Delayed Umbilical Cord Clamping and Cord Milking

Edward F. Bell

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Learning Objectives

1. Summarize the evidence for and against delayed clamping of the umbilical cord at the birth of term infants
2. Summarize the evidence for and against delayed cord clamping for preterm infants
3. Describe how this information should be translated into practice
4. Describe an alternative method of increasing the placental transfusion at birth
Historical Perspective on Timing of Cord Clamping

- Until the 20th century, babies were delivered at home by midwives, who usually waited to clamp the cord.
- Immediate cord clamping evolved with deliveries in hospital, in part to reduce postpartum hemorrhage.
- Adverse effects on infant recognized by mid 20th century.
THE EFFECT OF DEPRIVING THE INFANT OF ITS PLACENTAL BLOOD

ON THE BLOOD PICTURE DURING THE FIRST WEEK OF LIFE

Q. B. DeMARSH, M.S., B.M.
H. L. ALT, Ph.D., M.D.
AND
W. F. WINDLE, Ph.D.
WITH THE COOPERATION OF
DAVID S. HILLIS, M.D.
CHICAGO

JAMA 1941; 116:2568-73
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Although much has been written concerning the blood of the infant, knowledge of the early postnatal blood picture including changes at birth and during the first week of life is incomplete and controversial. Our interest in the blood of the newborn was stimulated by the numerous recent reports on collection of placental blood for "blood banks." Those who have advocated the use of placental blood for transfusion purposes, have failed to recognize possible deleterious effects on the infant when it is deprived of this blood. It is essential to clamp the umbilical cord immediately after birth in order to salvage an adequate amount of placental blood. Even when placental blood is not collected, the practice of clamping the cord promptly at birth is a rather common one.

It is natural for the newborn infant to retrieve most of the blood in its placental circulation if severing of the cord is delayed for a sufficiently long time. Haselhorst and Allmeling found that the average amount of blood in the placental vessels of 120 infants was 104 cc. They showed that 51 per cent of this flowed into the infant from the placenta in the first minute

COMMEN

Deprivation of the infant of placental blood by clamping the umbilical cord immediately results in significantly lower values for red blood corpuscles and hemoglobin during the first week of life than are encountered when clamping is delayed. In addition, there is an increase in the number of reticulocytes in the blood; this indicates an increased demand for blood on the part of the infant. The placental blood normally belongs to the infant, and his failure to get this blood is equivalent to submitting him to a rather severe hemorrhage.
CLAMPING OF THE UMBILICAL CORD*

Its Effect on the Placental Transfusion

Anthony E. Colozzi, M.D.†

Arlington, Massachusetts

CLAMPING OF THE UMBILICAL CORD*

Its Effect on the Placental Transfusion

ANTHONY E. COLOZZI, M.D.†

ARLINGTON, MASSACHUSETTS

It is difficult to assay the various methods of umbilical-cord clamping. Every physician employs a different technic and usually establishes a pattern that he carries out routinely in his obstetric work. At times this pattern is influenced by the equipment, the nursing situation, hospital policy in care of the newborn and various emergencies arising in the mother or the infant. Thus, in some cases, the infant is placed on the mother's abdomen while the physician attends to a bleeding episiotomy, or on a small delivery table beneath the level of the mother, with consequent delay in cord clamping. It has been observed that the cord is often clamped immediately, either as a routine procedure or so that the infant can be handed to a nurse for resuscitation and aspiration. At times, and because of recently renewed interest in the subject,

**Summary and Conclusions**

The fetal-placental circulatory physiology is briefly reviewed.

A study of four technics of cord clamping and their effect on the blood of 100 normally delivered infants is presented. Cord stripping is considered the most efficacious method of improving the infant's blood picture, with delayed clamping next in preference. Immediate clamping, by far the worst method, deprives the infant of blood.

Cord clamping apparently has no influence on the weight or general well-being of the normal infant delivered without obstetric complications. Such an infant can adjust itself adequately to a moderate anemia. Conversely, it is apparently no better off, at least clinically, with an increased amount of blood.

Cord stripping or delayed cord clamping or both are urged to effect a maximum placental transfusion in infants who are shocked after a traumatic delivery, anemic after a bleeding accident before or during birth, delivered by cesarean section or born prematurely.

