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Delayed Cord Clamping in Very Preterm Infants Reduces the Incidence of Intraventricular Hemorrhage and Late-Onset Sepsis: A Randomized, Controlled Trial

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. This study compared the effects of immediate (ICC) and delayed (DCC) cord clamping on very low birth weight (VLBW) infants on 2 primary variables: bronchopulmonary dysplasia (BPD) and suspected necrotizing enterocolitis (SNEC). Other outcome variables were late-onset sepsis (LOS) and intraventricular hemorrhage (IVH).

STUDY DESIGN. This was a randomized, controlled unmasked trial in which women in labor with singleton fetuses <32 weeks’ gestation were randomly assigned to ICC (cord clamped at 5–10 seconds) or DCC (30–45 seconds) groups. Women were excluded for the following reasons: their obstetrician refused to participate, major congenital anomalies, multiple gestations, intent to withhold care, severe maternal illnesses, placenta abruption or previa, or rapid delivery after admission.

RESULTS. Seventy-two mother/infant pairs were randomized. Infants in the ICC and DCC groups weighed 1151 and 1175 g, and mean gestational ages were 28.2 and 28.3 weeks, respectively. Analyses revealed no difference in maternal and infant demographic, clinical, and safety variables. There were no differences in the incidence of our primary outcomes (BPD and suspected NEC). However, significant differences were found between the ICC and DCC groups in the rates of IVH and LOS. Two of the 23 male infants in the DCC group had IVH versus 8 of the 19 in the ICC group. No cases of sepsis occurred in the 23 boys in the DCC group, whereas 6 of the 19 boys in the ICC group had confirmed sepsis. There was a trend toward higher initial hematocrit in the infants in the DCC group.

CONCLUSIONS. Delayed cord clamping seems to protect VLBW infants from IVH and LOS, especially for male infants.
The current obstetric practice in the United States is to clamp the umbilical cord of the very low birth weight (VLBW) infant immediately after delivery. However, delaying cord clamping and lowering the infant below the perineum or incision site at cesarean section have been shown to significantly increase transfer of blood from the placenta to the infant. A delay of 30 to 45 seconds in cord clamping of preterm infants results in an 8% to 24% increase in blood volume (2–16 mL/kg after cesarean birth and 10–28 mL/kg after vaginal birth). Immediate cord clamping (ICC) may deprive the VLBW infant of essential blood volume and create a state of potential circulatory compromise resulting in hypotension and poor perfusion of tissues.

Nine randomized, controlled trials over the last decade have documented the safety and efficacy of delayed cord clamping (DCC) in low birth weight or VLBW infants. Benefits include higher blood pressure, higher hematocrit levels, more optimal oxygen transport and higher red blood cell flow, fewer days on oxygen and ventilation, fewer transfusions, and lower rates of intraventricular hemorrhage (IVH). Previous studies of cord-clamping interventions, however, have been limited by small sample size, inconsistent definition of variables, and lack of follow-up beyond 6 weeks.

In a prior pilot study, we validated the feasibility and safety of the protocol for DCC as well as immediate and short-term physiological advantages of DCC. Findings included higher initial blood pressure, less suspected necrotizing enterocolitis (SNEC), and fewer infants discharged on oxygen. Based on this pilot data, we hypothesized that the additional red blood cells obtained by delaying cord clamping may result in lower incidence of bronchopulmonary dysplasia (BPD).

The objective of this study was to compare the incidence of BPD in infants <32 weeks’ gestation randomly assigned to early (<10 seconds) and late (30–45 seconds) cord clamping. The study was also designed to evaluate the effects of DCC on other neonatal morbidities, including late-onset sepsis (LOS), IVH, and retinopathy of prematurity (ROP).

**MATERIALS AND METHODS**

This randomized, controlled trial was conducted between August 2003 and December 2004 at Women and Infants’ Hospital of Rhode Island. The study was approved by the institutional review boards at Women and Infants’ Hospital and the University of Rhode Island. An independent data safety and monitoring committee consisting of a maternal-fetal medicine obstetrician, a neonatologist, a nurse physiologist, and a nurse statistician reviewed the data after 14 and again after 50 patients were randomly assigned.

The primary outcome variable was BPD and the secondary outcome variables were SNEC, IVH, LOS, and ROP. Other outcome variables included: Apgar scores, temperature on arrival in the NICU, the highest serum bilirubin level, initial and hourly blood pressures for 4 hours, initial hematocrit, and need for blood transfusion during the infant’s hospital stay.

All women admitted between 24 and 31.6 weeks’ gestation with preterm labor were candidates for inclusion in the study. The gestational age assessment using last menstrual period and/or early pregnancy ultrasound was used to establish eligibility for the study. Exclusion criteria included: obstetrician’s refusal to participate, major congenital anomalies or multiple gestations, intent to withhold care, severe maternal illnesses, or placenta abruption or previa. Women had to be admitted to the hospital at least 2 hours before delivery to allow time for enrollment. Once a potential subject was identified, approval of the attending obstetrician was obtained, the mother was approached, and written informed consent was obtained.

A statistician who was not involved in the trial developed a computer-generated random number system. Block-stratified randomization was used to assign the intervention to the subjects above and below 28 weeks with a prespecified equal probability to avoid unequal numbers of participants in each gestational age group. Two sets of cards labeled for randomization were enclosed in sequenced, opaque envelopes containing group assignment and kept in the labor unit. Research assistants who were registered nurses and the principal investigator (J.S.M.) shared an on-call schedule to screen potentially eligible women, enroll them, and attend the births. When called for a subject’s impending birth, the principal investigator or RN opened the next randomization card, informed the staff of the group assignment, reviewed the protocol with the attending obstetrician, attended the birth, and timed the cord clamping.

Women were assigned to receive either ICC or DCC. For the ICC group, the obstetrician clamped the umbilical cord immediately (<10 seconds) after birth. For the DCC group, the obstetrician clamped the cord at 30 to 45 seconds and held the infant in a sterile towel or blanket approximately 10 to 15 inches below the mother’s incision at vaginal delivery or below the level of the incision at cesarean section. Care was taken that no tension or traction was placed on the cord. A stopwatch was used to mark the time when the infant’s buttocks were delivered from the vagina or the uterus (or head if breech), and then the time elapsed was counted out in 10-second intervals for the obstetrician. At 30 to 45 seconds, the obstetrician clamped and cut the umbilical cord, and the infant was moved to the radiant warmer for care. Infants in both groups were supplied with an additional warming mattress (Transwarmer Infant Mattress; Cooper Surgical, Trumbull, CT) to assist in maintaining temperature. The obstetricians could alter the protocol based on their clinical judgment, although this
event did not occur throughout the course of the study. In the event that the timing of the cord clamping was <30 seconds and the infant was randomly assigned to the DCC group, a protocol violation report was completed and the infant remained in the late clamped group (intention to treat).

The subsequent clinical management of the infants was at the discretion of the attending neonatologists. Because of the obvious nature of the intervention, the study could not be blinded. Our institutional policy requires the presence of a pediatric staff member because of low gestation. However, staff that attended each birth adhered to the principal investigator’s request not to reveal the infant’s grouping in the infant’s medical charts.

Prenatal and delivery data were collected from the mothers’ charts. Time of cord clamping, placement of the infant, Apgar scores, and time and date of birth were collected in the labor unit. Infant data were collected after 12 hours of age and after discharge. BPD was defined as requiring oxygen therapy up to 36 weeks’ postmenstrual age or death. SNEC was defined as clinical impression when the neonatology staff ordered a radiograph to rule out NEC and the infant was made NPO (nothing by mouth) for at least 24 hours. Cranial ultrasound (CUS) readings used the grading system of Papile: grade 1 is a germinal matrix hemorrhage; grade 2 is extension into the lateral ventricle with blood filling <50% of the ventricular area; grade 3 is IVH with distension or dilatation of the lateral ventricles with blood; and grade 4 is IVH with parenchymal involvement. CUS were read by a single pediatric radiologist (M.W.) who was blinded to the infant’s grouping. Late-onset sepsis was defined as blood culture-positive in infants >72 hours of age. NEC was diagnosed based on Bell’s criteria and ROP was identified by an ophthalmologist per our routine eye examinations during the infants stay in the nursery.

Power analysis was based on the event rate of BPD (56%) in the control group of our pilot study with a 30% relative reduction that would result in a 39% event rate. An α level of .05, and a β level of .20 with a medium effect size ($r = 0.30$), was used to determine that 26 infants were needed in each cord-clamping interval group. An oversampling of 20% brought each group to 36 infants for a total of 72 subjects. All data were analyzed on an intention-to-treat basis. Despite directional primary hypotheses, we used 2-tailed tests to be as conservative as possible. Continuous variables were examined with Student $t$ test and categorical variables were tested by using $\chi^2$ and Fisher’s exact test if cells contained counts <5. Logistic regression was used to control for gestational age and obtain odds ratios for significant findings.

RESULTS

Figure 1 shows the distribution of the 296 women who were admitted with preterm labor and who were screened for eligibility for this study. All additional analyses were performed on the 72 randomly assigned subjects.

There were 7 protocol violations. Six occurred in the DCC group with cord-clamping time ranging between 2 and 18 seconds instead of 30 seconds. These were mainly as a result of miscommunication at births. There was 1 protocol violation in the ICC group when a physician delayed clamping for 25 seconds as a result of a misunderstanding of the protocol. All infants remained in their assigned groups for analyses.

Table 1 shows no significance difference in maternal demographics, clinical characteristics, and medical management.

Table 2 shows no significant difference in the demographic and clinical characteristics of the study infants. Cord-clamping time was significantly different per protocol; infants in the DCC group had significantly longer cord-clamping times (32 ± 13 vs 7 seconds ± 4; $P < .001$). All other neonatal variables, including those used for safety (1- and 5-minute Apgar scores, temperature on admission, serum bilirubin levels), were not significantly different between the groups.

