): 53 (5)	Mean difference (95% CI): 3.5 (2.4, 4.6), p<0.001	High
Andersson, 2011	Sweden	RCT	400 infants	57 (EC 25 DC 32)	4 months, mean (SD): 33 (2)	4 months, mean (SD): 33 (2)	Mean difference (95% CI): -0.2 (-0.7, 0.2), p=0.28	High

SR systematic review, RCT randomised controlled trial, RR risk ratio, M-H Mantel-Haenzsel, CI confidence interval, EC early clamping, DC delayed clamping, NA not available, SD standard deviation

Appendix 1

Table 7. Outcome variable: Infant jaundice requiring phototherapy

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	Australia Canada UK Libya Zambia	SR	5 RCTs (McDonald Nelson, Oxford midwives, Ehmahed, van Rheenen) 1762 infants	NA	28/852	50/910	RR (M-H, Fixed, 95% CI) 0.59 (0.38, 0.92)	See Table 1 for risk of bias according to McDonald and Middleton
Andersson, 2011	Sweden	RCT	400 infants	19 (EC 11 DC 8)	At 2 days: 2/189 (1.1%)	At 2 days: 1/192 (0.5%)	p=0.96	High

SR systematic review, RCT randomised controlled trial, NA not applicable, RR risk ratio, M-H Mantel-Haenszel, CI confidence interval, EC early clamping, DC delayed clamping

## Appendix 1

Table 8. Outcome variable: Apgar score &lt; 7 at five minutes

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Late clamping		
McDonald and Middleton, 2008	Australia USA	SR	2 RCTs (McDonald, Spears) 1342 infants	NA	30/672	24/670	RR (M-H, Fixed, 95% CI) 1.23 (0.73, 2.07)	See Table 1 for risk of bias according to McDonald and Middleton
Andersson, 2011	Sweden	RCT	400	18 (EC 11 DC 7)	8/189 (4.2%)	5/193 (2.6%)	p>0.05	High

SR systematic review, RCT randomised controlled trial, NA not applicable, RR relative risk, M-H Mantel-Haenszel, CI confidence interval, EC early clamping, DC delayed clamping

Appendix 1

Table 9. Outcome variable: Admission to special baby nursery or neonatal intensive care unit

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	Australia Argentina Canada	SR	3 RCTs (McDonald, Ceriani-Cernadas, Nelson) 1293 infants	NA	19/599	24/694	RR (M-H, Fixed, 95% CI) 1.03 (0.56, 1.90)	See Table 1 for risk of bias according to McDonald and Middleton

SR systematic review, RR risk ratio, NA not applicable, M-H Mantel-Haenszel, CI confidence interval

Appendix 1

Table 10. Outcome variable: Severe postpartum hemorrhage  $\geq 1000$  ml

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	Australia Zambia Argentina Mexico	SR	4 RCTs, (McDonald, van Rheenen, Ceriani- Cernadas, Chaparro) 1684 women	NA	20/786	28/898	RR (M-H, Fixed, 95% CI) 0.84 (0.48, 1.49)	See Table 1 for risk of bias according to McDonald and Middleton

SR systematic review, RR risk ratio, NA not applicable, M-H Mantel-Haenszel, CI confidence interval

Appendix 1

Table 11. Outcome variable: Need for manual removal of retained placenta

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
McDonald and Middleton, 2008	Australia UK	SR	2 RCTs McDonald, Oxford midwives 1515 women	NA	18/736	12/779	RR (M-H, Fixed, 95% CI) 1.59 (0.78, 3.26)	See Table 1 for risk of bias according to McDonald and Middleton

SR systematic review, RR risk ratio, NA not applicable, M-H Mantel-Haenszel, CI confidence interval