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<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF CASES</th>
<th>RANGE ($x10^6$)</th>
<th>AVERAGE AFTER 24 HR. ($x10^6$)</th>
<th>AVERAGE AFTER 72 HR. ($x10^6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed, baby above plac</td>
<td>25</td>
<td>4.65-6.40</td>
<td>5.71</td>
<td>5.82</td>
</tr>
<tr>
<td>Immediate</td>
<td>25</td>
<td>3.99-5.50</td>
<td>4.74</td>
<td>4.78</td>
</tr>
<tr>
<td>Stripped</td>
<td>25</td>
<td>5.60-7.10</td>
<td>6.46</td>
<td>6.47</td>
</tr>
<tr>
<td>Delayed, baby below plac</td>
<td>25</td>
<td>4.50-6.50</td>
<td>5.80</td>
<td>5.80</td>
</tr>
</tbody>
</table>
Waiting to Clamp the Umbilical Cord May Be Better for Babies

Cord blood and stem cells continue to flow to newborn in minutes after birth, review finds

*Bloomberg Business Week, May 26, 2010*
Study Finds Benefits in Delaying Severing of Umbilical Cord

(cites new Cochrane review)
Study Finds Benefits In Delaying Severing Of the Umbilical Cord

BY CATHARINE SAINT LOUIS

In most hospital delivery rooms, doctors routinely clamp and sever the umbilical cord less than a minute after an infant's birth, a practice thought to reduce the risk of maternal hemorrhaging.

But a new analysis has found that delaying clamping for at least a minute after birth, which allows more time for blood to move from the placenta, significa-

Blood weight also was significantly higher on average in the late clamping group, in part because babies had been born with more blood from their mothers.

Delayed clamping did not increase the risk of severe postpartum hemorrhage, birth loss or reduced hemoglobin levels in mothers, the analysis found.

"It's a persuasive finding," said Dr. Ekelund. "It's tough to not think that delayed cord clamping, including better iron stores and higher hemoglobin, is a good thing.

The World Health Organization recommends clamping of the cord after one to three minutes because it "improves the iron status of the infant." Occasionally delayed clamping can lead to jaundice in infants, caused by liver trouble or an excessive loss of red blood cells, and so the W.H.O. advises that access to therapy for jaundice be taken into consideration.

By contrast, in December a committee opinion by the American College of Obstetricians and Gynecologists reviewed much of the evidence as the new analysis, but found it "insufficient to confirm or refute the potential benefits from delayed umbilical cord clamping in terms infant health, especially in settings with rich res-

Newborns with later clamping had higher hemoglobin levels 24 to 48 hours postpartum and were less likely to be iron-deficient three to six months after birth, compared with term babies who had early cord clamping, the analysis found.

The committee cited the risks of jaundice and the relative inre-

frequency of iron deficiency in the United States as reasons for not changing longstanding practice.

But Dr. Tonio Raju, a neonatologist and an author of the guidelines, said he personally favored delayed cord clamping, even more so after this "very strong paper.

The new report assessed data from 15 randomized trials involving 2,581 women and infant pairs. Eileen Batten, a midwife who has been a researcher at McMaster University in Ontario and published a systematic review on cord clamping, called the report "comprehensive and well done" but said she felt the conclusion was "weakly worded," consider-

ing the sum of evidence on the benefits of delayed cord clamping for neonates.

"The implications are huge," Dr. Batten said. "We are talking about delaying babies' access to iron for 80 percent of their blood at birth and just because we've learned a practice that's bad.

Said Dr. Raju, a medical officer at the National Institute of Child Health and Human Development: "It's a good chunk of blood the baby is going to get. If you wait a minute and a half or two minutes. They need that extra amount of blood to fill the lungs. Healthy babies manage to compensate if they do not get the blood from the cord, he said, but researchers do not know how.

American doctors hesitate to recommend delaying cord clamping universality, Dr. Raju said, because there can be situations in which early clamping is required — if an infant requires resuscitation, for example, or aspirates meconium, or infant stool.

The new analysis also found a 2 percent increase in jaundice among babies who got delayed cord clamping, compared with those who did not. Dr. Raju noted that the risk, although slight, increases the need for follow-up testing three to five days postpartum.

Susan McDonald, the lead author of the Cochrane review and a professor of midwifery at La

More time for blood to move from the placenta, at no added risk to the mother.

Trebo University in Melbourne, Australia, said, "in terms of a healthy start for a baby, one thing we can do by delaying cord clamping is boost their iron stores for a little bit longer.

The new analysis did not include many women who had Caesarean sections, so some experts noted.

