Umbilical cord clamping: influence on newborn iron endowment

Source: Chaparro and Lutter, PAHO 2007
Overview

• Anemia prevalence
• History of cord clamping practices
• “Placental transfusion” and effect of delayed clamping on newborn iron endowment
• Evidence for longer-term impact on iron status
• Other considerations: Risks of delayed clamping?
• Implications for practice
• Summary, conclusions and research needs
Prevalence of anemia in preschool-age (< 5 years) and pregnant women by WHO region

Prevalence and trends of anemia in preschool-age (< 5 years) and pregnant women in Latin America and the Caribbean

When to clamp the umbilical cord?

• Long-standing debate as to the “best” time to clamp the umbilical cord after delivery
  – “Early” or “immediate” clamping: within first 15-30 seconds after delivery
  – “Delayed” or “late” clamping: 2-3 minutes after delivery, or at the end of cord pulsations
ZEO NOMIA;

Another thing very injurious to the child, is the tying and cutting the navel-string too soon; which should always be left till the child has not only repeatedly breathed, but till all pulsation in the cord ceases. As otherwise the child is much weaker than it ought to be; a part of the blood being left in the placenta, which ought to have been in the child; and at the same time the placenta does not so naturally collapse, and withdraw itself from the sides of the uterus, and is not therefore removed with so much safety and certainty.

LONDON:
PRINTED FOR J. JOHNSON, IN ST. PAUL'S CHURCH YARD.
1801.

Erasmus Darwin
(1731 - 1802)
When to clamp the umbilical cord?

• Practices appeared to have shifted towards early cord clamping in the early 20th century when clamping at the end of cord pulsations (~3-4 minutes) was the “present, prevailing practice” (Book, 1935)

• Why?
When Should We Clamp the Umbilical Cord?

Why is this practice controversial?

Not very controversial. Check the literature and the practice guidelines.

During the third stage of labor, when the placenta is delivered, there are several potential reasons for clamping the umbilical cord:

1) Concern about polycythemia and hyperbilirubinemia.

2) The presence of a pediatrician or neonatologist at the delivery, who is eager to start “taking care” of the baby.

3) Desire to obtain blood from the umbilical cord to screen for fetal asphyxia with pH and blood gases.

4) The perceived need to initiate skin-to-skin contact with the mother (and breastfeeding) as soon as possible.

5) More recently, to conform with a recommendation to provide active management of the third stage of labor to minimize PPH.
When to clamp the umbilical cord?

- Recently, renewed interest in determining the optimal timing of cord clamping
  - Iron status
  - Others (premature/low birth weight infants)
Delayed clamping and “placental transfusion”

• For approximately 3 minutes after delivery, circulation continues between the newborn and the placenta
  – Umbilical vessels naturally close due to oxygen saturation of cord blood, temperature, hormones, prostaglandins
  – Cord clamping time will have profound effect on blood volume
Majority of transfer in ~ 1st minute

van Rheenen, P. F et al. BMJ 2006;333:954-958
Positioning of infant relative to mother

With permission of Patrick van Rheenen
Importance of body iron at birth

- **Newborn total body iron (TBI):**
  - ~70% in circulation (hemoglobin)
  - ~25% in stores (ferritin)
- **High hemoglobin at birth (~ 17 g/dL)**
  - Recycled and added to iron stores
- **Newborn TBI= main source of iron for growth and development during first 6 months of life**
  - Cord clamping time will affect length of time iron stores remain adequate
Iron provided by delayed clamping

If cord is clamped 2-3 min (~ at the end of cord pulsations) after delivery:

3.2 kg x 30 ml/kg from placenta = 96 ml blood
96 ml x 17 g/100 ml = 15.4 g Hb
15.4 g Hb x 3.4 mg Fe/g Hb ≈ 52 mg Fe

• 52 mg is approximately 2.5 months worth of iron requirements (0.7 mg/day)
Implications for clinical practice?

• Immediate cord clamping causes an iatrogenic loss of infant iron stores at birth
  – Iron deficiency is likely not the first outcome that comes to mind when a practitioner is deciding when to clamp the cord

• Pressure of other medical procedures on cord clamping times?
  – Cord blood banking
  – Active management of the third stage of labor for the prevention of postpartum hemorrhage
What are the long term effects of cord clamping time on iron status in term infants?

