Umbilical Cord Clamping: Does Timing Matter?

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Do you think the time of umbilical cord clamping matters?
A. Yes, for all infants
B. Yes, but only in preterm infants
C. Yes, but only in term infants
D. No, not at all

What do you think the timing of umbilical cord clamping should be for infants <32 weeks gestation?
A. Immediately, no milking
B. Immediately after milking
C. 10-30 seconds
D. 31-60 seconds
E. >60 seconds
F. I didn’t know there were so many options

What do you think the timing of umbilical cord clamping should be for infants >37 weeks gestation?
A. Immediately, no milking
B. Immediately after milking
C. 10-30 seconds
D. 31-60 seconds
E. >60 seconds
F. Now I know there are many options, but I still don’t know which is best
Overview

- Physiology
- Preterm infants
  - Randomized controlled trial
  - Meta-analysis
  - Policies
  - UCSF Protocol
- Term infants
  - Meta-analysis
  - Randomized controlled trial
  - Guidelines

Terminology

- Preterm
  - Delayed cord clamping (DCC): >30 seconds
  - Immediate cord clamping (ICC): <15 seconds
- Term
  - Delayed cord clamping (DCC): >3-5 minutes
  - Immediate cord clamping (ICC): <15 seconds

An old idea...

- “Another thing very injurious to the child, is the tying and cutting of 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 portion of the blood being left in the placenta which aught to have been in the child”
- Erasmus Darwin, Zoonomia, 1801

The Evolution of Cord Clamping

- 1946 Sir Joseph Barcroft described placental blood transfer at birth
- Physiological studies in late 1950s-1970s.
- ICC in 1980s to rapidly transport neonate.
- There are no current ACOG guidelines.
- A new body of literature has emerged in the 1990s-2000s.
Physiology

- Distribution of volume between infant and placenta
- Length of time: hypoperfusion vs overload
- Position of infant

What happens in nature?

Placental Transfusion in the Naturally Born Lamb (Yao 1977)

- Unassisted (9)
  - RCV: 36 ml/kg
- Early clamping (8)
  - < 10 seconds
  - RCV: 30 ml/kg
- Late clamping (5)
  - 3-5 minutes
  - RCV: 50 ml/kg

RCV = mean red cell volume
Nature’s regulation

- Ewes chew the cord
- Cord stretches until it breaks

Increased Red Cell Volume with DCC

- Term
  - Usher et al, 1963
  - Oh et al, 1966
  - Oh et al, 1966
  - Yao et al, 1968
  - Saigal et al, 1972

- Preterm
  - Yao et al, 1969
  - Saigal et al, 1972

Red Cell Volume

<table>
<thead>
<tr>
<th>Term</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate &lt;5 seconds</td>
<td>Immediate &lt;5 seconds</td>
</tr>
<tr>
<td>- RCV 33 ml/kg</td>
<td>- RCV 32 ml/kg</td>
</tr>
<tr>
<td>Delayed 3-5 minutes</td>
<td>Delayed 5 minutes</td>
</tr>
<tr>
<td>- RCV 49 ml/kg</td>
<td>- RCV 46 ml/kg</td>
</tr>
<tr>
<td>Increase 50%</td>
<td>Increase 50%</td>
</tr>
</tbody>
</table>

Saigal et al, 1972

Does Position Matter?

A. Yes
B. No

62% vs 38%
Pros of DCC:

- Proposed benefits of DCC include:
  - Higher BPs (Mercer, Nelle, Rabe, Ibrahim)
  - Fewer RBC transfusions for anemia (Kinmon, Ibrahim, Rabe)
  - Decreased IVH (Mercer, Hofmeyer)
  - Decreased late onset sepsis (Mercer)

Cons of DCC:

- Does the increase in blood flow from the placenta cause harm?
  - Increased risk of hyperbilirubinemia (Rabe, Saigal).
  - Increased risk of polycythemia. (Saigal)

- Does delay cause hypothermia?
  - No difference in temperature (Pietra, Oh)

- Is the delay in resuscitation harmful?
  - No difference in 5 minute Apgar (Mercer, Hofmeyr)
Hyperbilirubinemia

Saigal et al, 1972

Preterm Infants

• Randomized controlled trials
• Meta-analysis
• Protocols

US Randomized Control Trial

• 72 Infants; <32 weeks gestation
• Randomized to:
  – ICC 5-10 seconds
  – DCC 30-seconds
• DCC group:
  – Infant held 10 to 15 inches below introitus for VD
  – Infant held below incision for C/S
• Exclusion criteria:
  – OB refusal
  – Major anomalies
  – Multiple gestations
  – Intent to withhold care
  – Severe maternal illness
  – Abruption or previa

