WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)
Susan Niermeyer, MD

Date Submitted for review:
February 26, 2009 (worksheet v.1)
October 27, 2009 (worksheet v. 2)

Clinical question.

In neonates (P) does delayed cord clamping (I) versus standard management (C), improve outcome (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? intervention

State if this is a proposed new topic or revision of existing worksheet: revision

Conflict of interest specific to this question: none

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? no

Search strategy (including electronic databases searched).


Embase: 'placenta'/exp AND 'blood transfusion'/exp; 'placental transfusion'; 'umbilical cord clamping'; 'newborn infant'/exp AND 'umbilical cord'/exp AND 'blood volume'/exp

Cochrane Database of Systematic Reviews: umbilical cord

AHA ECC EndNote database: placenta AND blood transfusion; umbilical cord

Article reference lists were reviewed and forward searching using Google Scholar and SCOPUS was carried out for selected articles.

State inclusion and exclusion criteria

Articles included were limited to those published in the peer-reviewed literature (no abstract-only studies). Only human data are considered. Randomized clinical trials and controlled trials are included in the formal evidence evaluation. Other studies (cohort, case studies), review articles, meta-analyses and systematic reviews, and editorials are referenced in the analysis and discussion of the evidence. All original research meeting the inclusion criteria is evaluated, regardless of language of publication.

Number of articles/sources meeting criteria for further review:

21 additional articles were reviewed in an update of the 2005 worksheet.

Cord milking was considered in a separate worksheet.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
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<tr>
<td></td>
<td>Chaparro 2006</td>
<td>Baenziger (P)2007, Aladangady(P) 2006</td>
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<td>[McDonald 2008]</td>
<td>[Rabe(P) 2004]</td>
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### Combined 2005 and 2010 evidence grid – Evidence Supporting Clinical Question

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<th>Level of evidence</th>
<th>Good</th>
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<tr>
<td></td>
<td>Ceriani Cernadas 2006</td>
<td>Baenziger (P)2007, Aladangady(P) 2006</td>
<td>Kugelman (P) 2007Strauss(P) 2008</td>
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<td>Chaparro 2006</td>
<td>Mercer(P) 2006</td>
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<td>Grajeda 1997</td>
<td>[Rabe(P) 2004]</td>
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<td>[Hutton 2007]</td>
<td>[vanRheenen 2004]</td>
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<td>Mercer (P) 2003</td>
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### Level of evidence

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
- **P** = hematological indices/postnatal stabilization
- **Term (no designation)** = hematological indices
- **Italics** = Animal studies
**Evidence Neutral to Clinical question**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>vanRheenen 2007</th>
<th>Jahazi 2008</th>
<th>Wiberg 2008 E</th>
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**Combined 2005 and 2010 evidence grid – Evidence Neutral to Clinical Question**

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**Evidence Opposing Clinical Question**

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**Level of evidence**

A = Return of spontaneous circulation  
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D = Intact neurological survival  
E = Other endpoint

*Italic* = Animal studies
There are now a multitude of contemporary studies conducted with randomized or concurrent control designs and acceptably high quality in both term and preterm infants. The clinical questions differ between the two groups, and so term and preterm infants will be considered separately.

For term infants, the outcome of interest is iron status in early infancy. Most individual studies (Ceriani Cernadas 2006, Chaparro 2006, Emhamed 2004, Grajeda 1997, Gupta 2002) and several meta-analyses (Hutton 2007, McDonald 2008, van Rheenen 2004) show benefit with respect to hematologic indices in the range 3-6 months (hemoglobin, hematocrit, ferritin). Meta-analyses have suggested more clinical jaundice among infants after delayed cord clamping compared to immediate clamping (McDonald 2008, vanTheenen 2004). Some analyses have shown greater use of phototherapy (McDonald 2008), but these studies are confined to the industrialized world and the criteria for use of phototherapy were neither strictly defined nor controlled.