• 14 studies have analyzed the effect of cord clamping time on hematological or iron status past the neonatal period through 6 months of age:
  – Earlier studies (4 from 1940s-1960s): several study design and assessment limitations
  – 8 of remaining 10 were conducted in the last 10 years
  – Two meta-analyses (2007, 2008)
Late vs. early clamping of the umbilical cord in full-term neonates: Systematic review and meta-analysis of controlled trials (Hutton and Hassan, JAMA, 297(11) 2007)

• 15 trials, 1912 infants
  – Included studies focused on neonatal outcomes

• Benefits of DC (2-6 months of age):
  – Greater hematocrit (at 6 hrs, 24-48 hours, 5 days and 2 months of age), hemoglobin concentration (at 7 days and in one trial at 2 months of age), ferritin concentration (at 2, 3 and 6 months of age)
  – Clinically important reduction in the risk of anemia (at 24-48 hrs and 2-3 months of age)
Late vs. early clamping of the umbilical cord in full-term neonates: Systematic review and meta-analysis of controlled trials (Hutton and Hassan, cont’d)

• Risks of DC:
  – No significant differences in mean serum bilirubin (24, 72 hrs), clinical jaundice (24-48 hrs)
  – Late clamped infants were at an increased risk of experiencing asymptomatic polycythemia (at 7, 24-48 h)
    • Polycythemia existed in both early and late-clamping groups
    • Generally treatment for asymptomatic polycythemia not warranted
    • Limiting analysis to high-quality studies: no significant difference between groups in polycythemia
Late vs. early clamping of the umbilical cord in full-term neonates: Systematic review and meta-analysis of controlled trials (Hutton and Hassan, JAMA, cont’d)

• Conclusions:
  – Delayed clamping of a minimum of 2 minutes is beneficial to the newborn and infant
  – Increased polycythemia in late-clamped infants appears to be benign
Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes (McDonald and Middleton, Cochrane Database of Systematic Reviews, 2008)

• 11 RCT of 2989 mothers and infants

• Maternal outcomes:
  – No significant difference between EC and DC for
    • Maternal PPH or severe PPH
    • Length of the third stage of labor
    • Manual removal of placenta
Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes (McDonald and Middleton, cont)

• Neonatal outcomes:
  – DC significantly improved infant iron status
  – No significant difference in clinical jaundice or polycythemia
  – Significant increase in “phototherapy required for jaundice” among DC infants
    • However, no mention of criteria used for phototherapy across studies
    • Treatment guidelines have changed over time
Effect of timing of umbilical cord clamping on iron status in Mexican infants: a randomised controlled trial


• 476 infants randomized to EC (~10 sec) or DC (~2 min); 358 followed through 6 months of age
• Main outcome: infant iron status at 6 months of age
  – Also analyzed interaction effects with factors associated with infant ID:
    • Maternal ID
    • Birthweight
    • Feeding
Mean cord clamping time by treatment group

$p < 0.0001$
DC significantly increased infant ferritin concentration\(^1\)

\[ p = 0.0002 \]

\[ \text{Ferritin (μg/L)} \]

\[ \begin{array}{c}
| \text{EC} | | \text{DC} | \\
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>34.4</td>
<td>50.7</td>
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\end{array} \]

\(^1\) Adjusting for maternal ferritin and employment
DC significantly increased infant body storage iron\textsuperscript{1}

\[ \text{Body storage iron (mg)} \]

\[ \begin{align*}
\text{EC} & : 29 \\
\text{DC} & : 38
\end{align*} \]

\[ p = 0.0003 \]

27 mg Fe = 1.25 mo Fe requirements

\textsuperscript{1} Adjusting for maternal ferritin and employment
DC increased body iron more in infants born to ID mothers\textsuperscript{1}

\( p = 0.008 \) for interaction term

<table>
<thead>
<tr>
<th></th>
<th>Iron-replete mothers</th>
<th>Iron deficient mothers</th>
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<td>Infant body Iron (mg/kg)</td>
<td>EC (46.7)</td>
<td>DC (47.5)</td>
</tr>
<tr>
<td></td>
<td>EC (42.1)</td>
<td>DC (48.6)</td>
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</table>

ID = ferritin < 12µg/L
DC increased body iron more in infants with birth weight ≤ 3000 g

- Birth weight > 3000 g
  - EC: 45.2 mg/kg
  - DC: 47.7 mg/kg
  - p = 0.04 for interaction term

- Birth weight 2500 to 3000 g
  - EC: 41.2 mg/kg
  - DC: 48.3 mg/kg
DC increased body iron more in infants not receiving iron-fortified formula or milk.