Table 3 shows that there were no significant differences in the incidence of death or BPD, NEC, amount of blood loss and transfusion, and ROP between the 2 groups. There were also no differences between the infants in surfactant use (27 vs 24), days of ventilation (39 vs 35), and oxygen use at 28 days (11 vs 13) for the ICC and DCC groups, respectively.

Table 4 shows that infants in the DCC group had less IVH (five [14%] vs 13 [36%]; $P = .03$) during the first 28 days in the NICU. The incidence of IVH was equally divided between the stratified groups (~28 weeks = 10; 28 ± weeks = 8), although the majority occurred in infants <30 weeks gestation (data not shown). In the infants <28 weeks, 7 (47%) of the 15 infants in the ICC group had IVH vs 3 (21%) of the 14 infants in the DCC group (not significant), whereas in those born after 28 weeks, 6 (29%) of 21 in the ICC group and 2 (10%) of 22 in the DCC group had IVH.

Similar number of infants in each group received low-dose indomethacin for IVH prophylaxis within the first 24 hours. All of the infants between 24 and 27 weeks had indomethacin, whereas 59% and 62% received indomethacin in the DCC and ICC groups, respectively. The grade 4 IVH was not seen until day of life 12. One infant in the DCC group with IVH was a protocol violation and had ICC.

We compared all infants with IVH ($n = 18$) with all infants without IVH ($n = 54$). Infants with IVH had shorter time between birth and cord clamping (13 vs 22 seconds; $P = .04$) and were less likely to have had a
cesarean delivery (three [17%] vs 15 [48%]; \(P = .03\)). There was no relationship between IVH and sepsis.

Table 4 shows that infants in the DCC group were less likely to have blood culture-proven sepsis during the NICU stay (3% vs 22%; \(P = .03\)). Six cases of confirmed sepsis occurred in the 24- to 27-week-old infants, whereas 3 were in infants 28 to 31 weeks. Of the 9 infants who had LOS, 7 (78%) occurred between 11 and 18 days of age. Infants with sepsis had lower initial hematocrit levels at birth (48 ± 6 vs 42 ± 5; \(P = .03\)) even when controlling for gestational age.

Analyses by gender revealed that male infants had an advantage with DCC for IVH, sepsis, and NEC. Gender effects are shown in Table 5.

There were no adverse events or deaths in the DCC group. Three infants died in the ICC group. The causes of...
TABLE 1  Maternal Demographics, Clinical Characteristics, and Prenatal Medical Management

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ICC (n = 36)</th>
<th>DCC (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s age, mean ± SD, y</td>
<td>26.8 ± 6.5</td>
<td>27.1 ± 6.7</td>
</tr>
<tr>
<td>Primiparas, n (%)</td>
<td>25 (69)</td>
<td>23 (64)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4 (11)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>White</td>
<td>20 (56)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (30)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Public insurance, n (%)</td>
<td>17 (47)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>Received antenatal steroids, n (%)</td>
<td>36 (100)</td>
<td>36 (100)</td>
</tr>
<tr>
<td>Received antenatal MgSO4 in 24 h before birth, n (%)</td>
<td>21 (58)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>Premature rupture of membranes, mean ± SD, h</td>
<td>40 ± 44</td>
<td>41 ± 47</td>
</tr>
<tr>
<td>Cesarean section, n (%)</td>
<td>14 (39)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Reasons for preterm birth, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
<td>19 (53)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>19 (53)</td>
<td>16 (44)</td>
</tr>
<tr>
<td>Presumed chorioamnionitis</td>
<td>10 (28)</td>
<td>11 (31)</td>
</tr>
<tr>
<td>Incompetent cervix</td>
<td>5 (14)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension</td>
<td>5 (14)</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

None of the differences are statistically significant.

a Some mothers had >1 condition.

TABLE 2  Neonatal Demographic, Clinical, and Safety Variables

<table>
<thead>
<tr>
<th></th>
<th>ICC (n = 36)</th>
<th>DCC (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, mean ± SD (range), g</td>
<td>1151 ± 379</td>
<td>1175 ± 346</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>28.2 ± 2.4</td>
<td>28.3 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>24 wk 0 d to 27 wk 6 d, n</td>
<td>15</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>28 wk 0 d to 31 wk 6 d, n</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>19/17</td>
<td>23/13</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score, median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>7 (1–9)</td>
<td>7 (1–9)</td>
<td>NS</td>
</tr>
<tr>
<td>5 min</td>
<td>8 (1–9)</td>
<td>8 (2–9)</td>
<td></td>
</tr>
<tr>
<td>Temperature on admission to NICU, °F (range)</td>
<td>96.8 ± 1.5 (92.8–99.3)</td>
<td>97.1 ± 1.2 (94–99.4)</td>
<td>NS</td>
</tr>
<tr>
<td>°C (range)</td>
<td>36 ± 0.8(33.8–37.4)</td>
<td>36.2 ± 6 (34.4–37.4)</td>
<td></td>
</tr>
<tr>
<td>Maximum serum bilirubin, mg/dL (range)</td>
<td>9.5 ± 2.10 (5.5–13.8)</td>
<td>10.1 ± 2.4 (6.6–15.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial hematocrit, %</td>
<td>46 ± 6 (34–60)</td>
<td>49 ± 6 (37–62)</td>
<td>.06</td>
</tr>
<tr>
<td>Mean of first 4-h mean blood pressure</td>
<td>31.9 ± 6</td>
<td>33.8 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>SNAP scores</td>
<td>13.3 ± 12</td>
<td>12.3 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Cord clamp time, sec (range, median)</td>
<td>6.9 ± 4.3 (1–25.5)</td>
<td>32.1 ± 12.6 (2–49.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant; SNAP, Score for Neonatal Acute Physiology.

death included fulminating NEC (two) and terminal respiratory failure with probable sepsis syndrome.

Additional multivariate analyses were performed to evaluate the association of cord clamping with IVH and LOS. The impact of cord-clamping group on IVH was evaluated adjusting for gestational age and cesarean section. The final model indicated that the IVH rate was >3 times higher in the ICC group (odds ratio [OR]: 3.5, 95% confidence interval [CI] 1.1–11.1). A similar model for LOS adjusted for gestational age showed that infants in the DCC group were less likely to have sepsis (OR: 0.10, 95% CI: 0.01–0.84).

The eligible women not enrolled during the study period did not differ from the 72 randomly assigned participants on any of the demographic variables. They differed from randomly assigned women only in antenatal steroid use (87% vs 100%; P = .01), premature rupture of membranes in hours (20 ± 36 vs 40 ± 45; P = .01), and cesarean section rate (64% vs 40%; P = .01). Infants of eligible women not enrolled differed from study infants only on admission temperature (96.3 ± 1.4 vs 97 ± 1.4; P = .01). There was no significant difference in the overall incidence of IVH (25% vs 18%; P = .35) or sepsis (3% vs 8%; P = .42) between the subjects and the infants of eligible women not enrolled.

DISCUSSION

Our primary null hypothesis was that infants in the DCC group would have the same rate of BPD based on the results from the pilot study. The null hypothesis proved to be true. The reason for the failure to reject the null hypothesis is that the study event rate of BPD in the ICC
group (25%) turned out to be much lower than the event rate used for sample size calculation (56%) resulting in an underpowered estimate. The finding that DCC resulted in less IVH and less sepsis was unanticipated.

Our data indicates that a brief delay in cord-clamping time accompanied by lowering the infant to hasten the placental transfusion offers protection from IVH and LOS. The fact that the groups had almost identical demographic and baseline characteristics shows that the randomization process was successful. Like in our previous pilot study, this study provided evidence that the protocol does not put even the smallest infants at risk of harm.

The theoretical foundation for the study was that the additional blood volume received as a result of DCC would help to reduce neonatal morbidity by providing more blood volume and improving cardiovascular stability. The preterm infant has less fetal-placental blood volume in his body at any point in time than the term infant making him more likely to have a deficit if immediate reduced blood pressure or lower hematocrit immediately reduced blood pressure or lower hematocrit may be disruption of the autoregulation essential to stabilize cerebral blood flow and prevent a pressure-passive circulation.21 If the infant is not homeodynamically stable, there may be ischemic injury to the brain, the gastrointestinal tract, and the lung.

Reduced blood volume does not necessarily result in immediately reduced blood pressure or lower hematocrit because the infant’s cardiovascular system increases vascular resistance to stabilize blood pressure.25 Increased capillary permeability in the preterm newborn allows rapid fluid shifts.5 These factors and lack of available accurate measurement techniques for blood volume, make hypovolemia difficult to verify in the newborn, although its effect may be profound. DCC allows time for placental transfusion to supply essential blood volume to the infant and lowering the infant speeds the transfer of blood volume.26

The finding that IVH was higher in the immediately clamped group is consistent with the recent meta-analysis of randomized, controlled trials on DCC in preterm infants.11 Other authors have reported reduced cerebral blood volume preceding development of IVH.27,28 Any reduction in IVH is important because of its association with later morbidity, mortality, and/or developmental delay.29 Even grades 1 and 2 are not without sequelae.30

Our nursery practiced prophylactic indomethacin to prevent IVH based on the study of Ment et al.31 However, the number of infants receiving this intervention was similar between the 2 study groups.