Appendix 1

Table 12. Outcome variable: Correct sampling of arterial and venous blood from the umbilical cord for blood gas and acid-base analysis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention Early clamping	Control Delayed clamping		
De Paco, 2011	Spain	RCT	158	22 (EC 10 DC 12)	55*/69 (79.7%) (*analysis performed on both artery and vein, but not stated whether "correct"*** sampled)	44*/67 (65.7%) (*analysis performed on both artery and vein but not stated whether "correct"*** sampled)	*"Correct sampling" not an outcome and not defined in this study. No statistics performed on this outcome in the article. P=0.10 (Stat Calc)	Low

RCT randomised controlled trial, EC early clamping, DC delayed clamping

\*\* if "correct" sampled (i.e. both artery and vein) pH should be  $\leq 0.03$  and pCO<sub>2</sub>  $\geq 1.0$  kPa in the umbilical artery as compared with the umbilical vein

## Appendix 2

Study (author, publication year)	Reason for exclusion
Ahmad et al., 1982	Cohort study with no unique outcome
Alexiou et al., 1982	Not correct outcome
Begley et al., 2010	Not correct intervention
Begley, 1990	Not correct intervention
Bertolini et al., 1995	Cohort study. Not correct patients and intervention
Capasso et al., 2003	Cohort study. Not correct PICO
Chaparro et al., 2007	Not correct outcome
Colozzi, 1954	Cohort study with no unique outcome
Daily et al., 1970	Quasirandomised study
Donaldson et al., 1999	Not correct outcome
Grajeda et al., 1997	Not correct PICO
Hudson, 1967	Cohort study with no unique outcome
Hutton et al., 2007	Both RCTs and not RCTs included
Jaleel et al., 2009	Wrong outcome (cord Hb and bilirubin)
Kagiya et al., 1989	Not correct outcome

## Appendix 2

Study (author, publication year)	Reason for exclusion
Kliot et al., 1984	Quasirandomised study
Lanzkowsky, 1960	Quasirandomised study
Pafumi et al., 2000	Not correct PICO
Pafumi et al., 2001	Not correct PICO
Pafumi et al., 2002	Commented in report, belong to “others”
Pascale et al., 2008	Not correct comparison
Philip1973	Not correct outcome
Prendiville et al., 1988	Not correct intervention
Rogers et al.,1998	Not correct intervention (preterm)
Shirvani et al., 2010	Not correct comparison
Walsh, 1968	Cohort study
van Rheenen et al., 2006	Not correct study design
Wu et al., 1960	Quasirandomised
Yao et al., 1969	Not correct outcome

### **Appendix 3: Search strategy, study selection and references**

#### **Question at issue:**

Is early umbilical cord clamping not different from or better than late umbilical cord clamping regarding postpartum infant iron deficiency and iron deficiency anaemia variables, long-term cognitive function, loss of stem cells, maternal postpartum haemorrhage, manual removal of retained placenta and correct sampling for blood gas analysis?

**PICO** (Patient, Intervention, Comparison, Outcome)

**P**= Newborn infants and mothers with full-term pregnancy ( $\geq 37$ )

**I**= Early umbilical cord clamping ( $< 1$ min)

**C**= Delayed or late umbilical cord clamping ( $\geq 1$  min)

**O<sup>1</sup> (Infant)** =

Primary outcomes:

Iron-deficiency, late\*

Ferritin level, late

Anaemia, early\* and late

Haemoglobin level, early and late

Haematocrit, early and late

Cognitive function

Loss of stem cells

(\*Early defined as within 0-48 h and late as after 2-6 months)

Secondary outcomes:

Need for phototherapy

Apgar score  $< 7$  at five min

Admission to neonatal intensive care units (NICU)

**O<sup>2</sup> (Mother)** =

Severe postpartum haemorrhage  $\geq 1000$ ml

Manual removal of retained placenta

**O<sup>3</sup> (Methodological)** =

Correct sampling of arterial and venous blood from the cord for blood gas analysis

#### **Eligibility criteria:**

Study design:

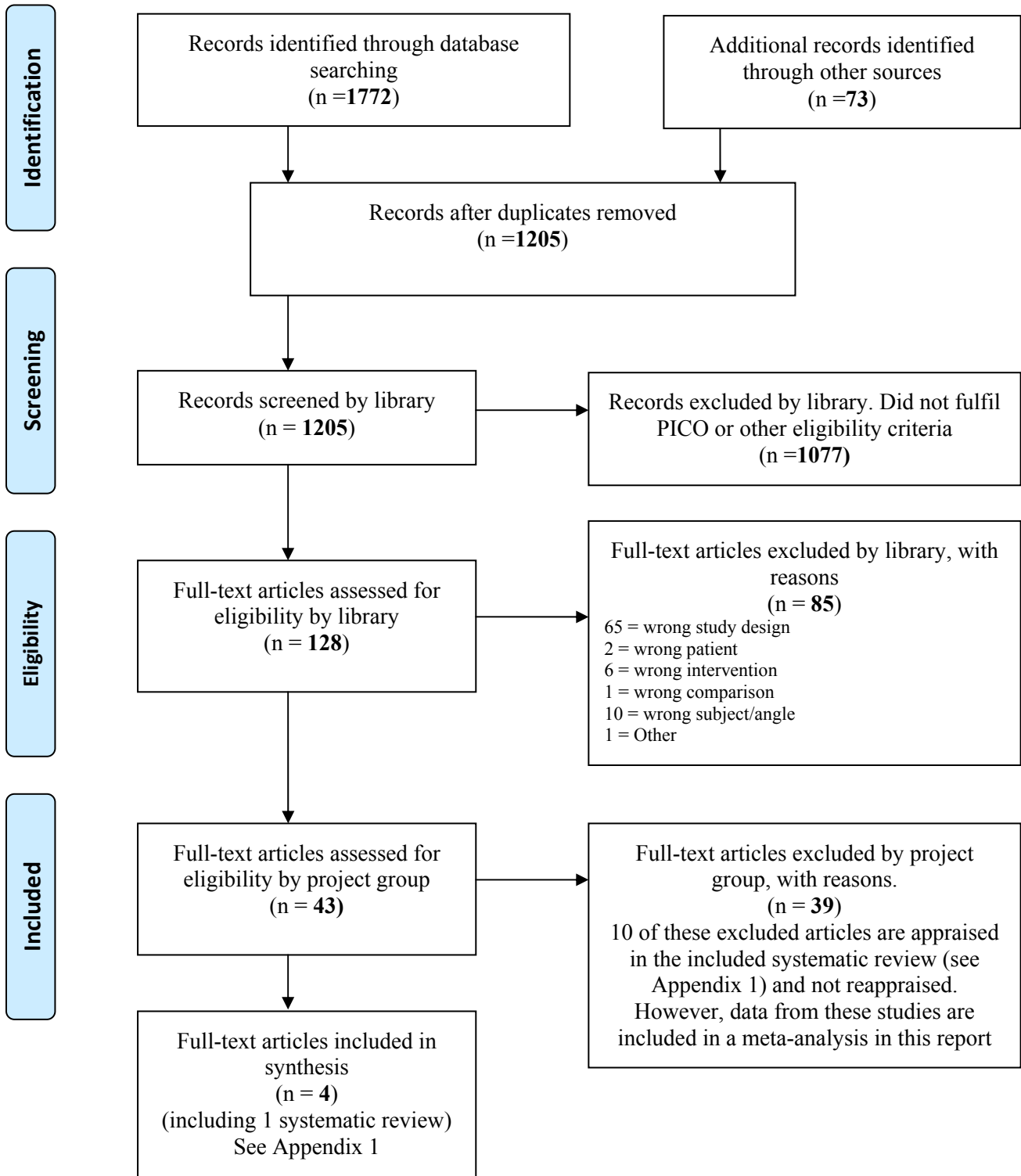
Randomized controlled trials – for O<sup>1</sup> and O<sup>2</sup> (Infant and Maternal outcomes)