Mercer et al, 2006

RCT results: decreased IVH and LOS

<table>
<thead>
<tr>
<th>Table 4: IVH and LOS in Study Infants</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC (n = 36)</td>
<td>DCC (n = 36)</td>
<td>P</td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All IVH 13 (36)</td>
<td>5 (16)</td>
<td>.03</td>
<td>3.5</td>
<td>1.1-11</td>
</tr>
<tr>
<td>Grade 1  4 (11)</td>
<td>3 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2  8 (22)</td>
<td>2 (6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4  1 (3)</td>
<td>0 (0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis   8 (22)</td>
<td>1 (3)</td>
<td>.03</td>
<td>.01</td>
<td>0.01-0.84</td>
</tr>
</tbody>
</table>

Mercer et al, 2006
**Meta-Analysis, Rabe 2008**

- 10 studies, 454 infants
- Included 7 studies from Cochrane 2004
- Additional studies:
  - Mercer et al 2003 (32 infants <32 weeks)
  - Mercer et al 2006 (72 infants, <33 weeks)
  - Aladangady et al 2005 (46 infants, <33 weeks)
- Delayed cord clamping 30-120 seconds
- Variable positioning of infants
- Most included both vaginal and cesarean sections

**Meta-Analysis Summary**

Pros: ICC vs DCC

- IVH
  - RR 1.9 (95% CI 1.27-2.84)
  - 329 infants (7 studies)
- Transfusion
  - RR 2.01 (95% CI 1.24-3.27)
  - 111 infants (3 studies)
- Hematocrit 1 hour
  - MD -3.05 (95% CI -4.82, -1.29)
  - 216 infants (5 studies)

*No statistically significant differences in cord blood pH, Apgars, death or temperature on admission*

**Why a decrease in IVH with DCC?**

- DCC avoids disruption in cerebral blood flow autoregulation (Papile).
- ICC causes a rise in systemic resistance that may cause capillary rupture (Pietra)
- DCC increases cerebral oxygenation (Baenziger)
- DCC increases umbilical cord stem cells (Meier, Arien-Zakay)

**Why a decrease in late-onset sepsis with DCC?**

- Increased hematopoietic cells improve infant immunocompetence.
- Differences in expression of cytokines.
What is in cord blood?

Mankind’s first natural stem cell transplant

Jose N. Tolosa 1, Dong-Hyuk Park 3-5, David J. Eve 6, Stephen K. Klasko 6, Cesario V. Borlongan 1, Paul R. Sanberg 1 2 6

What about cord milking?

<table>
<thead>
<tr>
<th>RCT</th>
<th>Weight/GA</th>
<th>IVH</th>
<th>Trans</th>
<th>Bili</th>
<th>Other</th>
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<tbody>
<tr>
<td>Rabe et al, 2011</td>
<td>&lt;33wks</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Temp NS</td>
</tr>
<tr>
<td>(58) DCC vs milking</td>
<td>(1250gms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hosono et al,</td>
<td>&lt;39wks</td>
<td>NS</td>
<td>6 vs 13</td>
<td>NS</td>
<td>MBP 28 vs 24</td>
</tr>
<tr>
<td>2008 (40) ICC vs</td>
<td>(27)</td>
<td></td>
<td>p=0.03</td>
<td></td>
<td>p=0.04</td>
</tr>
<tr>
<td>milking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CLD @ 36wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

Preterm Literature summary

Pros

Cons

Preterm Protocols

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>24-32 weeks</th>
<th>24-32 weeks</th>
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</thead>
<tbody>
<tr>
<td>Delay</td>
<td>30-45 seconds</td>
<td>30-60 seconds</td>
</tr>
<tr>
<td>Position</td>
<td>Low w/o tension</td>
<td>Below placenta</td>
</tr>
<tr>
<td>Handling</td>
<td>Wrapped in towel</td>
<td>Dry/warm infant</td>
</tr>
<tr>
<td>Alternative</td>
<td>Cord milking</td>
<td>NA</td>
</tr>
</tbody>
</table>
UCSF Protocol Criteria:

- <35 weeks gestation,
- Singletons or di-di twins
- Delay >30 seconds
- Positioning below introitus, or by incision at cesarean
- Warm/dry infant