"We don't have enough information on the effects of delayed cord clamping for some undergoing a Caesarean delivery in terms of postpartum hemorrhage," said Dr. Cynthia Gyamfi-Bannerman, medical director of the perinatal clinic at Columbia University. "Waiting 30 or 60 seconds in a vaginal delivery in a low-risk patient is probably something we could do and wouldn't have maternal conse-

quences, but in a caesarean delivery, you're hitting into a pronounced uterus that has a huge amount of blood." In some sce-

narios, there's an increased risk of postpartum hemorrhage.

Dr. McDonald acknowledged that the review did not include data on the long-term neurological outcomes for babies.

"What will sway ACOG are a couple of studies in progress showing a potential long-term neurological benefit," Dr. Raju said. Improved iron stores in the ers could help reduce the risk of learning deficiencies and cogni-

tive delay in children, which have been linked to iron-deficiency anemia in school-age children.
Term Infants
Early vs Delayed Cord Clamping for Term Infants

- Systematic review and meta-analysis
- 15 controlled trials, 1912 infants
- Delayed ≥ 2 minutes

- Delayed clamping associated with
  - Higher hematocrit (including more polycythemia, apparently benign) through 6 months
  - Higher iron stores (ferritin levels)
  - Less anemia

Hutton EK & Hassan ES. *JAMA* 2007;297:1241-52
Early vs Delayed Cord Clamping for Term Infants – Cochrane Review

- 15 controlled trials, 3911 infants

- Maternal outcomes
  - No difference in severe postpartum hemorrhage, regardless of whether uterotonic drugs were used
  - No difference in blood loss
  - No difference in hemoglobin 24-72 hours after delivery

Early vs Delayed Cord Clamping for Term Infants – Cochrane Review

- Neonatal outcomes
- Delayed cord clamping associated with
  - Higher birth weight (101 g, 95% CI 45-157)
  - Higher hemoglobin at 24-48 h (1.5 g/dl, 95% CI 1.2-1.8); trend toward increased polycythemia
  - Higher iron stores (ferritin levels) and lower risk of iron deficiency at 3-6 mo
  - More phototherapy for hyperbilirubinemia

## Birth Weight

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>early clamping</th>
<th>late clamping</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Al-Tawil 2012</td>
<td>90</td>
<td>3110.6 (540.8)</td>
<td>90</td>
<td>3348 (390.8)</td>
<td>-8.1 %</td>
</tr>
<tr>
<td>Andersson 2011</td>
<td>189</td>
<td>3533 (486)</td>
<td>193</td>
<td>3629 (460)</td>
<td>10.9 %</td>
</tr>
<tr>
<td>Cernadas 2006</td>
<td>93</td>
<td>3390 (395)</td>
<td>183</td>
<td>3422 (372)</td>
<td>10.8 %</td>
</tr>
<tr>
<td>Chaparro 2006</td>
<td>171</td>
<td>3196 (362)</td>
<td>187</td>
<td>3318 (369)</td>
<td>12.3 %</td>
</tr>
<tr>
<td>Emhamed 2004</td>
<td>46</td>
<td>3428 (424)</td>
<td>58</td>
<td>3390 (421)</td>
<td>6.8 %</td>
</tr>
<tr>
<td>Gupta 2002</td>
<td>29</td>
<td>2707 (417)</td>
<td>29</td>
<td>2744 (408)</td>
<td>4.9 %</td>
</tr>
<tr>
<td>Jahari 2008</td>
<td>30</td>
<td>3009 (573)</td>
<td>34</td>
<td>3272 (329)</td>
<td>4.3 %</td>
</tr>
<tr>
<td>McDonald 1996</td>
<td>480</td>
<td>3374 (493)</td>
<td>483</td>
<td>3416 (495)</td>
<td>13.3 %</td>
</tr>
<tr>
<td>Nelson 1980</td>
<td>26</td>
<td>3489 (453)</td>
<td>28</td>
<td>3437 (439)</td>
<td>4.1 %</td>
</tr>
<tr>
<td>Oxford Midwives 1991</td>
<td>256</td>
<td>3406 (441)</td>
<td>296</td>
<td>3432 (445)</td>
<td>12.4 %</td>
</tr>
<tr>
<td>Philip 1973</td>
<td>28</td>
<td>3543 (534)</td>
<td>29</td>
<td>3850 (452)</td>
<td>3.7 %</td>
</tr>
<tr>
<td>van Rheenen 2007</td>
<td>45</td>
<td>3119 (328)</td>
<td>46</td>
<td>3412 (326)</td>
<td>8.3 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1483</strong></td>
<td></td>
<td><strong>1656</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 5235.09; Chi² = 29.01, df = 11 (P = 0.002); I² = 62%