In preterm infants, there are consistently observed benefits with respect to stability in immediate postnatal transition (hematocrit, blood pressure, use of pressors) as well as benefits in regard to lesser need for acute and later transfusion (Rabe 2004, Baenziger 2006, Mercer 2006, Rabe 2008, Ultee 2008, Kugelman 2007, Strauss 2008, Emman 1971, Kinmond 1993). Clinical jaundice occurs frequently in preterm infants, regardless of the timing of cord clamping. As seen with term infants, studies reporting increased use of phototherapy are conducted in the industrialized world with poorly defined and controlled criteria for intervention (Rabe 2004). There have been no demonstrated adverse effects, such as increased need for exchange transfusion (for either bilirubin or polycythemia), unintentional hypothermia, or increased respiratory distress with delayed cord clamping in preterm infants (Rabe 2004, 2008).

The endpoint of need for resuscitation has not been adequately addressed in contemporary studies of the timing of umbilical cord clamping. Most infants who require resuscitation are excluded from experimental protocols. Only one study in preterm infants (Aladangady 2006) reported initiation of positive-pressure ventilation before cord clamping. Physiological studies which form the foundation of modern neonatology suggest that there may be harm in immediate clamping and remind us that delayed clamping was the standard until the advent of modern obstetrical practice (Lind 1959, Klebe 1986, Hon 1968, Barcroft 1947). Immediate cord clamping in the infant who is not breathing has been shown to result in onset of bradycardia or persistence of bradycardia, highly analogous to the response of the fetus to umbilical cord occlusion (Brady 1962). In normal term infants, immediate clamping of the cord has been demonstrated to result in sudden decrease in cardiac volume for several beats, associated with baroreflex responses (Peltonen 1981). Especially in preterm infants, whose blood volume is distributed preferentially to the placenta during fetal life, immediate clamping may provoke or prolong a bradycardia which becomes the indication for positive-pressure ventilation in the first 30-60 seconds of life (Moss 1967).

Delay in umbilical cord clamping for at least one minute should be considered for both term and preterm infants. Future studies should collect data on infants who do not breathe at birth and document heart rate responses to early and delayed cord clamping.

Finally, there is active research in the area of active management of the third stage of labor. Many studies examining neonatal outcomes with respect to timing of cord clamping do not simultaneously collect maternal outcomes. In those studies reporting both neonatal and maternal outcomes, delayed clamping compares favorably with respect to maternal hemorrhage. There is some suggestion that the third stage of labor is shortened with placental drainage and the need for manual removal of the placenta is decreased. Some protocols have clamped and cut the umbilical cord immediately and then unclamped the placental side of the cord to allow drainage. There is an urgent need for coordination of experimental protocols and a harmonization of the approach to umbilical cord clamping for the welfare of both mothers and their newborns.

Acknowledgements:

Recent meta-analyses and systematic reviews of delayed cord clamping

<table>
<thead>
<tr>
<th>Meta-analysis citation</th>
<th>Population inclusion/exclusion criteria</th>
<th>Significant outcomes, other outcomes conclusions</th>
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<tbody>
<tr>
<td>Reference</td>
<td>Immediate</td>
<td>Delaying umbilical cord clamping (uncertain treatment implications)</td>
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<tr>
<td>Hofmeyr 1993</td>
<td>With or without oxytocin, with or without baby held below placenta, with or without cord milking</td>
<td>No clear effect on hematocrit at birth or 1 hour. No clear conclusion regarding respiratory effects, NEC, mortality.</td>
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<tr>
<td>Kinmond 1993</td>
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<td>Conclusion: Delaying umbilical cord clamping between 30 and 120 seconds in the preterm infant appears to be better than clamping within 30 seconds, as it is associated with a reduction in the risk of IVH and need for blood transfusion.</td>
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<td>McDonnell 1997</td>
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<td>Nelle 1998</td>
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<td>Oh 2002</td>
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<tr>
<td>Rabe 2000 (also 1996 and 1998)</td>
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<tr>
<td>Rabe H, Reynolds G, et al. A systematic review and meta-analysis of a brief delay in clamping the umbilical cord of preterm infants. Neonatology (formerly Biology of the Neonate) 2008; 93(2):138-144.</td>
<td>Preterm infants &lt; 37 weeks N = 454 Early clamping less than 20 sec Delaying clamping – 30 seconds or more</td>
<td>Hematologic: Hematocrit at birth and 1 hour was significantly higher with delayed clamping; number of infants transfused for anemia and number of transfusions needed were significantly fewer with late clamping.</td>
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<tr>
<td>Hofmeyr 1988</td>
<td></td>
<td>Cardiovascular: Blood pressure was higher and there was less need for inotropic support in the first 24 hours with delayed clamping; however, this was not significant (3 studies).</td>
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<tr>
<td>Hofmeyr 1993</td>
<td></td>
<td>Conclusion: Delayed cord clamping is possible and safe in appropriately configured perinatal centres. Therefore, it seems reasonable to recommend a slight delay of cord clamping of at least 30 seconds as routine practice in preterm infants.</td>
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<td>Aladangady 2005</td>
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<tr>
<td>Term infants</td>
<td></td>
<td>No significant differences in Apgar or tachypnea. No conclusions regarding need for phototherapy.</td>
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<tr>
<td>Term infants</td>
<td></td>
<td>Conclusion: There exists no scientific evidence of benefit from early cord clamping. There is no clear evidence to favor early or delayed clamping. A large, randomized controlled trial is needed.</td>
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<tr>
<td>Term infants</td>
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<tr>
<td>Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates. JAMA 2007; 297:1241-1257. Randomized: Ceriani Cernadas 2006 Chaparro 2006 Enhamed 2004 Gupta 2002 Nelson 1980 Oxford Midwives Research Group 1991 Geethanath 1997 Saigal 1972 Non-randomized: Nelle 1996 Abdel Aziz 1999 Grajeda 1997 Linderkamp 1992 Nelle 1993 Yao 1971 Oh 1967 Nelson 1980</td>
<td>Term infants N = 1912 randomized Controlled trials and randomized controlled trials</td>
<td>Mean hematocrit at around 6 hours, 24, 48 hours, 5 days, and 2 months was higher with delayed clamping. Hemoglobin results were less consistent, but higher at about 7 hours and at 2-3 months. There was no significant difference in mean serum bilirubin levels between the 2 groups. Ferritin at 2-3 and 6 months was higher with delayed cord clamping, and fewer infants had ferritin levels &lt; 50 mcg/L (indicator for deficient iron stores). One trial found higher iron stores at 6 months after delayed clamping.</td>
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<tr>
<td>Randomized: Ceriani Cernadas 2006</td>
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<td>Anemia was decreased at 24-48 hours and at 2-3 months with delayed cord clamping. Risk of polycythemia was increased with delayed clamping. There was no observed difference in tachypnea, grunting, or NICU admission between the 2 groups.</td>
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<tr>
<td>Chaparro 2006</td>
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<td>Subgroup analysis: The favorable effect of delayed clamping on hematocrit in the first days of life remained significant whether newborns were kept at</td>
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| Oxford Midwives Research Group 1991  
Geethanath 1997  
Saigal 1972 | the level of the placenta or placed on the mother’s abdomen.  
Conclusion: Delaying clamping of the umbilical cord in full-term neonates for a minimum of 2 minutes following birth is beneficial to the newborn, extending into infancy. Although there was an increase in polycythemia among infants in whom cord clamping was delayed, this condition appeared to be benign. |

Cernadas 2006  
Chaparro 2006  
Emhamed 2004  
Geethanath 1997  
Gupta 2002  
McDonald 1996  
Nelson 1980  
Oxford Midwives 1991  
Saigal 1972  
Spears 1966  
Van Rheenen 2007 | Term infants  
N = 2989  
Hematologic: There were significant increases in hemoglobin levels with late cord clamping, although these differences did not persist as long as 6 months. Ferritin was higher in the delayed clamping group at 6 months. There was a significant increase in infants needing phototherapy for jaundice with delayed cord clamping.  
Post-partum hemorrhage: Among 5 trials that reported on maternal well-being, there was no difference between early and delayed cord clamping with respect to postpartum hemorrhage or severe postpartum hemorrhage.  
Hematologic: Hemoglobin levels were significantly increased in the delayed clamping group up to 6 months; ferritin levels were also higher in this group. There was a significant increase in infants needing phototherapy for jaundice in the delayed clamping group.  
Conclusion: A more liberal approach to delaying clamping of the umbilical cord in healthy term infants appears to be warranted, particularly in light of growing evidence that delayed cord clamping may be of benefit in the longer term in promoting better iron stores in infants, as long as access to treatment for jaundice requiring phototherapy is easily accessible. |