All the infants with confirmed LOS had immediate cord clamping. The one listed for the DCC group was a protocol violation and her cord was clamped at 3 seconds. This finding is important as LOS continues to be an important cause of morbidity and mortality in the NICU and neurodevelopmental delay.32 We speculate that sepsis may be a result of immunocompromise as a result of loss of protective primitive hematopoietic progenitor cells along with blood volume at birth. The cord blood of preterm infants (24–31 weeks) contains the highest concentration of primitive hematopoietic progenitor cells

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**TABLE 3** Neonatal Morbidities, Blood Loss, and Transfusions

<table>
<thead>
<tr>
<th></th>
<th>ICC (n = 36), n (%)</th>
<th>DCC (n = 36), n (%)</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or BPD (O2 therapy at 36 wk)</td>
<td>9 (25)</td>
<td>8 (22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge on O2</td>
<td>4 (12)</td>
<td>5 (14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>20 (56)</td>
<td>14 (39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC, Bell’s19 stage</td>
<td>No sign</td>
<td>25 (69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2a</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perfusion</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood loss: week 1, mL</td>
<td>11.4 ± 5.8</td>
<td>11.3 ± 5.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants transfused</td>
<td>22 (61)</td>
<td>18 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusions</td>
<td>2.47 ± 3.7</td>
<td>1.94 ± 3.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total amount transfused, mL</td>
<td>33 ± 45</td>
<td>27 ± 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROP (all)</td>
<td>13 (40)</td>
<td>10 (28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (8)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of the differences are statistically significant.

* Number of 33 for the ICC group because 3 infants in the ICC group died before 1 month of age.

---

**TABLE 4** IVH and LOS in Study Infants

<table>
<thead>
<tr>
<th></th>
<th>ICC (n = 36), n (%)</th>
<th>DCC (n = 36), n (%)</th>
<th>P</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH</td>
<td>All IVH</td>
<td>13 (36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 1</td>
<td>4 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>8 (22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>1 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>8 (22)</td>
<td>1 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**TABLE 5** Gender Differences in IVH, LOS, and NEC Among Infants With ICC and DCC

<table>
<thead>
<tr>
<th></th>
<th>ICC</th>
<th>DCC</th>
<th>Boys (n = 19),</th>
<th>Girls (n = 17),</th>
<th>Boys (n = 23),</th>
<th>Girls (n = 13),</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>IVH</td>
<td></td>
<td></td>
<td>8 (42)</td>
<td>5 (29)</td>
<td>2 (9)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
<td>6 (32)</td>
<td>2 (12)</td>
<td>0 (0)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>NEC</td>
<td></td>
<td></td>
<td>3 (16)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>

* Differences for boys between groups; P < .05, Fisher’s exact test.
and long-term culture-initiating cells when compared with the cord blood of infants closer to term.33

The apparent protective effect of delayed cord clamping for the male infants suggests the hypothesis that the additional blood volume the infant obtains may have gender-specific neuroprotective and immunoprotective effects. This finding is of interest because there is increasing evidence of gender-specific differences in neonates. For example, indomethacin has been shown to exhibit gender-specific effects on cerebrovascular reactivity, which were associated with a significantly decreased rate of IVH in boys.34

Limitations of this study are that the primary null hypothesis was accepted because the study was underpowered as a result of the use of a high event rate from our pilot study and the rejection of secondary null hypothesis that is unanticipated. Nonetheless, the fact that our findings are consistent with the result of the recent meta-analysis11 strengthens the idea that these findings are generalizable to the population of VLBW preterm infants. This study adds to the growing body of knowledge on the benefits of delayed cord clamping in preterm infants.11 It may be that the small amounts of addition blood preterm infants obtain by delaying cord clamping helps to stabilize cerebral blood flow, autoregulation, increase oxygen delivery to vulnerable tissues, prevent ischemia and cytokine release, and provide additional stem cells to establish adequate immunocompetence.

We have demonstrated that a brief delay in cord-clamping time, accompanied by lowering the infant to hasten the placentation transfusion, offers protection from IVH and LOS. The innovation of this study is the simplicity of the intervention of delaying cord clamping 30 to 45 seconds and lowering the infant. The additional blood volume received seems to contribute to the improved outcomes of tiny preterm infants.

ACKNOWLEDGMENTS

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Statistical consultation was provided by Jenifer Allsworth, PhD (Division of Research, Department of Obstetrics and Gynecology, Women and Infants’ Hospital, Providence, RI), and Yeong Kwak, RN, PhD (University of Connecticut School of Nursing, Storrs, CT).

We wish to thank the parents and infants who participated in this study and the nurses and doctors at Women and Infants’ Hospital. Without their trust and cooperation, this study would not have been possible.

REFERENCES


### WHEN TRUST IN DOCTORS ERODES, OTHER TREATMENTS FILL THE VOID

“The most telling evidence of Americans’ dissatisfaction with traditional health care is the more than $27 billion they spend annually on alternative and complementary medicine, according to government estimates. In ways large and small, millions of people are taking active steps to venture outside the mainstream, whether by taking the herbal remedy echinacea for a cold or by bettering their lives on an alternative cancer treatment, as did Coretta Scott King, who died this week at an alternative hospice clinic in Mexico. They do not appear to care that there is little, if any, evidence that many of the therapies work. Nor do they seem to mind that alternative therapy practitioners have a fraction of the training mainstream doctors do or that vitamin and herb makers are as profit-driven as drug makers. . . . Distrust in the medical industrial complex, as some patients call it, stems in part from suspicions that insurers warp medical decision making, and in part from the belief that drug companies are out to sell as many drugs as possible, regardless of patients’ needs, interviews show.”

*Carey B. New York Times. February 3, 2006*

Noted by JFL, MD
Delayed Cord Clamping in Very Preterm Infants Reduces the Incidence of Intraventricular Hemorrhage and Late-Onset Sepsis: A Randomized, Controlled Trial
Judith S. Mercer, Betty R. Vohr, Margaret M. McGrath, James F. Padbury, Michael Wallach and William Oh
Pediatrics 2006;117;1235
DOI: 10.1542/peds.2005-1706

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CURRENT BEST EVIDENCE: A REVIEW OF THE LITERATURE ON UMBILICAL CORD CLAMPING

Judith S. Mercer, CNM, DNSc, FACNM

ABSTRACT

Immediate clamping of the umbilical cord can reduce the red blood cells an infant receives at birth by more than 50%, resulting in potential short-term and long-term neonatal problems. Cord clamping studies from 1980 to 2001 were reviewed. Five hundred thirty-one term infants in the nine identified randomized and nonrandomized studies experienced late clamping, ranging from 3 minutes to cessation of pulsations, without symptoms of polycytemia or significant hyperbilirubinemia. Higher red blood cell flow to vital organs in the first week was noted, and term infants had less anemia at 2 months and increased duration of early breastfeeding. In seven randomized trials of preterm infants, benefits associated with delayed clamping in these infants included higher hematocrit and hemoglobin levels, blood pressure, and blood volume, with better cardiovascular adaptation and fewer days of oxygen and ventilation and fewer transfusions needed. For both term and preterm infants, few, if any, risks were associated with delayed cord clamping. Longitudinal studies of infants with immediate and delayed cord clamping are needed. J Midwifery Womens Health 2001;46:402–414 © 2001 by the American College of Nurse-Midwives.

After decades of discussion, debate, and dialogue, there is little agreement about the optimal time to clamp the umbilical cord after birth. Similarly, consensus regarding the potential benefits or harm to the newborn infant that can be attributed to delayed cord clamping is lacking. Clear clinical guidelines based on solid data from research are thus needed.

In a recent survey of members of the American College of Nurse-Midwives, 35% of certified nurse-midwives (CNMs) and certified midwives (CMs) reported that they waited until pulsation stopped to clamp the cord (1), whereas 26% reported that they clamp the umbilical cord before 1 minute. The reason stated for the delay was to promote optimal neonatal transition by providing oxygen, nutrients, and additional blood volume through the pulsating cord; the reasons given for immediate cord clamping were the beliefs that time makes no difference and/or that early cord clamping prevents jaundice and polycythemia. Most midwives offered few references for their beliefs and practices, indicating the lack of evidence-based practice and need for a current review of the literature. A 1950 survey of physician practices (the only one found) described most doctors as believing that cord clamping time was unimportant, although 24% reported milking the cord (2). Does delayed cord clamping have any benefits for infants? Or, does it cause harm such as neonatal jaundice or polycythemia? What is the evidence?

The purpose of this article is to evaluate the literature on cord-clamping practices published between 1980 and 2001 to provide the best possible foundation for clinical practice. The use of evidence-based research guidelines will allow clinicians to look beyond unsystematic clinical experiences, the pathologic emphasis on neonatal transition, and institutional routines and assist them to interpret the evidence obtained from clinical research (3).

BACKGROUND

Over the last decade there has been a shift in how clinicians and researchers examine clinical questions—from relying on the opinions of experts or authorities (authority-based) to a careful critique of the completed research on the subject of interest. The latter approach, introduced by Dr. Archie Cochrane (4,5), has been labeled "evidence-based medicine" or "evidence-based practice." Authority-based medicine continues to be an important component of clinical judgment when evidence is lacking and is not to be lightly discarded on the basis of a few studies. However, a careful review of the literature to establish the current best evidence offers the most defensible answers for the clinical questions faced by health professionals, when applied judiciously and conscientiously (6).

Many practices in health care, especially in maternity care, were developed because of expediency, habit, or logic and were not subjected to the rigor of good science. The near abandonment of breastfeeding a few decades ago because of lack of knowledge about its benefits is a prime example.

Immediate clamping of the umbilical cord can reduce the number of red blood cells available to an infant by more than 50% (7) as seen in Figure 1. This practice originated with changes in obstetrics and the development of neonatology and is just now beginning to receive the scientific review worthy of its potential impact on the neonate. Delayed clamping allows time for a transfer of
the fetal blood in the placenta to the infant at the time of birth.

As Figure 1 shows, "placental transfusion" can provide the infant with an additional 30% more blood volume and up to 60% more red blood cells, the only oxygen-carrying component in the body (8). Both are lost with immediate cord clamping. What is debated is whether this transfusion is harmful or beneficial.

In the literature, it is common to find a theoretic association postulated between delayed cord clamping and symptomatic polycythemia with increased viscosity, hyperbilirubinemia, and transient tachypnea in term infants, although reference to specific well-designed studies (9–12) is lacking. Benefits, such as less anemia (13,14) and better cardiopulmonary adaption (16,17), are rarely mentioned, except in specialized reports (13–16) and by way of the public media (18).