Test for overall effect: Z = 3.51 (P = 0.00044)
Test for subgroup differences: Not applicable

## Hemoglobin at 24-48 hours

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>early clamping</th>
<th>late clamping</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Uterotonic at, or after, clamping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 2011</td>
<td>160</td>
<td>17.5 (1.9)</td>
<td>162</td>
<td>18.9 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Emhamed 2004</td>
<td>46</td>
<td>17.1 (1.9)</td>
<td>58</td>
<td>18.5 (2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>206</strong></td>
<td><strong>18.3 (1.6)</strong></td>
<td><strong>220</strong></td>
<td><strong>19.0 (1.8)</strong></td>
<td></td>
</tr>
<tr>
<td>2 Use of uterotonic not specified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Tawil 2012</td>
<td>90</td>
<td>16.8 (2.9)</td>
<td>90</td>
<td>19.6 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Cernadas 2006</td>
<td>89</td>
<td>17.03 (2.3)</td>
<td>189</td>
<td>18.34 (2.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>179</strong></td>
<td><strong>17.9 (2.5)</strong></td>
<td><strong>279</strong></td>
<td><strong>19.0 (2.2)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>385</strong></td>
<td><strong>17.9 (2.5)</strong></td>
<td><strong>499</strong></td>
<td><strong>19.0 (2.2)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 6.56, df = 1 (P = 0.01); \hat{I}^2 = 85\%$

Test for overall effect: $Z = 6.68 (P < 0.00001)$

Test for subgroup differences: $\chi^2 = 0.83, df = 1 (P = 0.36), \hat{I}^2 = 0\%$
Iron Deficiency at 3-6 months

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>early clamping</th>
<th>late clamping</th>
<th>Risk Ratio M-H(Random,95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H(Random,95% CI)</td>
<td></td>
</tr>
<tr>
<td>1 Uterotonic at, or after; clamping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson 2011 (1)</td>
<td>10/175</td>
<td>1/172</td>
<td>12.0 % [1.27, 75.95]</td>
<td></td>
</tr>
<tr>
<td>van Rheenen 2007 (2)</td>
<td>28/39</td>
<td>27/39</td>
<td>27.7 % [0.78, 1.38]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>214</strong></td>
<td><strong>211</strong></td>
<td><strong>39.7 % [0.19, 40.19]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 38 (early clamping), 28 (late clamping)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 3.28; Chi² = 6.92, df = 1 (P = 0.01); I² = 86%</td>
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<tr>
<td>Test for overall effect: Z = 0.73 (P = 0.46)</td>
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<td></td>
</tr>
<tr>
<td>2 Use of uterotonic not specified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Tawil 2012 (3)</td>
<td>12/78</td>
<td>2/82</td>
<td>16.7 % [1.46, 27.28]</td>
<td></td>
</tr>
<tr>
<td>Cernadas 2006 (4)</td>
<td>13/86</td>
<td>16/166</td>
<td>24.7 % [0.79, 3.11]</td>
<td></td>
</tr>
<tr>
<td>Chaparro 2006 (5)</td>
<td>12/154</td>
<td>3/161</td>
<td>18.9 % [1.20, 14.53]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>318</strong></td>
<td><strong>409</strong></td>
<td><strong>60.3 % [1.18, 7.20]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events: 37 (early clamping), 21 (late clamping)</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Tau² = 0.33; Chi² = 4.11, df = 2 (P = 0.13); I² = 51%</td>
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<tr>
<td>Test for overall effect: Z = 2.31 (P = 0.021)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>532</strong></td>
<td><strong>620</strong></td>
<td><strong>100.0 % [1.04, 6.73]</strong></td>
<td></td>
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<tr>
<td>Total events: 75 (early clamping), 49 (late clamping)</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Tau² = 0.80; Chi² = 21.94, df = 4 (P = 0.000021); I² = 82%</td>
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<td>Test for overall effect: Z = 2.05 (P = 0.041)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0.0%</td>
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</tbody>
</table>
Preterm Infants
Hypothetical Benefits of Delayed Cord Clamping for Preterm Infants

- Provides an extra endowment of progenitor cells:
  - Increased RBC production
  - Increased WBCs may boost host immune defenses
Proven Benefits of Delayed Cord Clamping for Preterm Infants