UCSF Consider Exclusion for:

- Congenital anomalies/chromosome abnormalities
- Meconium stained amniotic fluid
- Protocol may be terminated at Obstetrician/Pediatrician discretion

Umbilical Cord Clamping in Term Infants

- Multiple large studies in countries with a high prevalence of anemia
- JAMA Meta-analysis 2007
- Cochrane review 2008

Meta-Analysis Summary: Term Infants

- 15 studies
- 1912 infants
- Delay >2 minutes
- Findings at 2-4 months:
  - Hematocrit WMD 3.7 (CI 2.0-5.4)
  - Ferritin months WMD 17.9 (CI 16.6-19.2)
  - Stored iron months WMD 19.9 (CI 7.7-32.1)
  - Anemia RR 0.5 (CI 0.4-0.7)
  - Initial asymptomatic polycythemia RR 3.32 (1.11-13.2)

Hutton et al, 2007
Term Randomized Control Trial BMJ (country with low prevalence iron def )

- 400 Infants; >37 weeks gestation
- Randomized to:
  - ICC <10 seconds
  - DCC >180 seconds
- DCC group:
  - Infant held 20 cm below introitus for VD (x10 sec)
  - Placed on mother’s lap for C/S
  - Excluded for abruption or previa
- Outcomes (4 months):
  - higher mean ferritin concentration
    - 117 µg/L v 81 µg/L (P<0.001)
  - lower prevalence of iron deficiency
    - 1 (0.6%) v 10 (5.7%), P=0.01, nnt=20
  - No difference in polycythemia, jaundice or phototherapy

Andersson et al, 2011

What do you think the timing of umbilical cord clamping should be for infants <32 weeks gestation?

A. Immediately, no milking
B. Immediately after milking
C. 10-30 seconds
D. 31-60 seconds
E. >60 seconds
F. The literature is confusing me

What do you think the timing of umbilical cord clamping should be for infants >37 weeks gestation?

A. Immediately, no milking
B. Immediately after milking
C. 10-30 seconds
D. 31-60 seconds
E. >60 seconds
F. You are confusing me
Summary

• Preterm
  – UCSF Protocol delayed cord clamping > 30 secs
    • Decreased IVH
    • Decreased transfusions

• Term
  – Delayed Cord Clamping 1-3 minutes
    • Increase in ferritin (2-6 months)
    • Decrease in iron deficiency (2-6 months)

References

• Andersson O,Hellstrom-Westas L, Andersen D, Domellod M. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ. 2011;343:d7157
• Hutton E, Hassan E, Late vs Early Clamping of the Umbilical Cord in Full-term Neonates Systematic Review and Metaanalysis of Controlled trials. JAMA 2007;297:1341-1352

Thank You!

Perinatology
• Miriam Kuppermann
• Marya Zlatnik
• Mari-Paule Thiet

Neonatology
• Ronald Clyman
• Tom Shimotake
• Yao Sun

References

• Windle W. Brain Damage by Asphyxia at Birth. Scientific American 1969 Oct; 221(4):76-84
### RCT (n) Weight/GA (mean) Delay Posit

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight/GA (mean)</th>
<th>Delay</th>
<th>Posit</th>
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</thead>
<tbody>
<tr>
<td>Hofmeyr, 1988 (38)</td>
<td>&lt;35 wks (2100gm)</td>
<td>60s</td>
<td>--</td>
</tr>
<tr>
<td>Hofmeyr, 1993 (86)</td>
<td>&lt;2,000 gm</td>
<td>60-120s</td>
<td>Level</td>
</tr>
<tr>
<td>Kinmond, 1993 (36)</td>
<td>27-33wks (30)</td>
<td>30s</td>
<td>20cm</td>
</tr>
<tr>
<td>McDonnell, 1997 (46)</td>
<td>26-33wks (30)</td>
<td>30s</td>
<td>Level</td>
</tr>
<tr>
<td>Nelle, 1998 (19)</td>
<td>&lt;1,500 gm</td>
<td>&gt;30s</td>
<td>30cm</td>
</tr>
<tr>
<td>Rabe, 2000 (40)</td>
<td>&lt;33 wks (30)</td>
<td>45s</td>
<td>20cm</td>
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<tr>
<td>Oh, 2002 (33)</td>
<td>24-28 wks</td>
<td>30-45s</td>
<td>--</td>
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</table>