SEARCH STRATEGY

The studies reviewed in this article were obtained through a variety of sources. Some references were available through the Cochrane Library, although a complete review has not been undertaken as of this writing. Entering the key words "umbilical cord clamping" in the PubMed Database of the National Library of Medicine revealed in a large number of articles on the subject. These articles yielded many secondary references. The four older review articles provided analyses and references of still older, but not necessarily unimportant, articles (36–39).

TYPES OF INTERVENTION

The primary study intervention examined was delayed clamping of the umbilical cord. In studies of delayed cord clamping for preterm infants, the term "delayed" meant no longer than 30 to 45 seconds (24–30). For term
infants, the “delay” ranges from 3 minutes (22,31–34) to cessation of any pulsations in the cord (20,22,23) or up to 10 minutes (35). The definitions used for “early” cord clamping ranged from immediate (20,21,31–34) to before 1 minute (22,23,35) for term infants. For preterm infants, most studies defined “early” cord clamping as immediate (24,26,29,31); however, for two studies “immediate” implied a 20-second delay (25,27).

Other factors that have a significant impact on placental transfusion were also noted; these include the level at which the infant was held during the delay and the use of oxytocic medications for the mother after delivery. For example, variations range from holding the infant at the introitus or level of the placenta (20,24), to placing the infant on the maternal abdomen (22,23,29,31–33,35), to lowering the infant from 10 to 30 cm below the level of the placenta (20,21,25–28,30). One study identified two placement levels (20).

TYPES OF OUTCOME MEASURES

Outcome measures for all infants are highly diverse, preventing a meaningful meta-analysis at this time. For term infants, they include physiologic variables such as hematocrit and ferritin levels (20,21,23,31–35), bilirubin levels, time of cord separation, breastfeeding rates (22), neonatal jaundice (22,23), and many variables that did not seem to differ between treatment groups. Examination of psychological and developmental variables were secondary efforts in two studies whose purpose was evaluation of the safety of a Leboyer birth (which includes delayed cord clamping) (23,35). These secondary variables included the Brazelton Neonatal Assessment and the mother’s opinion at 8 months postpartum as to whether the birth had influenced the infant’s behavior (23). Studies involving preterm infants looked at the need for transfusions (24,25,30), hematocrit and blood pressures (24,26–30), bilirubin levels (24,30), and days of ventilation and oxygen use (30). The duration of any long-term follow-up of preterm infants was 4 to 6 weeks and included the number of transfusions received between birth and 4 to 6 weeks of life (24,25). All studies included can be found in Appendix A for term infants and Appendix B for preterm infants.

However, the method of evaluating outcome measures after the birth was blinded whenever possible (23). All patients were accounted for at the end of the trials, and most investigators specifically ensured that data were analyzed with subjects in their intended groups. Authors of two of the four randomized trials on term infants stated that they did not enroll parents who had a strong preference for delayed cord clamping (22,23).

DATA ANALYSIS

A careful review of two issues of primary concern was conducted: 1) Is harm done to term or preterm infants by delaying cord clamping? 2) Are there real or potential benefits from delaying clamping for any infants? Alleged harmful effects examined include symptomatic polycythemia and/or increased viscosity (10–12), increased incidence of jaundice and hyperbilirubinemia (11,12), increased transient tachypnea for term babies (12), and any adverse outcome for preterm infants.

DESCRIPTION OF STUDIES

The methodologic quality of the studies included ranged from satisfactory to rigorous. The search strategy revealed no published meta-analyses. One unpublished meta-analysis on preterm infants and cord clamping was found (40), but the results were extremely limited, because the studies differed widely on variables, methods, and conditions. Four randomized clinical trials involving term infants (20–23) and seven with preterm infants as subjects were found (24–30). In addition, there are five well-designed “controlled trials” (without randomization) on term infants from the last decade (31–35). Overviews of the randomized clinical trials and “controlled trials” on cord clamping in term infants from 1980 to 2001 are presented in Appendix A. Current randomized clinical trials involving preterm infants follow in Appendix B. Older studies are cited in the narrative.

One randomized clinical trial offered poorly defined variables, listed no times of cord clamping, and did not state whether the investigator was present for the birth, but it is included because it was only one of four randomized clinical trials with term infants as subjects (21). Four review articles from 1967 to 1982 offer summaries of the research available before their dates of publication (36–39). In addition, three expert opinion articles (15,16,41), two expert committee reports (13,14), and two case studies were found (42,43).

ESSENTIAL PHYSIOLOGIC PARAMETERS

Reasonable evaluation of the benefits or harms related to the timing of cord clamping requires a basic understand-
TABLE 1
Effects of Delayed Umbilical Cord Clamping on Neonatal Systems in the First Hours After Birth

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Change*</th>
<th>Parameters</th>
<th>Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume/components</td>
<td></td>
<td>Other cardiac effects</td>
<td></td>
</tr>
<tr>
<td>Blood volume (7,36,51)</td>
<td></td>
<td>Heart rate (53,55,63)</td>
<td></td>
</tr>
<tr>
<td>Red cell mass (7,36,51)</td>
<td></td>
<td>Cardiac size (53)</td>
<td></td>
</tr>
<tr>
<td>Plasma volume (7,36,51)</td>
<td></td>
<td>Preejection period (60)</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (52,53)</td>
<td></td>
<td>Murmurs (53)</td>
<td></td>
</tr>
<tr>
<td>Vascular pressures</td>
<td></td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery (54,55)</td>
<td></td>
<td>Glomerular filtration rate (56)</td>
<td></td>
</tr>
<tr>
<td>Atrial pressure (54)</td>
<td></td>
<td>Urine flow (56)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (53)</td>
<td></td>
<td>Urinary sodium excretion (56)</td>
<td></td>
</tr>
<tr>
<td>Blood flow</td>
<td></td>
<td>Respiration</td>
<td></td>
</tr>
<tr>
<td>Renal blood flow (56)</td>
<td></td>
<td>Respiratory rate (53,59,61)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous blood flow (57,58)</td>
<td></td>
<td>Lung compliance (61,62)</td>
<td></td>
</tr>
<tr>
<td>Systemic/pulmonary resistance (59)</td>
<td></td>
<td>Function residual capacity (61,62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expiratory grunting (63)</td>
<td></td>
</tr>
</tbody>
</table>

*↑ = increased; ↓ = decreased; "-" = no change found.

Owing of neonatal transitional physiology plus consideration of potential confounding factors. Approximately 110 to 115 mL/kg of blood are in the fetal-placental circulation at any point in time (44). Approximately 40% of the fetal cardiac output goes to the placenta per minute, whereas 8% to 10% goes to the fetus’ lungs (45,46). The fetal lung is an organ of excretion producing up to 400 mL of amniotic fluid per day (47). During labor, the production of fluid decreases but does not cease. Thus, at birth, the newborn’s lung must make immediate dramatic changes in both function and structure. The lung function must change from a fluid-producing organ in the fetus to one of gas exchange in the neonate. The lung structure must change from the fluid-filled state in the fetus to that of open gas-filled alveoli with excellent capillary circulation (48,49).

These dramatic changes are precipitated by a massive increase in blood flow to the lung—from 8% of the cardiac output in fetal life to 45% immediately after birth (46). The increased blood flow causes the pulmonary capillaries to become erect, thereby pulling open the alveoli and easing the entry of air (48,49). Immediate cord clamping limits access to the blood volume the infant needs to accomplish this huge task, because there is no reservoir within the body from which to draw. See Figure 1.

If the volume of blood in the capillary bed of the placenta is unavailable to the newborn because of early cord clamping, the necessary volume must be drawn from other organs, potentially causing their underperfusion. However, having lost placental support, all other organs must now function independently and need optimal perfusion as they begin vital functions essential for life. When the cord is not clamped, the umbilical circulation ceases when the umbilical arteries close and the cord stops pulsating. The umbilical arteries constrict spontaneously when oxygen levels in the infant’s circulating venous blood rise to more than 36 mmHg, paralleling the changes noted between fetal levels and neonatal levels of oxygen (50).

Table 1 provides an overview of the findings from several well-designed “controlled trials” completed before 1980 that examined the physiologic effect of delayed cord clamping on the newborn’s systems in the first few hours of life (51–63). Most of the differences result from increased vasodilation and perfusion and include such findings as higher vascular pressures, higher peripheral temperatures, and increased renal blood flow. Many of these findings have been validated by the results from more recently completed trials.

Confounding Factors in Cord Clamping Studies

Events that occur during labor and birth, as well as measurement factors, may confound the results of research on cord clamping. Four birth-related factors in addition to the timing of cord clamping influence the speed and amount of placental transfusion at birth. They include the level at which the infant is held (64); the type and method of delivery (28,65); uterine contractions during third stage (66); and oxytocic use at birth (67).

Problematic measurement factors in studies include the difficulty in measuring blood volume, inaccuracy of the hematocrit in reflecting blood volume in hypoxic babies, and effects of capillary leak syndrome (16,68). Other factors occurring during labor that might decrease a neonate’s blood volume at birth, but are beyond the scope of this article, include hypoxia (69), nuchal cord (42,70), and hypertonic uterine contractions.

Level Infant Is Held. Delaying cord clamping and keeping the infant at the level of the introitus for 45
seconds results in an 11% increase in blood volume, but a 24% increase in oxygen-carrying red blood cells, as shown in Figure 1 (7). Raising the infant significantly (30–60 cm) delays placental transfusion and lowering the infant 30 to 60 cm speeds the transfusion of blood from the placenta from 3 minutes to 1 minute (64).

Vaginal vs. Cesarean Birth. Because infants born by cesarean section tend to have lower blood volumes, the route of delivery must be noted in any study or review. Several authors have documented that placental transfusion occurs more successfully after vaginal birth than after a cesarean delivery (28,65). Narendra et al (28) found increased blood volume with delayed cord clamping at all births, but there was a smaller increase when preterm infants were born by cesarean section than when they were born vaginally.