$p = 0.07$ for interaction term
Randomized controlled trial (n = 276) through 6 mo of age
  - Ferritin significantly higher in the delayed group (3 min) vs. early group
  - Iron-deficiency anemia 3 times more likely in the early clamped group as compared to the delayed group
Effect of delayed versus early umbilical cord clamping on neonatal outcomes and in randomised controlled trial

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- Halmstad, Sweden
- In Europe: 3-7\% of young children IDA, 27\% ID
- 400 infants randomized to EC (< =10 s) or DC (>=180 s); 382 analyzed
Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial

- Follow-up at 4 months found
  - 45% higher ferritin concentration in DC infants
  - All other iron status indicators (TfR, MCV, MCH) except hemoglobin were significantly higher in DC infants
  - ID was significantly higher in EC infants
- No infants were polycythemic after birth
- Jaundice and treatment for phototherapy were not significantly different between groups
Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial

• In separate publication, authors report no significant differences in maternal bleeding/PPH, duration of third stage of labor
• Authors also plan to report development outcomes at 4 months and 12 months, and iron status again at 12 months (future publications)
What about pre-term, LBW and SGA/IUGR infants?

• Frequently, for premature infants, cord clamped immediately for fear of delaying resuscitation measures or causing hypothermia

• Hypovolemia in pre-term infants caused by early cord clamping may have significant negative effects

• SGA/IUGR infants—special case?
Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (Rabe H et al, Cochrane Database of Systematic Reviews 2012)

• 15 studies, 738 preterm infants (24-36 weeks)
• Delay in clamping between 30-180 s; immediate clamping ~10 s
• Benefits of delayed clamping:
  – Decreased need for blood transfusions for anemia
    • Also for low blood pressure, though did not reach significance
Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (Rabe H et al, Cochrane Database of Systematic Reviews 2012)

- Lower incidence of intraventricular hemorrhage (IVH)
  - IVH = bleeding into brain’s ventricular system
  - More severe grades of IVH are associated with negative effects on neurodevelopment

- Lower incidence of necrotizing enterocolitis (NEC)
  - NEC = death of intestinal tissue
Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (cont’d)

• **Negative effects of delayed clamping**
  – Peak bilirubin concentration in DC infants was significantly higher than in EC infants
    • Bilirubin levels warranting treatment in premature infants; no consensus on treatment guidelines, and vary by birthweight and gest. age
      • Peak levels in DC infants ranged 139-222 umol/L
      • Phototherapy treatment
        • At 80 umol/L at 24 weeks gestation
        • At 250 umol/L at 36 weeks gestation
Other potential benefits of DC for preterm infants (individual studies)

- Greater hematocrit levels, oxygen transport (including cerebral oxygenation) and red blood cell flow
- Fewer days on oxygen, fewer days on or a decreased need for mechanical ventilation, a decreased need for surfactant
Delayed cord clamping in very pre-term infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: A randomized controlled trial (JS Mercer et al Pediatrics 2006: 117)

- RCT of 72 mother/infant pairs (28.2 weeks, 1151-1175 g):
  - EC: 5-10 seconds
  - DC: 30-45 seconds

<table>
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<tr>
<th></th>
<th>EC  (n = 36)</th>
<th>DC  (n = 36)</th>
<th>p-value</th>
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<th>95% CI</th>
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<td>All IVH</td>
<td>13/36 (36)</td>
<td>5/36 (14)</td>
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<td>3 (8)</td>
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<td>Grade 4</td>
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<td>Sepsis</td>
<td>8/36 (22)</td>
<td>1/36 (3)</td>
<td>0.03</td>
<td>0.10</td>
<td>0.01-0.84</td>
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</table>

DC decreased the odds of all IVH by 72% and decreased the odds of late-onset sepsis by 90%
Delayed cord clamping in very pre-term infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: A randomized controlled trial
(JS Mercer et al Pediatrics 2006: 117)

• Sepsis responsible for 23% of neonatal deaths
• Mechanism? Greater levels of hematopoietic progenitor cells in DC infants thus improving immune defenses?
Effects of delayed umbilical cord clamping on peripheral blood hematopoietic stem cells in premature neonates


- RCT
- n= 42 VLBW infants: ~1300 g birthweight, ~29 weeks gestation
- No significant difference in circulating levels of hematopoietic progenitor cells between EC and DC infants
  - Levels tended to be lower in DC infants
    - Authors hypothesized that other factors also provided in placental transfusion affected the “homing” of progenitor cells to their target organs, thus decreasing their circulating levels in DC infants
Long-term effects in premature/LBW infants?