Cohort studies with  $\geq 100$  patients – for O<sup>3</sup> (Methodological outcomes)

Systematic reviews

**Language:** Swedish, Norwegian, Danish, English, German

**Selection process – flow diagram**



2012-06-21

### **Search strategy**

**Database:** PubMed

**Date:** 2011-11-22

**No of results:** 711

Search	Most Recent Queries	Result
#9	Search #6 NOT #7 Limits: English, German, Danish, Norwegian, Swedish	711
#8	Search #6 NOT #7	772
#7	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR case reports[ptyp])	2520158
#6	Search #1 AND #2 AND #3	855
#5	Search #1 AND #3	8300
#4	Search #1 AND #2	1976
#3	Search immediate OR prompt OR early OR late OR delay OR delayed OR time OR timing	3617368
#2	Search clamping OR clamp OR cutting OR cut OR detachment OR separation OR (active management)	426301
#1	Search umbilical cord	32140

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**Database:** EMBASE (OVID SP)

**Date:** 2011-11-22

**No of results:** 489

#	Searches	Results
1	exp umbilical cord/	38808
2	umbilical cord.ti,ab,kw.	14766
3	1 or 2	43755
4	(clamping or clamp or cutting or cut or detachment or separation).ti,ab,kw.	339060
5	"active management".ti,ab,kw.	1029
6	4 or 5	340052
7	exp clamp/	5860
8	6 or 7	341687
9	(immediate or prompt or early or late or delay or delayed or time or timing).ti,ab,kw.	3168390
10	3 and 8 and 9	676
11	limit 10 to (embase and (danish or english or german or norwegian or swedish))	489

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2012-06-21

**Database:** PsycINFO (OVID SP)

**Date:** 2011-11-22

**No of results:** 45

#	Searches	Results
1	umbilical cord.af.	804
2	(clamping or clamp or cutting or cut or detachment or separation).af.	78464
3	"active management".af.	204
4	2 or 3	78662
5	(immediate or prompt or early or late or delay or delayed or time or timing).af.	910809
6	1 and 4 and 5	62
7	limit 6 to (danish or english or german or norwegian or swedish)	61
8	limit 7 to all journals	45

**Database:** Mosby Nursing Index

**Date:** 2011-11-22

**No of results:** 245

No.	Query	Results
#1	'umbilical cord'/exp	9112
#2	('umbilical'/exp OR 'umbilical') AND cord	7220
#3	#1 OR #2	10432
#4	clamping OR clamp OR cutting OR cut OR detachment OR separation OR 'active management'	56933
#5	immediate OR prompt OR early OR late OR delay OR delayed OR time OR timing	864464
#6	#3 AND #4 AND #5	279
#7	#6 AND ([danish]/lim OR [english]/lim OR [german]/lim OR [norwegian]/lim OR [swedish]/lim)	245

**Database:** The Cochrane Library (Wiley)

**Date:** 2011-11-22

**No of results:** 150

*Cochrane reviews* 8

*Other reviews* 5

*Clinical trials* 137

*Technology Assessments* 0

*Economic evaluations* 0

Line	Search	Hits
#1	umbilical cord:ti,ab,kw	682
#2	MeSH descriptor Umbilical Cord	148
#3	#1 OR #2	682
#4	immediate OR prompt OR early OR late OR delay OR delayed OR time OR timing:ti,ab,kw	206680
#5	clamping OR clamp OR cutting OR cut OR detachment OR separation OR "active management":ti,ab,kw	7358
#6	#3 AND #4 AND #5	150

2012-06-21

**Database: CRD – Centre for Reviews and Dissemination**

**Date:** 2011-11-22

**No of results:** 31

*DARE 23*

*NHS EED 4*

*HTA 4*

**Comment:** A update of the search in 2012-03-23 with umbilical cord in all fields did not retrieve any relevant references