Geethanath 1997  
Grajeda 1997  
Gupta 2002  
Lanzkowski 1960  
Linderkamp 1996  
Nelle 1993  
Nelle 1995/1996  
Saigal 1972 | Term infants  
N = 565  
Minimum age at follow-up 2 months  
Mean infant hemoglobin: 2 of 4 studies from developing countries favor delayed cord clamping. One study found a significant difference in ferritin at 3 months. Polycythemia in first week: 3 of 4 studies from industrialized countries show significantly higher hematocrit in delayed cord clamping. No trial reported clinical manifestations of polycythemia. Hyperbilirubinemia in first week: Bilirubin > 15 mg/dL noted with delayed clamping. No trials reported need for phototherapy or exchange transfusion.  
Conclusion: Delayed cord clamping reduces the risk of anemia in term infants. Longer follow-up studies are needed to establish whether this procedure is effective in reducing anemia in later infancy. The potential value of delayed cord clamping should be urgently investigated in malarious areas where fetal anemia is common. |

Grajeda 1997  
Gupta 2002 | Term and preterm infants (30-42 wks) including a proportion of SGA infants  
N = 230  
Delayed clamping ≥ 30 sec  
Severely limited number of trials prevented drawing strong conclusions.  
Conclusion: In a group of infants including AGA and SGA members, hemoglobin is higher at 2-3 months and there is a significant reduction in anemia among those with delayed cord clamping. |
Citation List


   LOE 1 (fair, supporting)

   COMMENTS: Randomized, PRETERM, end point: blood volume. Of 46 infants, 26 were delivered by cesarean section. There was greater blood volume in the delayed clamping group at cesarean section, but this was not significant and the blood volume of these infants did not reach euvoemia. Infants were held as low as cord length would allow and mother were given oxytocin at cesarean section with delivery of the presenting part. There was no difference in blood volume between 60s and 90s cord clamping. Two infants received endotracheal and 7 facemask ventilation before the cord was clamped.


   LOE 1 (fair, supporting)

   COMMENTS: Randomized, PRETERM, neonatologist blinded to the group allocation, end point: cerebral oxygenation. Study population was a subgroup of a multicenter trial on effects of placentofetal transfusion. Hematocrit was higher in the delayed group at 4, 24, and 72 hours. BP also higher in the delayed group at 4 hours, with no difference at 24 and 72 hours. St02 was higher at 4 and 24 hours in the delayed clamping group, but not at 72 hours. Results are intriguing relative to PVL, in light of Fukuda S, Pediatrics 2006; 117:1 which suggests that the insult resulting in PVL might occur close to the time of birth.


   LOE 1 (good, supporting)

   COMMENTS: Randomized, TERM, blinded to evaluators of outcomes but not clear if the neonatologist knew the assignment or not, end point: hematocrit and bilirubin. All neonates not breathing spontaneously at 10 seconds were excluded. Primary outcome was hematocrit at 6 hours; secondary outcomes were hematocrit at 24 to 48 hours and neonatal morbidity and mortality. Polycythemia defined as Hct>65 was significantly increased in the 3 min. clamping group, but there was no difference in the bilirubin levels in the 3 groups and no difference in other morbidities. Even though there were no differences in mean hematocrit between the groups significantly more in the earlier-clamped groups (8.9% versus 1.15 and 0
% had anemia defined as hematocrit <45% at 6 hours. Maternal outcomes of postpartum blood volume and hematocrit at 24 hours showed no differences.