Uterine Contractions. Uterine contractions after birth hasten the transfer of blood in the placenta to the baby (66). Occurring at regular intervals during third stage, they usually begin between 1 and 3 minutes postpartum (71).

Use of Oxytocic Drugs Immediately Postpartum.
There are major differences in the use of oxytocics in the United States and Europe. Mothers in European studies are usually given oxytocic drugs immediately after delivery of the anterior shoulder (22,25) or after birth (17). In contrast, the usual practice in the United States is to wait until the placenta is delivered. The use of oxytocic drugs has been shown to speed up placental transfusion (67) to the infant, making it inappropriate to compare these infants with those whose mothers were not given oxytocic drugs until after the placenta delivered.

Method and Speed of Delivery. One birth practice common in the United States is to deliver the shoulders and body of the infant rapidly after birth of the head. This practice does not allow for the continued placental circulation that occurs while waiting for restitution and the next contraction. Delivering the shoulders and body immediately followed by rapid cord ligation results in significantly less placental transfusion at birth than the infant would receive with a slower, more physiologic birth.

Blood Volume Measurement. Currently, there is no direct, simple, accurate, and rapid way to measure blood volume. Blood volume has been measured by the tagging of one of its elements, such as albumin or red blood cells, with a tracer substance (44). Tagging red blood cells with nonradioactive chromium, or a similar substance, is the most accurate method; in fact, using red cell tagging, Faxclius found a 60% correlation between blood volume and hematocrit in more than 290 neonatal intensive care unit admissions (68). However, it requires specialized equipment and more than 5 days to analyze, making the test of little use for clinical decision making (68,72). Albumin tagging with radioactive substances such as iodine (125I) was used in several older studies (7,73–75); however, the practice is no longer considered ethical, now that danger of exposure to radioactive substances is known.

Capillary Leak Syndrome. Capillary leak syndrome occurs when hypoxia causes vascular endothelial integrity to be compromised (16). Failure of the capillary endothelium allows components of plasma such as salt, water, and albumin to leak from the intravascular circulation. Albumin leakage raises the colloid osmotic pressure on the extravascular side of the capillary membrane, pulling fluid out of the circulation and resulting in hemoconcentration that elevates hematocrit. Capillary leak syndrome masks hemoconcentrated hypovolemia, and, as a result, hematocrit can be an unreliable and misleading indicator of blood volume and adequacy of the blood for oxygen transport and tissue perfusion in the neonate (16,74).

RESULTS

Issues of Harm with Delayed Cord Clamping

The concerns regarding delayed cord clamping include the possibility of precipitating polycythemia, hyperviscosity, hyperbilirubinemia, and transient tachypnea of the newborn. Each of these variables is discussed in detail.

Polycythemia. Saigal and Usher (75) initially raised the concern about the potential for polycythemia with delayed cord clamping in 1977. They coined the phrase "symptomatic neonatal plethora" to describe a subgroup of babies with various times of cord clamping who either had hypervolemia or elevated hematocrit develop and were symptomatic. Polycythemia is defined as a venous hematocrit level greater than 65% to 70% (11,12) and has been associated with neurologic sequelae (9). Although clinical manifestations of polycythemia are nonspecific (76), Saigal reported such generalized symptoms as plethoric skin color, tachypnea, retraction, rales, cyanosis, grunting, hypotension, and hypoglycemia in addition to such neurologic symptoms as apneic spells, depression, and irritability (75). However, a 1992 randomized clinical trial found no differences in neurologic outcomes at 30 months when polycythemic infants and control infants returned for follow-up evaluation (77). In the most extreme part of this protocol, term and preterm infants were held 30 cm below the introitus, and
cord clamping was delayed for 5 minutes. Hematocrit and blood volume were measured using radioactive iodine-tagged albumin at 4 hours of age. Of this group, none of the preterm infants had polycythemia develop, but two of the term infants had hematocrit levels greater than 70 at 4 hours, and one became symptomatic. Eleven preterm infants and three term infants were labeled “symptomatic,” although only one of the term and none of the preterm infants had an elevated hematocrit. The diagnosis of “hypervolemia” in the preterm infants was most likely due to capillary leak syndrome because the blood volumes listed for these infants were higher than plausible. This study is the only one found that suggests a link between delayed cord clamping and polycythemia and lacks the methodologic rigor found in later studies. The results have not been replicated.

Other causes for polycythemia are better documented than delayed cord clamping. Preexisting maternal conditions such as diabetes, preeclampsia, and hypertension increase the risk for chronic hypoxia in utero, and the resultant erythroipoiesis may lead to polycythemia at birth. In a study of diabetic mothers, 5% of infants had polycythemia (78). Kurlat (79) found that the risk of polycythemia in appropriate-for-gestational-age infants of hypertensive mothers was 12.6-fold greater than that of the general population. Gruenwald (80) found higher residual placental blood volumes, despite higher hematocrits, in infants of preeclamptic mothers, indicating that preexisting hemoconcentration rather than placental transfusion was responsible.

Time of sampling and location of the blood draw may affect the results of hematocrit or hemoglobin studies. Shohat et al (81) assessed hematocrit over the first 16 hours in infants with cord clamping at 30 seconds and found a consistent elevation at 4 hours. However, all hematocrit levels returned to the birth level or lower by 16 hours. Oh and Lind (52) found that peripheral hematocrit was lower when drawn from warmed heels and remained higher than venous or arterial measurements.

The data from the randomized clinical trials and the “controlled trials” over the last two decades do not support the theory that delayed cord clamping causes symptomatic polycythemia, despite the fact that hematocrit levels are higher in late-clamped term and preterm infants. Symptomatic polycythemia was not found in the 531 late-clamped term infants in the studies or in any of the preterm infants. Only two infants, both asymptomatic, had hematocrit levels above 65%, and both had been lowered while clamping was delayed for 3 minutes (20). Other studies completed before 1980 reported no symptomatic polycythemia even when infants were held at the level of the perineum or lowered and cord clamping was delayed until pulsations ceased. One case report was found that attributed polycythemia to a water birth with delayed clamping (43). Because delayed cord clamping occurs routinely at water births, this singular report requires more investigation. Currently, the American Academy of Pediatrics does not recommend routine examination of newborn’s hematocrit levels to check for polycythemia (82).

Hyperviscosity, Hyperviscosity, which often, but not always, accompanies polycythemia, is another concern raised by proponents of early cord clamping. Although earlier reports linked a hyperviscosity syndrome with poor neurologic outcomes (83), a later study failed to document any consistent pattern of damage (77). Blood transfusion and placental transfusion do increase whole blood viscosity in newborns. A marked rise in viscosity was found in late-clamped infants in two studies examining blood rheology (study of the flow of liquids and semisolids) (31,34). However, this increased viscosity was accompanied by a significant decrease in vascular resistance in the late-clamped newborn, resulting in increased pulmonary and generalized vasodilation—essential components of a normal transition. Principles of physics governing flow of liquid through a tube state that viscosity must increase for a fluid to dilate the “tube” (in this case, arterioles and capillaries). Thus, an increased viscosity and a corresponding decrease in vascular resistance may be essential to effect the massive dilation of blood vessels required immediately after birth to adequately perfuse the lung and other organs. Examining only one parameter of blood rheology can be misleading, because checks and balances are essential to this intricate system.

Hyperbilirubinemia. Most infants experience some elevation of bilirubin. Elevated bilirubin levels are more common in preterm infants, whereas late-onset hyperbilirubinemia occurs frequently in term infants who are breastfed. Reports of hyperbilirubinemia from delayed cord clamping were found only in preterm infants in one older study (73); however, inclusion of some infants who were probably small for gestation age confounded the finding. Of note are the 409 term infants in four randomized clinical trials with delayed cord clamping who showed no significant differences in bilirubin levels compared with the babies with early clamping (20–23). In two of the trials, bilirubin levels of 12 mg/dL or more occurred more frequently in the late clamped infants but did not reach significance (22,23). The only trial to report any significantly elevated bilirubin levels was one of the “controlled trials,” which reported that 3 of 15 late-clamped babies had bilirubin levels greater than 15 mg/dL (34); all infants in both groups were breastfed, but no other information on age of the infants at the time of diagnosis; treatment plan, or outcomes was offered (34). Even for preterm infants, no significant differences are noted in bilirubin levels between the 123 babies in the
late-clamped groups versus the 124 babies in the early-
clamped group in the seven randomized controlled trials
(24–30).

**Transient Tachypnea of the Newborn.** Transient
tachypnea of the newborn occurs soon after birth and is
diagnosed by mild cyanosis, grunting, retracting, flaring,
and tachypnea (84). The origin is believed to be from
delayed reabsorption of lung fluid, because it is seen
more commonly in infants born by cesarean section or
after prolonged labor. The studies reviewed here show no
indications of harm caused by transient tachypnea, al-
though respiration rates are increased in babies with
delayed cord clamping. The higher respiratory rates
reported in late cord-clamped infants (59,61) are thought
to be a result of greater pulmonary vascular filling,
necessitating more shallow rapid breathing. Yao et al
(63) found increased grunting in 7 of 33 late cord-
clamped newborns but reported that it disappeared within
3½ hours in the infants without sequelae or treatment. It
is important to note that these infants were observed
away from their mothers and were not offered the
opportunity to suckle during the first 2 hours of life, thus
creating a less than ideal transition to extrauterine life.
Allowing a newborn to suckle has been shown to
improve oxygenation and lowering of the heart rate (85);
thus, suckling should, theoretically, improve respiratory
transition and reduce signs of grunting. Unfortunately, no
studies on the effect of suckling on respiratory rates were
found.

**Beneficial Effects of Delayed Cord Clamping**

Does delaying cord clamping at the time of birth lead to
benefits for term or preterm infants compared with
immediate or early cord clamping? Although most of the
randomized controlled trials and “controlled trials” in-
volve small numbers of subjects and need replication,
several important findings are suggested.