Line	Search	Hits
1	(umbilical cord):TI IN DARE, NHSEED, HTA	22
2	MeSH DESCRIPTOR Umbilical Cord EXPLODE ALL TREES	15
3	#1 OR #2	31

**Search updated:** 2012-03-23, 37 new results (nothing relevant)

*DARE 55*

*NHS EED 6*

*HTA 7*

Line	Search	Hits
1	umbilical cord	61
2	MeSH DESCRIPTOR Umbilical Cord EXPLODE ALL TREES	18
3	#1 OR #2	68

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**Other HTA-databases 2011-11-23**

Searches have also been made in NHS Evidence, CADTH(Canadian Agency for Drugs and Technologies in Health) and TRIP(Turning Research into Practice as well as in the national HTA-databases in the Scandinavian countries; The Swedish Council on Health technology Assessment (SBU), Norwegian Knowledge Centre for the Health Services (NOKC), Danish Centre for Health technology Assessment (DACEHTA)

Nothing new was identified.

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**Reference lists:**

A comprehensive review of reference lists brought 73 new references

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High quality of evidence = ⊕⊕⊕⊕

Moderate quality of evidence = ⊕⊕⊕○

Low quality of evidence = ⊕⊕○○

Very low quality of evidence = ⊕○○○

Summary of Findings: Projekt Timing of umbilical cord clamping for neonatal and maternal outcomes

Outcome variable	Number of studies Design (No of studies included in SR)	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
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Infant iron deficiency (late)	1 RCT	No serious limitations	Not relevant	Serious indirectness (-1)	Imprecision (-1)	Unlikely	Not applicable	RR reduction (95% CI) 0,90 (0.38, 0.98)	NNT (95% CI) 20 (17, 67)	⊕⊕○○ Low
Infant serum ferritin (late)	1 SR (2 RCT) 1 RCT	Serious limitations (-1)	No serious inconsistency	Some uncertainty (0?)	No imprecision	Unlikely	Not applicable			⊕⊕⊕○ Moderate
Infant anaemia, early	1 RCT	Serious limitations (-1)	Not relevant	No uncertainty	Imprecision (-1)	Unlikely	Not applicable	RR reduction 0.80 (95% CI 0.22, 0.95)		⊕⊕○○ Low
Infant anaemia (late)	1 SR (2 RCT) 1 RCT	Some limitations (0?)	No serious inconsistency	Serious indirectness (-1)	No imprecision	Unlikely	Not applicable	OR (95% CI) 1.04 (0.71, 1.53)		⊕⊕⊕○ Moderate
Infant haemoglobin (early)	1 SR (4 RCT) 1 RCT	Some limitations (0?)	No serious inconsistency	Serious indirectness (-1)	No imprecision	Unlikely	Not applicable	Mean difference (95% CI) -17.86 (-27.55, -8.17)		⊕⊕⊕○ Moderate
Infant haemoglobin (late)	1 SR (4 RCT) 1 RCT	Some limitations (0?)	Some inconsistency (0?)	Serious indirectness (-1)	No imprecision	Unlikely	Not applicable	Mean difference (95% CI) -0.82 (-4.72, 3.08)		⊕⊕⊕○ Moderate

High quality of evidence = ⊕⊕⊕⊕  
 Moderate quality of evidence = ⊕⊕⊕○

Low quality of evidence = ⊕⊕○○  
 Very low quality of evidence = ⊕○○○

Summary of Findings: Projekt Timing of umbilical cord clamping for neonatal and maternal outcomes