LOE 1 (good, supporting)

COMMENTS: A retrospective analysis of a randomized trial. TERM, endpoint: infant lead status at 6 months. Inclusion criterion was availability of blood sample to carry out the blood lead and iron measures. Demographic data on the mother infant dyad was not included, but stated to be equivalent. Looking at the previous study numbers the infants not included in this study were equally distributed in the ECC and DCC groups. Multiple regressions controlled for maternal exposure to lead, placental lead levels and breast feeding. There was a significant 2-way interaction between feeding status and cord-clamping treatment group. Breast fed infants with early clamping had significantly higher blood lead concentration than similarly fed infants with delayed clamping. 23% of total effect of clamping time on the infant lead status could be explained by change in iron stores.


LOE 2 (fair, supporting)

COMMENTS: Randomized, TERM, blinding not mentioned except during analysis, end point: iron status at 6 months. History of maternal intake of iron during pregnancy was obtained retrospectively. Randomization was done at the time of admission for delivery for this large study. Hemoglobin and hematocrit were higher in the delayed group (ECC .59.5 and DCC .62.0%). Two infants had a venous hemocrit higher than 65% but were asymptomatic. Clinical jaundice did not differ significantly between the 2 groups. ECC group consumed iron fortified foods at 2 months and DCC group received more iron supplements at 4 months. Of note, this study was conducted at high altitude in Mexico City; high altitude has been associated with potentiation of jaundice, likely due to increased RBC mass.


LOE 1 (fair, supporting)

COMMENTS: Randomized, TERM, end point: hematocrit at 24 hours. Delayed clamping occurred when cord stopped pulsating mean 214 second. Infants were placed on the mother’s abdomen. 5.3% infants in DCC had polycythemia with hematocrit >65; however, there was no difference in bilirubin in the 2 groups. All the infants needing resuscitation were excluded from the analysis. No follow up information is provided. Short-term measures may not be the most powerful clinical evidence of benefit with respect to anemia.


LOE 1 (good, supporting)

COMMENTS: A well done systematic review of randomized and non randomized controlled studies till 2006 in TERN infants. End points were multiple. Even though the relative risk of hematocrit >65 was (3.44) higher in the DCC group none of these infants were symptomatic and did not have statistically significantly increased levels of bilirubin, although there was a trend. Clinical jaundice and need for phototherapy may vary systematically between North America/Europe and other parts of the world.


LOE 1 (fair, neutral)

COMMENTS: Randomized (coin toss), TERM, double-blinded, end point: hematocrit at 18 hours. Early group had the cord clamped at 30s and late at 3 minutes. Neonate held at the level of the introitus and in the delayed clamping group, dried and wiped on a table at the level of the introitus. No difference in hematocrit or polycythemia. There were no manifestations of polycythemia, although nearly 22% of infants were judged to have “asymptomatic polycythemia” (htc ?). Hematocrits were overall somewhat high; altitude variable in this region (2400-2700 feet?).

LOE 1 (poor, supporting)

COMMENTS: Randomized, PRETERM, blinded, end point: initial blood pressure (cuff or central) and initial hematocrit. More than half of eligible neonates did not enter the trial because of refusal by parents or technical problems such as rapid delivery or staff unavailability. DCC was 30 to 45 seconds. There was a difference in the mean BP in infants <1500gm 36 mm Hg versus 43 mmHg on subset analysis, but no significant difference in the whole group. Hematocrit was initially similar but was higher in the DCC at 24 hours. Differing methods of blood pressure measurement added variability and potential misclassification.


LOE 1 (good, supporting)

COMMENTS: Studies included TERM neonates till 2006. Early cord clamping defined as within 6o seconds and delayed as 2 minutes. Clinical jaundice was more likely to occur in DCC group, as was phototherapy. Again results regarding phototherapy were divergent with respect to US/European centers vs. elsewhere.


LOE 1 (fair, supporting)

COMMENTS: Randomized, PRETERM, unmasked, end point: BPD. DCC was 30 to 45 seconds and infants were held 10-15 inches below the introitus/incision in a warm towel. No comment on the resuscitation of these infants. Authors did not demonstrate a difference in BPD, however their secondary analysis showed a difference in IVH and late onset sepsis.


LOE 1 (good, supporting)

COMMENTS: Systematic meta-analysis PRETERM trials till 2004. Overall there is less need for transfusions and decrease in IVH, but no difference in jaundice.