**Hematologic Benefits.** Hematologic benefits were
seen for delayed cord clamping in term and preterm
infants. For term infants, improvements of higher hemat-
ocrit levels at 2 months of age and a trend toward
increased ferritin levels are especially important findings
(20,21). Anemia may have a larger impact on the normal
development of infants than is currently realized. Lozoff
and colleagues (86–88) report findings of altered central
nervous system development in children who had iron
deficiency anemia as infants. These results were evident
in children as young as 6 months of age and persisted in
these same children when reevaluated at 10 years of age
(86–88). Lozoff (89) believes that iron is an important
nutrient for myelination, which is occurring at a rapid
pace during infancy and early childhood. Hematologic
improvements for preterm infants include higher hemat-
ocrit and hemoglobin levels and a corresponding reduc-
tion in the need for transfusions in the first 4 to 6 weeks
of life.

The World Health Organization expert committee
report (13), the American Academy of Pediatrics state-
ment on cord blood collection (14), and one expert (41)
stress prevention of anemia as a reason to delay cord
clamping. Even with the small numbers in the current
study on anemia, the findings indicate a beneficial effect
of delayed cord clamping and support the need for further
study.

**Cardiopulmonary Benefits.** Cardiopulmonary bene-
fits of delayed cord clamping suggest better pulmonary
and systemic vasodilatation and higher red blood cell
flow to the brain, body, and intestines for all babies
(26,32). For preterm infants, these findings support
increased blood pressures (24,26,27), better cardiopul-
monary adaptation with less need for oxygen and fewer
days of ventilation (18), and decreased need for trans-
sfusions (24,25). Better capillary filling (58), higher
peripheral temperatures (57), and greater urine output (56)
have been documented in term infants because of increased
perfusion from delayed cord clamping. Increased vas-
dilatation accompanies increased perfusion and is especi-
ally important in the hemodynamics of neonatal lung
adaptation. Lack of adequate vasodilatation in the lungs
of newborns is a characteristic of persistent pulmonary
hypertension whose cause remains unknown. Increased
vasodilatation supports increased blood pressure, adequate
peripheral perfusion, and improved perfusion of organ
systems.

**Potential Behavior Effects.** An important potential
behavioral effect from delayed cord clamping is sug-
gested in the finding of increased early breastfeeding
duration in the Oxford Midwives’ study (22). This study
was the first to look at breastfeeding duration in delayed
and early clamped babies and did so only as a secondary
dependent variable. More mothers in the delayed clamping
group were still breastfeeding at 10 to 12 days
postpartum ($p < .05$). It is important to note that of the
296 babies assigned to the delayed clamping in this
study, 32 had early clamping because of intrapartum
problems. Because the data were analyzed according to
the intent-to-treat protocol, 32 babies with early clamping
who were assigned to the late group were analyzed as
part of the late group. This intent-to-treat analysis would
reduce the significance of the differences in breastfeeding
rates between groups.

This randomized controlled trial examined the differ-
ences in babies with cord clamping at 1 versus 3 or more
minutes. At 1 minute, babies may have received 50% of
their placental transfusion. The fact that the early group
had cord clamping at 1 minute, and thus potentially more blood volume, would also decrease significance of effects from cord clamping interval between babies in each group.

Based on a study that found better perfusion of and circulation to the gut after late clamping (32), further study is warranted to assess whether the improved perfusion results in better digestion with less abdominal discomfort and less crying. If so, fewer mothers may abandon breastfeeding in the early stages.

In summary, hemoglobinic benefits found in the studies reviewed earlier include findings of increased hematocrit and hemoglobin levels (20,24,26), blood pressure (27), and blood volume (28), and the reduced need for transfusions in the first 4 to 6 weeks in preterm infants (24,25); cardiopulmonary benefits consist of better adaptation with fewer days of oxygen and ventilation needed for preterm infants and higher red blood cell flow to vital organs in the first few days of life for all babies (26,32); behavioral benefits suggested by the randomized controlled trials were increased duration of early breastfeeding for infants with delayed cord clamping of at least 3 minutes duration compared with early clamped infants (22).

Are There Harmful Effects of Immediate Clamping?

The studies reviewed did not reveal obvious or direct harm from immediate cord clamping in either term or preterm infants, except for an increase in anemia of infancy. It is important to note that none of the studies examine any long-term sequelae. The delay interval of 30 to 45 seconds in preterm infants may be too short to assess the full potential benefits and reduction of harm that may be achieved with a longer delay. A large multisite randomized controlled trial involving 300 preterm subjects has just been completed in Europe (Wardrop, Scotland, 2001, personal communication). This study’s protocol involved a delay of 60 to 90 seconds with preterm infants lowered 30 cm. Analysis of the data will indicate whether a longer delay provides additional benefits. The analysis of the data should be completed and distributed by early 2002.

Does denial of 25% or more of an infant’s blood volume create any damage? There is one study using an animal model that suggests harm from blood loss at birth. Rajnik and colleagues (90) removed approximately 25% of newborn rat pup’s blood volume immediately after birth. There was no other intervention. The authors reported finding proinflammatory cytokines in the lungs and liver at 3 hours of age in the rat pups who had blood removed; rat pups with no loss of blood had no cytokines present in their organs. Proinflammatory cytokines are important markers for tissue damage and, thus, indicated damage to the rat pup’s lung and liver from removal of 25% of its blood volume. Figure 1 shows a reduction of approximately 30% in an infant’s blood volume from immediately clamping. Proinflammatory cytokines have been found to be significantly higher in early blood samples from babies who later have cerebral palsy develop (91). Consequently, these cytokines may be important markers to use in examining the effect of various obstetric practices on infant outcomes. This study by Rajnik et al (90) documents that the denial of 25% of rat pup’s blood volume alone, without any other intervention, elevated proinflammatory cytokines in the first 3 hours after birth. These findings lend support to the importance of reexamination of effects of immediate cord clamping in human infants.

DISCUSSION

For all but the last 50 to 100 years of human existence, it is highly likely that the umbilical cord of a newborn infant pulsed until it closed spontaneously. Along with important advances in obstetrics and neonatology, the current practice of immediate cord clamping has evolved in many institutions without adequate study of its potential short-term and long-term effects. The literature contains many unsubstantiated references to the fact that delaying cord clamping leads to a variety of harmful effects. Currently, the belief that delayed cord clamping causes polycythemia is so prevalent that one often finds it stated in the literature as an accepted fact not needing scientific references (10–12,76). The idea that delayed cord clamping is harmful is not supported by the findings from the 16 randomized controlled trials and 5 “controlled trials” completed over the last two decades involving term and preterm infants and reviewed here. See Appendices A and B.

Implications for Practice

Delayed cord clamping is consistent with gentle, physiologic birth. During the delay, the infant may be placed on the mother’s abdomen with no obvious harm noted with a delay of 3 or more minutes (23,31–35). The trials verified that increased blood volume occurs even when the infant is placed on the maternal abdomen and cord clamping is delayed 3 or more minutes. Figure 1 shows that maximum transfusion occurs in 3 or more minutes. One other finding should be noted. A study was conducted in Israel to find how to maximize cord blood harvesting (92). The author found that if the infant was placed on the abdomen and the cord was clamped in 30 seconds, 80 mL of cord blood could be collected. If the infant was placed on the obstetrician’s lap (lowered), only 30 mL was obtained when the cord was clamped at 30 seconds. The authors implied that no harm was done,
because hemoglobin levels were not significantly different at 24 hours. As stated earlier in the article, hemoglobin and hematocrit are not alone reliable indicators of harm or benefit from delayed cord clamping. However, if it is necessary to clamp the cord early and the CNM/CM wants to maximize the transfusion, then one should hold the infant lower than the placenta for the brief interval involved. This study has implications for placement of distressed babies who may be in greater need of blood volume (49). Any baby at risk for hypovolemia (very pale or mottled) can be lowered for 30 seconds to 1 minute before being placed on the abdomen or before the cord is clamped.

Implications for Research

Whether delayed cord clamping influences breastfeeding duration or other behavioral outcomes is an important question that needs to be examined in more detail, and the findings need to be replicated. The benefits to infants and mothers from breastfeeding are significant. Every effort should be made to ensure that birth practices are not contributing to breastfeeding difficulties.

Replication of the study by Grajeda et al (20) showing an association between immediate clamping and anemia in early infancy is important, and longitudinal follow-up should be added. The studies by Lozoff and colleagues (86-89) revealing behavioral and development problems in older children who experienced anemia in infancy adds urgency to the importance of repeating and lengthening this study to include examination of neurobehavioral development. Relatively noninvasive biologic research, such as measuring cytokines at birth, at 3 hours, and at later intervals in infants with immediate and delayed cord clamping, will tell us whether the rat pup's vulnerability is unique to that species or might affect our own.

All of the studies involving preterm infants have a relatively small number of subjects and need to be replicated and validated with larger samples of infants. Few deal with follow-up beyond 4 to 6 weeks. Studies examining progress and outcomes during the neonatal intensive care unit stay for preterm infants and follow-up beyond infancy are indicated on the basis of current findings.

CONCLUSIONS

Immediate clamping of the umbilical cord is an intervention that has developed in this country over the last century as birth moved into the hospital setting and represents the antipathy of the noninterventionist philosophy typical of midwifery care. None of the studies conducted before 1980 recommend immediate cord clamping—the most conservative recommendations were to delay 1 to 1½ minutes even for preterm infants (55,73). However, in our well-intended haste to transfer an infant to the pediatric staff, we may be denying the infant a significant part of his vital blood supply while placing him or her at risk of hypovolemia and resulting damage.

In this review of the literature, no cause for concern of harm is shown in more than 500 term infants enrolled in randomized controlled trials and “controlled trials” whose cords were clamped between 3 and 10 minutes, or when pulsations ceased. Indeed, one finds that benefits are clearly documented for preterm infants and suggested for term infants. There is no evidence that early cord clamping is better, and evidence is lacking regarding long-term harm from immediate or delayed cord clamping. Until we have sufficient appropriate evidence showing otherwise, it is better to mimic nature than to interfere with the intricate, complex, and only partially understood design of the physiologic neonatal transition.