- Increased blood volume
- Higher hemoglobin and blood pressure
- Reduced need for transfusion
- Improved cerebral oxygenation
- Reduced IVH, NEC, and late-onset sepsis
- One study found better neurodevelopmental outcome, but only followed to 7 months
- Only risk is increased hyperbilirubinemia
Delayed Cord Clamping (or Cord Milking) for Preterm Infants – Cochrane Review

- 15 trials, 738 infants
- Larger transfusion associated with
  - Higher hematocrit at 4 and 24 h
  - Reduced need for transfusion
  - Reduced IVH and NEC
  - Higher BP in first few hours
  - Higher peak serum bilirubin

Hematocrit at 4 hours

Transfused for Anemia

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1. More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 2. Transfused for anaemia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental trans</th>
<th>Less placental trans</th>
<th>Risk Ratio M-H (Fixed, 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio M-H (Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauss 2008</td>
<td>2/45</td>
<td>5/59</td>
<td></td>
<td>5.9 %</td>
<td>0.52 [0.11, 2.58]</td>
</tr>
<tr>
<td>Kugelman 2007</td>
<td>3/30</td>
<td>5/35</td>
<td></td>
<td>6.3 %</td>
<td>0.70 [0.18, 2.69]</td>
</tr>
<tr>
<td>McDonnell 1997</td>
<td>4/23</td>
<td>6/23</td>
<td></td>
<td>8.2 %</td>
<td>0.67 [0.22, 2.05]</td>
</tr>
<tr>
<td>Kinmond 1993</td>
<td>1/13</td>
<td>7/13</td>
<td></td>
<td>9.5 %</td>
<td>0.14 [0.02, 1.00]</td>
</tr>
<tr>
<td>Hosono 2008</td>
<td>7/20</td>
<td>14/20</td>
<td></td>
<td>19.0 %</td>
<td>0.50 [0.26, 0.97]</td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>9/19</td>
<td>16/20</td>
<td></td>
<td>21.2 %</td>
<td>0.59 [0.35, 1.00]</td>
</tr>
<tr>
<td>Mercer 2006</td>
<td>18/36</td>
<td>22/36</td>
<td></td>
<td>29.9 %</td>
<td>0.82 [0.54, 1.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>186</strong></td>
<td><strong>206</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.61 [0.46, 0.81]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 44 (More placental trans), 75 (Less placental trans)
Heterogeneity: $\chi^2 = 4.50$, df = 6 ($P = 0.61$); $I^2 = 0.0$
Test for overall effect: $Z = 3.46$ ($P = 0.00053$)
Test for subgroup differences: Not applicable
Inotropes for Low Blood Pressure

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: 19 Inotropics for low blood pressure

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental trans</th>
<th>Less placental trans</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
</tr>
<tr>
<td>Oh 2002</td>
<td>0/16</td>
<td>0/17</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>0/19</td>
<td>2/20</td>
<td>0.21 [0.01, 4.11]</td>
</tr>
<tr>
<td>McDonnell 1997</td>
<td>2/23</td>
<td>3/23</td>
<td>0.67 [0.12, 3.62]</td>
</tr>
<tr>
<td>Hosono 2008</td>
<td>7/20</td>
<td>17/20</td>
<td>0.41 [0.22, 0.77]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>78</td>
<td>80</td>
<td><strong>0.42 [0.23, 0.77]</strong></td>
</tr>
</tbody>
</table>