Outcome variable	Number of studies Design (No of studies included in SR)	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
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Infant hematocrit (24-48 hs)	1 SR (1 RCT) 1 RCT	Serious limitations (-1)	No serious inconsistency	No uncertainty	Uncertain (0?)	Unlikely	Not applicable	SR: RR (95% CI) (Hct < 45%) 6.03 (2.27, 16.07) RCT: Mean difference (95% CI) 3.5 (2.4, 4.6)		⊕⊕⊕○ Moderate
Infant hematocrit (late)	1 RCT	Some limitations (0?)	Not relevant	No uncertainty	Uncertain (0?)	Unlikely	Not applicable	Mean difference (95% CI) -0.2 (-0.7, 0.2)		⊕⊕⊕○ Moderate
Infant jaundice requiring phototherapy	1 SR (4 RCT) 1 RCT	Some limitations (0?)	Some inconsistency (0?)	Some uncertainty (0?)	Serious imprecision (-1)	Unlikely	Not applicable	OR (95% CI) 2.14 (0.68, 6.77)		⊕⊕○○ Low
Apgar score <7 at 5 mins	1 SR (1 RCT) 1 RCT	Serious limitations (-1)	No serious inconsistency	Serious indirectness (-1)	No imprecision	Unlikely	Not applicable	OR (95% CI) 1.13 (0.62, 2.05)		⊕⊕○○ Low

High quality of evidence = ⊕⊕⊕⊕

Moderate quality of evidence = ⊕⊕⊕○

Low quality of evidence = ⊕⊕○○

Very low quality of evidence = ⊕○○○

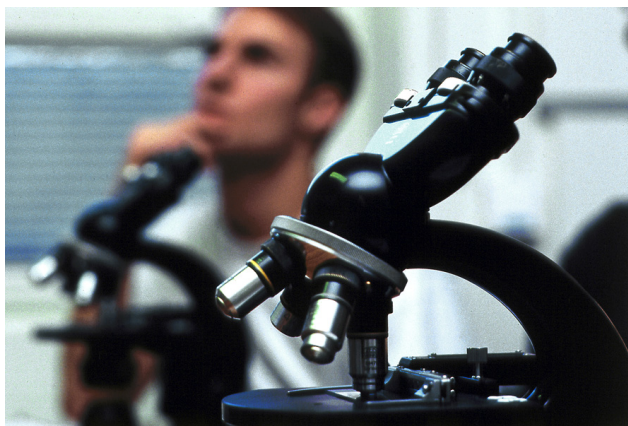
Summary of Findings: Projekt Timing of umbilical cord clamping for neonatal and maternal outcomes

Outcome variable	Number of studies Design (No of studies included in SR)	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
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Admission to neonatal ICU	1 SR (3 RCT)	Very serious limitations (-2)	Some inconsistency (0?)	Serious indirectness (-1)	No imprecision	Unlikely	Not applicable	RR (95% CI) 1.03 (0.56, 1.90)		⊕○○○ Very low
Severe postpartum hemorrhage ≥ 1000 ml	1 SR (4 RCT)	Serious limitations (-1)	No serious inconsistency	Serious indirectness (-1)	No imprecision	Unlikely	Not applicable	RR (95% CI) 0.84 (0.48, 1.49)		⊕⊕○○ Low
Manual removal of placenta	1 SR (2 RCT)	Serious limitations (-1)	Some inconsistency (0?)	Serious indirectness (-1)	Uncertain (0?)	Unlikely	Not applicable	RR (95% CI) 1.59 (0.78, 3.26)		⊕○○○ Very low
Correct sampling from cord	1 RCT	Very serious limitations (-2)	Not relevant	Serious indirectness (-1)	Uncertain (0?)	Unlikely	Not applicable	% Correct sampling 79.7% vs 65.7% p=0.10		⊕○○○ Very low

# Region Västra Götaland, HTA-centrum

Health Technology Assessment  
Regional activity-based HTA



## HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕ )
Moderate quality of evidence	= (GRADE ⊕⊕⊕⊖)
Low quality of evidence	= (GRADE ⊕⊕⊖⊖)
Very low quality of evidence	= (GRADE ⊕⊖⊖⊖)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.  
Head of HTA-centrum