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REFERENCES

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Study Population</th>
<th>Cord Management Placement of Infant</th>
<th>Sample Size</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grajeda, Perez-Escamilla, &amp; Dewey 1997 (20)</td>
<td>≥37 wks, ≥2,000 g singleton vaginal deliveries, no GD, AP hemorrhage, CPD or other anomalies</td>
<td>EC: immediately</td>
<td>21</td>
<td>At 2 mo, 88% of infants with delayed CC had Hct &gt; 0.33 versus 43% in the early group (p = .001). No differences between two late groups.</td>
<td>Recommends delay in CC as a feasible low-cost intervention that can reduce anemia in developing countries. No differences in polycythemia or jaundice. Two babies with Hcts &gt; 65% were asymptomatic. Set difference for significance at 30 ng/mL of ferritin. Did not report other variables.</td>
</tr>
<tr>
<td>Geethanath, Ramji, Thirupuram, Rao 1997 (21)</td>
<td>Term, vaginal births, mothers with Hgb &gt;10 g/dL</td>
<td>EC: immediately</td>
<td>48</td>
<td>Mean ferritin higher in LC: 73.6 ng/mL vs 55.7 ng/mL but did not reach significance level as set by PI.</td>
<td>Largest sample ever studied. No significant difference in jaundice. Highest BR levels = 12 mg/dL. 32 babies in LC group had early clamping (intent-to-treat analysis). Found that Leboyer method was not unsafe. Found no differences in polycythemia or jaundice.</td>
</tr>
<tr>
<td>Oxford Midwives Research Group-Healey, Greenish, Armstrong, &amp; Ayers 1991 (22)</td>
<td>37-42 wks, vertex vaginal delivery, no AP complications</td>
<td>EC: stat or ≤1 min</td>
<td>256</td>
<td>No significant difference in any variable except higher rates of continued BF at 10-12 days among mothers in LC group (p = .05).</td>
<td>Findings suggest more pronounced pulmonary vasodilation in the LC group in the first 5 days.</td>
</tr>
<tr>
<td>Nelson, Enkin, Saigal, Bennett, Milner, &amp; Sackett 1980 (33)</td>
<td>Low OB risk, ≥37 wks, wanted Leboyer birth, would attend prenatal classes</td>
<td>EC: &lt;60 sec</td>
<td>26</td>
<td>No differences on any variable except mothers' opinion at 8 mo that the birth influenced the child's behavior (p = .05).</td>
<td>Higher viscosity offset by lower vascular hindrance (marked vasodilation). Authors state EC deprives infants of placental transfusions and increases risk of hypovolemia and anemia.</td>
</tr>
<tr>
<td>Nelle, Kraus, Bastert, &amp; Lindenkamp 1996 (31)</td>
<td>30 FT neonates: from normal pregnancies and labors</td>
<td>EC: &lt;10 sec</td>
<td>15</td>
<td>Hcts were higher in LC (p &lt; .05). Pre-ejection period ratios indicated higher systemic and pulmonary resistance on day 1 and same as EC babies on day 5.</td>
<td>Example: For 3-kg infant; EC = 135 mL in placenta, 210 mL in baby. LC = 75 mL in placenta, 270 mL in baby. See Nelle 1995 for discussion of viscosity.</td>
</tr>
<tr>
<td>Nelle, Zilow, Bastert, &amp; Lindenkamp 1995 (32)</td>
<td>30 FT neonates: from normal pregnancies and labors</td>
<td>EC: &lt;10 sec</td>
<td>15</td>
<td>LC: BV 32% higher. Blood viscosity increased at 4 h by 32%; vascular hindrance 25% lower; RBC flow to brain and intestines 25% higher day 1 and 10% higher on day 5.</td>
<td>LC results in marked rise of blood viscosity caused by fluid shifting out of vascular space. No infants had any clinical symptoms. See Nelle 1995 re: viscosity.</td>
</tr>
<tr>
<td>Nelle, Zilow, Kraus, Bastert, &amp; Lindenkamp, 1993 (33)</td>
<td>Healthy, term, vaginal deliveries, pH ≥ 7.25, Apgar scores 9/10, all breastfed</td>
<td>EC: &lt;10 sec</td>
<td>15</td>
<td>Residual placental blood volume higher in EC infants; Hct rose from 49% at birth to 56% at 2 h, 56% at 24 h, and 54% at 120 h. Viscosity increased by 32% in LC at 2 h with no further change.</td>
<td>Completed random assignment to two Leboyer groups. Validated safety of Leboyer-type delivery.</td>
</tr>
<tr>
<td>Lindenkamp, Nelle, Kraus, &amp; Zilow 1992 (34)</td>
<td>39-40 wks, normal EFM, pH &gt; 7.25, Apgars 9/10, AGA, 3,390-3,620 g</td>
<td>EC: &lt;10 sec</td>
<td>15</td>
<td>RPBV = 15 vs 47 mL/kg in EC; Hct increased at 2 h; blood viscosity at 2 hs 40% higher; 3/13 with elevated BR over 15 mg/dL. All breastfed.</td>
<td></td>
</tr>
<tr>
<td>Kliot &amp; Silverstein 1984 (35)</td>
<td>Normal FT infants, from private practice</td>
<td>EC: &lt;60 sec</td>
<td>39</td>
<td>No significant difference in temperature, heart rate, Hct, BR, pH, Apgar scores, or other variables.</td>
<td></td>
</tr>
</tbody>
</table>

AP = antepartum; BF = breastfeeding; BR = bilirubin; BV = blood volume; CC = cord clamping; CL = lung compliance; CPD = cephalopelvic disproportion; CS = cesarean section; EC = early clamping; FT = full term; GD = gestational diabetes; GFR = glomerular filtration rate; Hct = hematocrit; HR = heart rate; LC = late clamping; PT = preterm; RBC = red blood cell; RPBV = residual placental blood volume; RR = respiratory rate; VI = vaginal delivery.
**APPENDIX B**

**LITERATURE OVERVIEW OF CORD CLAMPING IN PRETERM INFANTS (RANDOMIZED CONTROLLED TRIALS: 7 FOUND)**

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Study Population</th>
<th>Cord Management Infant Placement</th>
<th>Sample Size</th>
<th>Significant Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim, Krouskop,</td>
<td>500–1,250 g,</td>
<td>EC: stat; LC: at 20 sec; introitus</td>
<td>16</td>
<td>LC: improved mean BP (.01); Less use of albumin (.03); Higher RBCs (.003); Hct (.01, mean = 50%); Hgb (.0002); Fewer transfusions (.001) over 4-wk period, higher 5-min Apgar scores.</td>
<td>No significant difference in BR in spite of higher hct; decrease in transfusions is cost effective and safer. Study was of 4 wks duration.</td>
</tr>
<tr>
<td>Lewis, Dhanireddy,</td>
<td>24–29 wks, all</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001 (24)</td>
<td>vaginal births</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabe, Wacker, Hulskamp,</td>
<td>Singleton, &lt;33</td>
<td>EC: 20 sec; LC: 45 sec and</td>
<td>20</td>
<td>9 (LC) vs 16 (EC) transfused by day 42 (p = .05), OR 0.56 (CI .34-.94).</td>
<td>All mothers got oxytocic immediately after delivery; concludes that anemia of prematurity can be decreased by delayed cord clamping.</td>
</tr>
<tr>
<td>Franz, Everding, 2000</td>
<td>wks</td>
<td>lowered 20 cm + oxytocic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelle, Fischer, Conze,</td>
<td>C/S, ≤1,200 g,</td>
<td>EC: stat; LC: at 30 sec; infants held 30 cms below placenta</td>
<td>8</td>
<td>LC = higher mean BP, systemic vascular resistance, Hgb, systemic and cerebral Hgb transport; EC Group required more volume expansion in first 24 h.</td>
<td>LC resulted in sig. findings of most variables even with this small sample.</td>
</tr>
<tr>
<td>Beedgen, Linderkamp,</td>
<td>≥30 wks</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1998 (26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabe et al 1998 (27)</td>
<td>&lt;33 wks</td>
<td>EC: 20 sec; LC: 45 sec</td>
<td>15</td>
<td>BP: 10 (66%) of EC and 6 (40%) of LC had BP &lt;30 mmHg in first 24 h.</td>
<td>LC can help prevent low BP and low microcirculation.</td>
</tr>
<tr>
<td>Narendra et al 1998 (28)</td>
<td>24–31 wks</td>
<td>EC: routine; LC: ≥30 sec; lowered 30 cm, + oxytocic</td>
<td>23</td>
<td>LC: BV increased by 8–19 mL/kg overall; Vaginal births = 10–28.4 mL/kg increase; C/S = 2–16.4 mL/kg increase.</td>
<td>BV increased by 30 sec delay, most pronounced in VD. Analyzed by actual treatment, not intent-to-treat, subgroup of larger RCT.</td>
</tr>
<tr>
<td>McDonnell &amp; Henderson-Smar,</td>
<td>NVD and C/S,</td>
<td>EC: stat; LC: 30 sec; on maternal abdomen</td>
<td>24</td>
<td>Trend toward higher hct in LC infants but did not reach statistical significance. Delayed CC at C/S feasible.</td>
<td>Recommends to delay CC for more than 30 sec in trials and that infants be lowered in relation to the uterus.</td>
</tr>
<tr>
<td>1997 (29)</td>
<td>26–33 wks twins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinmond et al. 1993 (30)</td>
<td>SVDS 27–33 wks</td>
<td>EC: routine, stat or early, &lt; 10 sec; LC: 30 sec; 20 cm below introitus</td>
<td>19</td>
<td>Initial PCV higher in LC (.0013) and fewer RC Tfxs (.03). In ventilated infants: higher A-a O2 tension (.02), less supplemental O2 (.009). No difference in bilirubin levels.</td>
<td>Study is being replicated, and results should be available mid 2002. Overlapping outliers in each group.</td>
</tr>
</tbody>
</table>
Early versus delayed umbilical cord clamping in preterm infants

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Abstract

Background
Optimal timing for clamping of the umbilical cord at birth is unclear. Early clamping allows for immediate resuscitation of the newborn. Delaying clamping may facilitate transfusion of blood between the placenta and the baby.