Total events: 9 (More placental trans), 22 (Less placental trans)
Heterogeneity: $\chi^2 = 0.50, df = 2 (P = 0.78); I^2 = 0.0%$
Test for overall effect: $Z = 2.84 (P = 0.0045)$
Test for subgroup differences: Not applicable
Intraventricular Hemorrhage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental trans n/N</th>
<th>Less placental trans n/N</th>
<th>Risk Ratio M-H Fixed, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauss 2008</td>
<td>1/45</td>
<td>1/60</td>
<td>1.5 % 1.33 [0.09, 20.75]</td>
<td>1.5 %</td>
</tr>
<tr>
<td>McDonnell 1997</td>
<td>0/15</td>
<td>1/16</td>
<td>2.5 % 0.35 [0.02, 8.08]</td>
<td>2.5 %</td>
</tr>
<tr>
<td>Oh 2002</td>
<td>4/16</td>
<td>3/17</td>
<td>5.0 % 1.42 [0.37, 5.37]</td>
<td>5.0 %</td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>1/19</td>
<td>3/20</td>
<td>5.1 % 0.35 [0.04, 3.09]</td>
<td>5.1 %</td>
</tr>
<tr>
<td>Kugelman 2007</td>
<td>2/30</td>
<td>4/35</td>
<td>6.4 % 0.58 [0.11, 2.96]</td>
<td>6.4 %</td>
</tr>
<tr>
<td>Mercer 2003</td>
<td>3/16</td>
<td>5/16</td>
<td>8.6 % 0.60 [0.17, 2.10]</td>
<td>8.6 %</td>
</tr>
<tr>
<td>Hosono 2008</td>
<td>3/20</td>
<td>5/20</td>
<td>8.6 % 0.60 [0.17, 2.18]</td>
<td>8.6 %</td>
</tr>
<tr>
<td>Hofmeyr 1993</td>
<td>8/40</td>
<td>11/46</td>
<td>17.7 % 0.84 [0.37, 1.87]</td>
<td>17.7 %</td>
</tr>
<tr>
<td>Hofmeyr 1988</td>
<td>8/23</td>
<td>10/13</td>
<td>22.1 % 0.45 [0.24, 0.85]</td>
<td>22.1 %</td>
</tr>
<tr>
<td>Mercer 2006</td>
<td>5/36</td>
<td>13/36</td>
<td>22.5 % 0.38 [0.15, 0.97]</td>
<td>22.5 %</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

| Total | 260 | 279 |

Total events: 35 (More placental trans), 56 (Less placental trans)

Heterogeneity: Chi² = 4.55, df = 9 (P = 0.87); I² =0.0%

Test for overall effect: Z = 2.82 (P = 0.0048)

Test for subgroup differences: Not applicable

Risk Ratio: 0.59 [0.41, 0.85]
Necrotizing Enterocolitis

### Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

#### Comparison: 1. More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

#### Outcome: 22 Necrotising enterocolitis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental trans</th>
<th>Less placental trans</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kugelman 2007</td>
<td>0/30</td>
<td>0/35</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>0/19</td>
<td>1/20</td>
<td>0.35 [ 0.02, 8.10 ]</td>
<td></td>
</tr>
<tr>
<td>Oh 2002</td>
<td>2/16</td>
<td>4/17</td>
<td>0.53 [ 0.11, 2.51 ]</td>
<td></td>
</tr>
<tr>
<td>Mercer 2003</td>
<td>8/16</td>
<td>14/16</td>
<td>0.57 [ 0.34, 0.96 ]</td>
<td></td>
</tr>
<tr>
<td>Mercer 2006</td>
<td>14/36</td>
<td>20/36</td>
<td>0.70 [ 0.42, 1.16 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>117</strong></td>
<td><strong>124</strong></td>
<td><strong>0.62 [ 0.43, 0.90 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 24 (More placental trans), 39 (Less placental trans)
Heterogeneity: Chi² = 0.48, df = 3 (P = 0.92); I² = 0.0%
Test for overall effect: Z = 2.53 (P = 0.011)
Test for subgroup differences: Not applicable

More PT better | Less PT better
Death

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental trans</th>
<th>Less placental trans</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercer 2003</td>
<td>0/16</td>
<td>0/16</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Kinmond 1993</td>
<td>0/17</td>
<td>0/19</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Strauss 2008</td>
<td>0/45</td>
<td>0/60</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Ultee 2008</td>
<td>0/18</td>
<td>0/19</td>
<td>0.00 [0.00, 0.00]</td>
</tr>
<tr>
<td>Hofmeyr 1988</td>
<td>5/24</td>
<td>0/14</td>
<td>6.60 [0.39, 111.10]</td>
</tr>
<tr>
<td>Hofmeyr 1993</td>
<td>1/40</td>
<td>1/46</td>
<td>1.15 [0.07, 17.80]</td>
</tr>
<tr>
<td>Kugelman 2007</td>
<td>0/30</td>
<td>1/35</td>
<td>0.39 [0.02, 9.16]</td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>0/19</td>
<td>1/20</td>
<td>0.35 [0.02, 8.10]</td>
</tr>
<tr>
<td>McDonnell 1997</td>
<td>0/23</td>
<td>2/23</td>
<td>0.20 [0.01, 3.95]</td>
</tr>
<tr>
<td>Baezinger 2007</td>
<td>0/15</td>
<td>3/24</td>
<td>0.22 [0.01, 4.04]</td>
</tr>
<tr>
<td>Oh 2002</td>
<td>2/16</td>
<td>3/17</td>
<td>0.71 [0.14, 3.70]</td>
</tr>
<tr>
<td>Hosono 2008</td>
<td>2/20</td>
<td>3/20</td>
<td>0.67 [0.12, 3.57]</td>
</tr>
<tr>
<td>Mercer 2006</td>
<td>0/36</td>
<td>3/36</td>
<td>0.14 [0.01, 2.67]</td>
</tr>
</tbody>
</table>