- Particularly at risk of developing ID because of low iron stores at birth
- IVH, neonatal sepsis and male sex are also associated with poorer neurodevelopmental outcomes
- However, very few studies on effects of clamping time in premature/LBW infants
Long-term effects in premature/LBW infants? (cont’d)

• One RCT has shown evidence of improved hematological status at 10 weeks of age in preterm infants who received delayed clamping (3 min after delivery)

(Ultee K. et al, Delayed cord clamping in preterm infants delivered at 34-36 weeks gestation: A randomized controlled trial. Arch Dis Child Fetal Neonatal Ed. 2007 Feb 16 [epub])
Long-term effects in premature/LBW infants? (cont’d)

- Development outcomes (motor function) at 7 months in 1 study (n = 58) were not significantly different between early/delayed clamped preterm VLBW infants
  (Mercer J et al. Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping J Perinatol 2010; 30: 11-16)

- More research needed on long-term outcomes in preterm infants
What about SGA infants?

- SGA/IUGR infants are common in the developing world: ~24% of all births.
- SGA infants may have greater risk of polycythemia due to chronic hypoxemia in utero and increased erythropoiesis.
- However may not necessarily be the case in developing countries, where maternal anemia is common and cord hemoglobin is low.
- Analyses have not been done specifically on SGA infants.
Implications for practice: Cord blood banking

status. If cord clamping is done too soon after birth, the infant may be deprived of a placental blood transfusion, resulting in lower blood volume and increased risk for anemia in later life. Immediate cord clamping will, of course, increase the volume of placental blood for harvesting for cord blood banking. There may be a temptation to practice immediate cord clamping aggressively to increase the volume of cord blood that can be harvested for cord blood banking. This practice is unethical and should be discouraged.

Cord Blood Banking for Potential Future Transplantation: Subject Review
Work Group on Cord Blood Banking
Pediatrics 1999;104;116-118
DOI: 10.1542/peds.104.1.116
Implications for practice: Active management of the third stage of labor

WHO Recommendations for the Prevention of Postpartum Haemorrhage

Based on the review of evidence and discussions related to the individual components of the intervention, the panel agreed that the term “active management of third stage of labour” should include administration of an uterotonic soon after birth of the baby, delayed cord clamping and delivery of the placenta by controlled cord traction, followed by uterine massage.
What are current cord clamping practices?

• Limited data
• Variable by location, hospital, type of practitioner
• Included in norms and protocols in many Latin American countries
<table>
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<tr>
<th>Country</th>
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<th>Date</th>
<th>Definition</th>
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<td>Albania</td>
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Attitude of obstetricians towards delayed cord clamping: A questionnaire-based study

A. B. O. ONONEZE¹ & D. J. R. HUTCHON²

¹Lead Clinician in Obstetrics & Labour Ward, Consultant in Obstetrics & Gynaecology and ²Consultant in Obstetrics & Gynaecology, Darlington Memorial Hospital

• 37% of obstetricians surveyed never practiced delayed clamping
  – 50% unaware of the evidence supporting delayed clamping
  – 6% did not believe evidence
  – 38% difficulty in clinical practice
Summary and Conclusions

• Delayed clamping significantly improves iron status through 6 months of age
  – Increase in body iron \(~1-2\) months of infant iron needs
• Increased benefit for infants born to mothers with low ferritin, born with lower birth weight, and infants predominantly breastfed
• Delayed clamping would help to prevent iron deficiency from occurring before 6 months of age at which time other interventions could be more easily implemented
Summary and Conclusions

• Current international recommendations support delayed umbilical cord clamping
• Current cord clamping practices do not reflect these recommendations
• Greater advocacy and awareness is needed on:
  – Evidence for benefits of delayed cord clamping
  – Recommended practices
Research needs

• Safety and benefits/risks of DC in cesarean delivery
• Long-term effects of DC in full-term and preterm/LBW infants
• Development of a model including training and advocacy components for DC, skin-to-skin contact and early initiation of BF within the context of delivery and neonatal care protocols and programs
• Additional analysis from completed studies on effects (positive and negative) on SGA infants
• Harmonization of active management and neonatal resuscitation
  – timing of oxytocin administration in relation to cord clamping
  – feasibility of resuscitation with the cord intact
Acknowledgments

Dr. Camila Chaparro