LOE 1 (fair, supporting)

COMMENTS: Authors updated the Cochrane review by including 3 more studies in the analysis 2 that were reported before their initial analysis and one before 2004. Conclusions were no different.


LOE 1 (poor, supporting)

COMMENTS: Randomized, PRETERM, unblended, end point RBC volumes. Secondary end points hemodynamic status, clinical condition, need for RBC transfusion. Randomization was stratified into 30-36 weeks GA and < 30 weeks GA. Was powered to detect a 50% decrease in RBC transfusions. DCC was 1 minute. Uniform transfusion guidelines are said to be followed. All infants < 30 weeks ended up with immediate cord clamping “to permit prompt resuscitation”. Placental blood was then collected and transfused 10mL/kf “to mimic true delayed umbilical cord clamping”. Of the 27 infants < 30 weeks, 26 were lost to analysis due to unsatisfactory collection of placental blood (18) and insufficient volume for transfusion (7). 8% in the ECC and 4 % of infants in the DCC received blood transfusion. This was not statistically significant. More infants in DCC (73%) versus (53%) p=0.03 required phototherapy, which was at the discretion of individual neonatologists. Most infants experienced phototherapy. Hematocrits were higher in the DCC till day 28. They report no difference in IVH but not all the babies in the 30-36 weeks had cranial ultrasounds.


LOE 1 (fair, supporting)
COMMENTS: Randomized, late PRETERM, blinding not mentioned, end point: hemoglobin and ferritin levels. There was no difference in the ferritin levels. Hb./Hct were significantly higher at 1 hour and 10 weeks of age. No difference in bilirubin levels and no increase in polycythemia. Sample size was very small and limited to Caucasian parents.

   LOE 1 (fair, supporting)
   COMMENTS: Reasonable systematic review. TERM. However there were only 2 studies with a total of 46 babies in the ECC group and 73 in DCC group for inclusion for anemia in developing countries. These had different timings of cord clamping stopping of cord pulsations and after placenta in the vagina. In the developed countries analysis only hematocrit is reported. There was a reported increase in bilirubin, again only in industrialized-country studies, but no increase in use of phototherapy.

   LOE 1 (fair, neutral)
   COMMENTS: Randomized. TERM, unblended, end point: 6 months hemoglobin levels. Specifically stated objective to conduct the trial in malaria zone. Even though the hemoglobin levels were similar in the 2 groups at 4 months the number of infants with Hb<10.3 (cut off for anemia) was 21% in DCC and 41% in ECC group. At 6 months there were no differences.

   LOE 1 (poor, neutral)
   COMMENTS: An attempt at a systematic review of the effect of DCC in low birth weight infants. Authors use appropriate methods however they did not find any articles other than indirect evidence and reporting on SGA infants in 3 studies. 2 of these studies they assumed had SGA infants and 1 study reported 36% SGA infants. No specific conclusions can be made about this subset of SGA infants that may be increased risk of polycythemia.

   LOE 2 (fair, supporting)
   COMMENT: Controlled (alternate week assignment), TERM, not blinded, endpoint: hemoglobin and ferritin at 3 months. There were excellent controls on data collection and major effort to achieve more complete follow-up, however, this proved to be the major limitation of the study.

   LOE 4 (fair, neutral)
   COMMENTS: Observational study of effect of timing of cord clamping on venous blood gases and lactate concentrations. There seems to be no clinical relevance of the decrease in pH with a combined metabolic respiratory acidosis over 90 seconds. Most pronounced effect was at 45 seconds. Venous PO2 peaked at 45 seconds. This study relates more to reliability/validity of umbilical cord gases than to infant status.

   LOE 2 (fair, supporting)
   COMMENTS: Case control. TERM. DCC 4 minutes. End point limb perfusion and hemodynamics. Physiologic evaluation was done at a mean of 72 hours of age. Hematocrit was measured at 3 days of age. Do not provide information on the number of infants out of 11 who had hct. >65. Bilirubin levels were 8.1(138) and 7.9(136). Authors claim that increase LVD with no change in BF may help extrauterine adaptation. However there is no evidence presented for improved extrauterine adaptation.
Evidence that immediate cord clamping may increase the need for resuscitation (evidence for potential harm)