Total (95% CI) = 319 / 349 = 0.63 [0.31, 1.28]

Total events: 10 (More placental trans), 17 (Less placental trans)
Heterogeneity: Chi² = 5.14, df = 8 (P = 0.74); I² = 0.0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable
# Peak Serum Bilirubin

Review: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes

Comparison: More placental transfusion (delayed clamping) versus less placental transfusion (early clamping)

Outcome: Serum bilirubin peak (mmol/litre)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental transf</th>
<th>Less placental trans</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh 2002</td>
<td>13 (64.9)</td>
<td>16 (56.3)</td>
<td>4.2 %</td>
<td>29.06</td>
<td>-16.49, 74.61</td>
</tr>
<tr>
<td>Mercer 2003</td>
<td>20 (44.2)</td>
<td>20 (42.5)</td>
<td>8.8 %</td>
<td>1.69</td>
<td>-29.98, 33.36</td>
</tr>
<tr>
<td>Hosono 2008</td>
<td>20 (41.3)</td>
<td>20 (41.7)</td>
<td>12.2 %</td>
<td>6.80</td>
<td>-20.07, 33.67</td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>23 (47.9)</td>
<td>23 (42)</td>
<td>13.0 %</td>
<td>31.10</td>
<td>5.05, 57.15</td>
</tr>
<tr>
<td>McDonnell 1997</td>
<td>30 (47.9)</td>
<td>35 (39.33)</td>
<td>15.0 %</td>
<td>11.00</td>
<td>-13.27, 35.27</td>
</tr>
<tr>
<td>Kugelman 2007</td>
<td>36 (41.04)</td>
<td>36 (35.91)</td>
<td>19.0 %</td>
<td>22.40</td>
<td>0.87, 43.93</td>
</tr>
<tr>
<td>Mercer 2006</td>
<td></td>
<td></td>
<td>27.8 %</td>
<td>10.26</td>
<td>-7.55, 28.07</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>157</strong></td>
<td><strong>163</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>15.01 [5.62, 24.40]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.70, df = 6 (P = 0.72); I² = 0.0%
Test for overall effect: Z = 3.13 (P = 0.0017)
Test for subgroup differences: Not applicable
Delay in umbilical cord clamping for at least 1 minute is recommended for newborn infants not requiring resuscitation.

There is insufficient evidence to support or refute a recommendation to delay cord clamping in babies requiring resuscitation.
For all infants except those who require positive-pressure ventilation, cord clamping should be delayed for at least 1 min after birth (2012)

For preterm infants, delay of 30-120 sec is associated with reduced need for transfusion and reduced IVH (2006)

“The beneficial effects of delayed cord clamping may yield the greatest benefits in settings where access to health care is limited”
Timing of Umbilical Cord Clamping After Birth

ABSTRACT: The optimal timing for clamping the umbilical cord after birth has been a subject of controversy and debate. Although many randomized controlled trials in term and preterm infants have evaluated the benefits of delayed umbilical cord clamping versus immediate umbilical cord clamping, the ideal timing for cord clamping has yet to be established. Several systematic reviews have suggested that clamping the umbilical cord in all births should be delayed for at least 30–60 seconds, with the infant maintained at or below the level of the placenta because of the associated neonatal benefits, including increased blood volume, reduced need for blood transfusion, decreased incidence of intracranial hemorrhage in preterm infants, and lower frequency of iron deficiency anemia in term infants. Evidence exists to support delayed umbilical cord clamping in preterm infants, when feasible. The single most important clinical benefit for preterm infants is the possibility for a nearly 50% reduction in intraventricular hemorrhage. However, currently, evidence is insufficient to confirm or refute the potential for benefits from delayed umbilical cord clamping in term infants, especially in settings with rich resources.
However, . . .