### Cochrane: ICC vs DCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Infants</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans Low BP</td>
<td>2</td>
<td>58</td>
<td>2.58</td>
<td>1.17-5.67</td>
</tr>
<tr>
<td>Trans Anemia</td>
<td>3</td>
<td>111</td>
<td>2.01</td>
<td>1.24-3.27</td>
</tr>
<tr>
<td>Number Transfusions</td>
<td>3</td>
<td>98</td>
<td>1.28 (MD)</td>
<td>0.58-1.98</td>
</tr>
<tr>
<td>Hematocrit 4 hours</td>
<td>4</td>
<td>134</td>
<td>-5.4 (MD)</td>
<td>-7.28,-3.52</td>
</tr>
<tr>
<td>Treated hyperbili</td>
<td>1</td>
<td>39</td>
<td>0.95</td>
<td>0.58-1.56</td>
</tr>
<tr>
<td>Bilirubin Diff (mmol/L)</td>
<td>3</td>
<td>111</td>
<td>-21.49 (MD)</td>
<td>-38.0,-4.9</td>
</tr>
</tbody>
</table>

### Cochrane: CNS ICC vs DCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Infants</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH</td>
<td>5</td>
<td>125</td>
<td>1.74</td>
<td>1.08,2.81</td>
</tr>
<tr>
<td>IVH Grade 3,4</td>
<td>3</td>
<td>161</td>
<td>0.86</td>
<td>0.15,4.75</td>
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<tr>
<td>Periventricular Leukomalacia</td>
<td>1</td>
<td>31</td>
<td>0.31</td>
<td>0.01,7.15</td>
</tr>
</tbody>
</table>

### Cochrane Summary: ICC vs DCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Infants</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH</td>
<td>5</td>
<td>225</td>
<td>1.74</td>
<td>1.08,2.81</td>
</tr>
<tr>
<td>Trans Low BP</td>
<td>2</td>
<td>58</td>
<td>2.58</td>
<td>1.17,5.67</td>
</tr>
<tr>
<td>Trans Anemia</td>
<td>3</td>
<td>111</td>
<td>2.01</td>
<td>1.24,3.27</td>
</tr>
<tr>
<td>Bilirubin Diff (mmol/L)</td>
<td>3</td>
<td>111</td>
<td>-21.49</td>
<td>-38.0,-4.9</td>
</tr>
<tr>
<td>Treated hyperbili</td>
<td>1</td>
<td>39</td>
<td>0.95</td>
<td>0.58,1.56 NS</td>
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</table>
### Cochrane: Other ICC vs DCC

<table>
<thead>
<tr>
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<th>Number of Infants</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord pH</td>
<td>3</td>
<td>123</td>
<td>0.01</td>
<td>-0.03, 0.05</td>
</tr>
<tr>
<td>5 min Apgar &lt;8</td>
<td>3</td>
<td>161</td>
<td>1.17</td>
<td>0.62, 2.20</td>
</tr>
<tr>
<td>Temperature</td>
<td>1</td>
<td>39</td>
<td>-0.20 (MD)</td>
<td>0.43, 0.03</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>2</td>
<td>72</td>
<td>2.08</td>
<td>0.52, 8.37</td>
</tr>
</tbody>
</table>

### Cochrane: Respiratory ICC vs DCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Infants</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilated for RDS</td>
<td>3</td>
<td>121</td>
<td>0.91</td>
<td>0.65, 1.28</td>
</tr>
<tr>
<td>O2 at 28 days</td>
<td>1</td>
<td>36</td>
<td>6.30</td>
<td>0.35, 113.81</td>
</tr>
<tr>
<td>O2 at 36 weeks</td>
<td>2</td>
<td>65</td>
<td>0.97</td>
<td>0.35, 2.69</td>
</tr>
</tbody>
</table>

### Meta-analysis = Cochrane + 3

<table>
<thead>
<tr>
<th>RCT (n)</th>
<th>Weight/GA (mean)</th>
<th>Delay</th>
<th>Posit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercer, 2003 (32)</td>
<td>&lt;32 wks (27)</td>
<td>30-45s</td>
<td>10-15”</td>
</tr>
<tr>
<td>Aladangady, 2005 (46)</td>
<td>&lt;33wks</td>
<td>30-90s</td>
<td>Low</td>
</tr>
<tr>
<td>Mercer, 2006 (72)</td>
<td>&lt;33wks (28)</td>
<td>30-45s</td>
<td>10-15” ↓</td>
</tr>
</tbody>
</table>

### Cochrane Review: Decreased transfusion for low BP in DCC

- Analysis 1.3: Comparison 1 Early versus delayed cord clamping, Outcome 3 Transfused for low blood pressure.
Cochrane Review: Decreased IVH in DCC

Analysis 1.13. Comparison I Early versus delayed cord clamping, Outcome I3 Intraventricular haemorrhage.