- Despite evidence of efficacy, delayed cord clamping has not been widely incorporated into practice

- Possible reasons include concern about delaying newborn resuscitation of infants who need it – the ones who also stand to benefit the most from a larger placental transfusion
An Alternate Strategy for Increasing Placental Transfusion
Umbilical Cord Milking

- An alternate method of increasing volume transferred from placenta to infant at birth

Hosono et al.
- Arch Dis Child Fetal Neonatal Ed. 2008; 93:F14
- Arch Dis Child Fetal Neonatal Ed. 2009; 94:F328

RCT: 40 infants <29 weeks gestation
- Cord milking vs early clamping

- Infants in milking group had higher initial hemoglobin, higher BP, and reduced need for transfusion
Umbilical Cord Milking Techniques

- **Hosono 1** (published)
  - Cord milked 2 or 3 times toward infant before clamping

- **Hosono 2** (personal communication)
  - Cord clamped and cut as close to placenta as possible, then milked once toward infant

- **Rabe** (*Obstetrics & Gynecology* 2011)
  - Cord milked 4 times toward infant before clamping

- Estimated volume of blood transferred by milking 15 ml/kg
Video

- Hosono technique #2
Rabe et al Cord Milking Trial

- Randomized clinical trial of milking the cord four times vs 30-second delay in clamping
- 58 infants <33 weeks gestation
- Similar initial and subsequent hemoglobin levels
- No difference in need for transfusion
- Methods provide equivalent volumes of placental transfusion

Rabe et al. Obstet Gynecol. 2011
Umbilical Cord Milking vs Delayed Cord Clamping

- Unpublished estimates suggest similar volume can be provided
- Milking (Hosono’s second technique) occurs after infant handed off from obstetrician to neonatology team
- Takes less time: 10-15 sec vs 60-120 sec
- Reduces concerns about delaying resuscitation
Benefits shown for both techniques
- Increased initial hemoglobin
- Higher blood pressure
- Reduced need for transfusion

Benefits of delayed clamping not yet shown with milking
- Increased blood volume
- Improved respiratory function
- Improved cerebral oxygenation
- Reduced IVH
- Reduced NEC
Conclusions – Term Infants

- In term infants, delaying cord clamping for 60 to 120 seconds results in:
  - Transfer of larger volume of blood
  - Larger iron stores and less iron deficiency
  - No risk except more frequent hyperbilirubinemia and benign polycythemia

- This practice should be routine
Conclusions – Preterm Infants

- In preterm infants, delaying cord clamping for 60 to 120 seconds results in:
  - Increased blood volume
  - Raised hemoglobin and blood pressure
  - Reduced need for transfusion and inotropes
  - Improved cerebral oxygenation
  - Reduced IVH and NEC
  - Only risk is higher peak bilirubin

- This practice should be routine (However, ...)}
Conclusions – Preterm Infants

What about the infant whose resuscitation must be started before 60 seconds?

- The placenta may continue to provide adequate gas exchange until the cord is clamped
- Some advise proceeding with the resuscitation while the infant is attached to the placenta
- Cord milking may provide a good alternative – quicker (allowing resuscitation to be started sooner) and equally effective as delayed clamping; but, more research is needed, including long-term neurodevelopmental outcome
Unresolved Issues (Raju and Singhal)

- **Maternal**
  - How should cord clamping time be managed in the presence of maternal hemorrhage?

- **Resuscitation**
  - How should cord clamping be handled if the infant needs resuscitation?
  - Can resuscitation be conducted while the cord is still attached to the undelivered placenta?
  - When is the time of birth? How are other events timed with respect to birth?
Unresolved Issues

- **Cord Clamping**
  - How long should cord clamping be delayed? *
  - What should the baby’s position be while waiting to clamp the cord: in a vaginal birth; in a cesarean birth?
  - Should delayed cord clamping or milking be extended to the most preterm infants?

* See next slide
A Physiological Approach to the Timing of Umbilical Cord Clamping

- If the umbilical cord is clamped before the infant starts breathing, cardiac venous return and cardiac output will be compromised.

- Once the infant breathes, lung aeration triggers a large increase in pulmonary blood flow, cardiac filling, and left ventricular output.

- Therefore, the appropriate time for cord clamping is after breathing is established.

Physiological-Based Cord Clamping

Traditional Early Cord Clamping

Unresolved Issues

- Delayed Cord Clamping vs Cord Milking
  - Are the benefits and risks the same for these two techniques?
  - What length of cord should be milked?
  - How fast and how many times should the cord be milked?

- Infants at Increased Risk of Polycythemia
  - How should the placental transfusion be managed for infants born at high altitude? Infants of diabetic mothers? SGA or LGA infants?