- Review: Early versus delayed unclamped cord clamping in preterm infants
- Comparison: I Early versus delayed cord clamping
- Outcome: I3 Intraventricular haemorrhage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early</th>
<th>Delayed</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Heterogeneity Chi² (df = 1)</th>
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</thead>
<tbody>
<tr>
<td>Holloway 1988</td>
<td>10/13</td>
<td>8/03</td>
<td>3.42</td>
<td>2.21</td>
<td>1.17, 4.77</td>
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</tr>
<tr>
<td>Holloway 1993</td>
<td>1/16</td>
<td>4/0</td>
<td>477%</td>
<td>2.20</td>
<td>1.20, 53.4</td>
<td></td>
</tr>
<tr>
<td>McDonald 1997</td>
<td>1/16</td>
<td>0/0</td>
<td>29%</td>
<td>2.62</td>
<td>0.15, 44.39</td>
<td></td>
</tr>
<tr>
<td>Oh 2002</td>
<td>4/17</td>
<td>2/16</td>
<td>1.11%</td>
<td>1.00</td>
<td>0.46, 1.89</td>
<td></td>
</tr>
<tr>
<td>Rate 2000</td>
<td>3/20</td>
<td>1/9</td>
<td>37%</td>
<td>2.65</td>
<td>0.13, 5.06</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 112 113

Outcome Number of Studies Number of Infants RR/MD CI

IVH 7 329 1.90 1.27, 2.84

Cochrane Review: Decreased transfusion for anemia in DCC

Analysis 1.2. Comparison I Early versus delayed cord clamping, Outcome 2 Transfused for anemia.

- Review: Early versus delayed unclamped cord clamping in preterm infants
- Comparison: I Early versus delayed cord clamping
- Outcome: 2 Transfused for anemia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Early</th>
<th>Delayed</th>
<th>Risk Ratio</th>
<th>Weight</th>
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<tr>
<td>Kennedy 1993</td>
<td>10/13</td>
<td>9/03</td>
<td>1.90</td>
<td>1.00</td>
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<tr>
<td>McDonald 1997</td>
<td>1/16</td>
<td>0/0</td>
<td>29%</td>
<td>1.50</td>
</tr>
<tr>
<td>Rate 2000</td>
<td>1/16</td>
<td>1/11</td>
<td>20%</td>
<td>1.12</td>
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Total (95% CI) 56 55

Outcome Number of Studies Number of Infants RR/MD CI

Transfusion 3 111 2.01 1.24, 3.27

Meta-Analysis Summary: ICC vs DCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Infants</th>
<th>RR/MD</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH</td>
<td>7</td>
<td>329</td>
<td>1.90</td>
<td>1.27, 2.84</td>
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<td>Hematocrit 1 hour</td>
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<td>216</td>
<td>-3.05</td>
<td>-4.82, -1.29</td>
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<td>Transfusion</td>
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<td>2.01</td>
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</table>

- No statistically significant differences in cord blood pH, Apgars, death or temperature on admission

Rabe et al, 2008
### Increased Red Cell Volume with DCC

<table>
<thead>
<tr>
<th>Author</th>
<th>Time of Cord Clamping</th>
<th>Red Cell Volume (ml/kg)</th>
<th>Time of Cord Clamping</th>
<th>Red Cell Volume (ml/kg)</th>
<th>Increase (%)</th>
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<tr>
<td>Full-Term Infants</td>
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<td>Ecker, et al.</td>
<td>&lt;10</td>
<td>60.6</td>
<td>5</td>
<td>27.4</td>
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<tr>
<td>Oh, et al.</td>
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<td>&lt;15</td>
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<tr>
<td>You, et al.</td>
<td>2.0</td>
<td>67.4</td>
<td>3</td>
<td>23.8</td>
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<tr>
<td>Present Study</td>
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<td>67.5</td>
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<td>&lt;5</td>
<td>38.3</td>
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<td>47.3</td>
<td>3</td>
<td>47.3</td>
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</tr>
</tbody>
</table>

Saigal et al., 1972

### Residual placenta blood volume by time and position

![Graph showing residual placenta blood volume by time and position]