Objectives
To delineate the short- and long-term effects for infants born at less than 37 completed weeks' gestation, and their mothers, of early compared to delayed clamping of the umbilical cord at birth.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (2 February 2004), the Cochrane Neonatal Group's Trials Register (2 February 2004), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2004, Issue 1), PubMed (1966 to 2 February 2004) and EMBASE (1974 to 2 February 2004). We updated the search of the Cochrane Pregnancy and Childbirth Group's Trials Register on 30 November 2009 and added the results to the awaiting classification section.

Selection criteria
Randomized controlled trials comparing early with delayed (30 seconds or more) clamping of the umbilical cord for infants born before 37 completed weeks' gestation.

Data collection and analysis
Three reviewers assessed eligibility and trial quality.

Main results
Seven studies (297 infants) were eligible for inclusion. The maximum delay in cord clamping was 120 seconds. Delayed cord clamping was associated with fewer transfusions for anaemia (three trials, 111 infants; relative risk (RR) 2.01, 95% CI 1.24 to 3.27) or low blood pressure (two trials, 58 infants; RR 2.58, 95% CI 1.17 to 5.67) and less intraventricular haemorrhage (five trials, 225 infants; RR 1.74, 95% CI 1.08 to 2.81) than early clamping.
Authors’ conclusions

Delaying cord clamping by 30 to 120 seconds, rather than early clamping, seems to be associated with less need for transfusion and less intraventricular haemorrhage. There are no clear differences in other outcomes.

[Note: The 14 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

PLAIN LANGUAGE SUMMARY

Early versus delayed umbilical cord clamping in preterm infants

Delayed cord clamping for babies born early improves their health.

In the womb, blood flows to and from the baby and the placenta bringing oxygen to the baby from the mother’s blood. If the cord is left unclamped for a short time after the birth, some of the baby’s blood from the placenta passes to the baby to help the flow of blood to the baby’s lungs. In the review of studies on babies born prematurely, delaying cord clamping for just a very short time helped the babies to adjust to their new surroundings better. Further studies are needed on longer delays to see whether this brings even more benefits.
Introduction

Anemia is a major health problem in Iran, whose prevalence amongst children (6 – 60 months) from Yazd is 39% and 57.2% in Kashan (6 – 36 months). During the first six months of life, infants are largely dependent on the iron supply present at birth for growth and hemoglobin (Hgb) production. Maternal supplemental iron is not likely to have a strong effect on breast milk iron concentrations and its effect on fetal iron stores is unclear. Direct supplementation of infants with medicinal iron is a challenge because of compliance problems and potential risks of competition for absorption with other nutrients such as zinc, and a possible negative effect on the anti-infective properties of human milk lactoferrin saturation with iron in the breastfed infant’s gastrointestinal tract. Delayed cord clamping could increase iron status at birth and reduce anemia among toddlers. It is estimated that up to 50% of children in developing countries become anemic at 12 months of age; therefore, a successful intervention this word can be omitted to prevent iron deficiency could be of global importance. In general, most vaginally delivered neonates that breathe before the cord is...
clamped attain a functional blood volume. Those neonates clamped before the first breath have less than optimal blood volume, and premature, c-section, and depressed babies in this category are prone to severe compromise from hypovolemia and hypotension. The optimal time to clamp the umbilical cord for all infants, regardless of gestational age or fetal weight, is when the circulation in the cord has ceased, the cord is flat and no pulse is evident (approximately three or more minutes after birth). At the present time, both early and late clamping procedures are standard practices with some obstetrical textbooks recommending early clamping and others propose delayed clamping. Finally, others give no clear recommendation for either early or delayed clamping, citing a lack of sufficient evidence. In our delivery center there is no specific guideline for the time of cord clamping, to date.

The present study was designed to test the effect of cord clamp timing on neonatal iron status and its relation to delivery type.

**Materials and Methods**

This observational cohort study was designed to assess hospital born newborns delivered by either vaginal or cesarean section from uncomplicated pregnancies (mothers without eclampsia, preeclampsia, severe heart or renal disease, severe antepartum hemorrhage, Hgb greater than 10 gm/dL, and no history of more than five deliveries) from Oct 2007 to March 2008. Newborns were included if there were no twin or asphyxiated deliveries, no first 24 hours after birth icterus, no congenital malformations, no hyaline membrane or respiratory distress syndrome, no sepsis, birth weight <2000 g or gestational age <35 weeks.

In order to detect a 0.7 gm/dL difference in serum Hgb with an SD of 1.5 gm/dL between the two groups after 48 hours of delivery, with a power of 90% and probability of 5% (α=5%), therefore a total sample size of 100 newborns was required for the study. There were 100 mother-infant pairs who fulfilled the enrollment criteria. Cases were matched between vaginal and cesarean deliveries, and 50 cases from each delivery type were selected. Over a 100 day period, one neonate delivered vaginally and one by cesarean section were selected every other day. These cases were watched for cord clamp time and divided into 30 cases of early cord clamp (≤15 s) and 70 cases for late cord clamp (>15 s). Care was taken to prevent hypothermia in both groups by adequate drying and warmth, and infants were placed under a preheated warmer in the delivery room.

At the time of delivery, maternal venous blood (2 mL) was collected in vials that contained EDTA in order to estimate Hgb and hematocrit (Hct) levels. From the infants, 4 mL of blood was taken 48 hours after delivery in both plain tubes and ETDA-containing vials to estimate Hgb, Hct, and ferritin levels. Ferritin assay samples were centrifuged and the serum was separated into a sealed tube and stored at -20°C until evaluated.

Hgb was estimated with the use of the Sysmex (K 4500) 1000 cell counter. Serum ferritin was estimated by ELISA (Monobind Ferritine ELISA Kit, Germany). The ferritin quantitative test uses a solid phase ELISA technique which was performed according to the manufacturer’s instructions. Hct was measured by standard procedures.

Pretested structured questionnaires were used to collect socioeconomic, demographic, and maternal reproductive information in addition to neonatal gestational age, Hgb, ferritin, and newborn morbidity. At the time of delivery, an observer used a stopwatch to record the elapsed time before the umbilical cord was clamped, relative to head crowning and appearance of the newborn’s shoulders. All anthropometry was performed by the first author, following standard procedures. Weight of the newborns at birth, maternal age, weight, Hgb, delivery type, and number of live children were also measured. Newborn health was assessed within 1 hour of delivery and again 24 hours later by study medical personnel. This examination included a clinical assessment of neurological and motor development, jaundice, as well as gastrointestinal and respiratory functions.

This study was based on observation of cord clamping practices. Blood sampling of infants was performed with the permission of the mothers. All analyses were done using the SPSS for Windows statistical package (version 13). Baseline characteristics and measurements were compared across groups with the Chi-square statistic for categorical variables and Student’s t-test for continuous variables. Group means were compared by using the t student significant difference test. All results were based on two-tailed tests and a P value of 0.05.
was used as the criterion for significance. Linear and multivariate regression analysis was used for analysis of confounding and quantitative variables, respectively.

**Results**

There were 100 mother-infant pairs enrolled in this study who were assigned to either the early (≤15 s) or late (>15 s) cord clamp time groups. The early cord clamp time group consisted of 30 infants, whereas 70 were enrolled in the late cord clamp time group. The groups were comparable with regard to the baseline characteristics of: maternal age, weight, Hgb, number of live children, neonatal birth weight, gestational age (Table 1), and neonatal gender (P=0.9) Multivariate-regression analyses were performed to rule out the effects of potentially confounding variables on infant Hct and Hgb at 48 hours postpartum. The differences among groups remained significant after control for: gestational age, mother’s age and weight, infant birth weight, and number of children in the family (P<0.01). There was no significant difference in ferritin levels between the two groups (Table 2).

Ninety percent of vaginal delivery cases were from the late cord clamping group, which was significant (P<0.001). Polycytemia, a complication of delayed cord clamping, was not seen in any of the neonates within both groups.

Simple linear regression analysis between the time of cutting the cord and newborn Hct and Hgb levels 48 hours postpartum showed a positive effect due to early cord clamping on newborn Hgb in the Loess scatter plot (Figure 1).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Less than 15 s Mean±SD</th>
<th>More than 15 s Mean±SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers’ ages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>25.6±4.5</td>
<td>25.7±4.7</td>
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</tr>
<tr>
<td>Range</td>
<td>17–37</td>
<td>17–38</td>
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<tr>
<td>Mothers’ weights</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>71.2±13.6</td>
<td>70.8±11.8</td>
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<tr>
<td>Range</td>
<td>50–102</td>
<td>45–112</td>
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</tr>
<tr>
<td>Mothers’ Hgb</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12.3±2</td>
<td>13.1±1.27</td>
<td>0.06</td>
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<tr>
<td>Range</td>
<td>8.1–16</td>
<td>9.5–15.5</td>
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<tr>
<td>Number of live children</td>
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<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.1±0.1</td>
<td>1.3±1</td>
<td>0.5</td>
</tr>
<tr>
<td>Range</td>
<td>0–3</td>
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<td>Birth weight</td>
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<tr>
<td>Mean±SD</td>
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<td>3284.3±417.8</td>
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<td>Age at pregnancy</td>
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<tr>
<td>Mean±SD</td>
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<td>37.6±1.5</td>
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<tr>
<td>Range</td>
<td>35–45</td>
<td>35–42</td>
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Table 1. Baseline maternal and infant characteristics

<table>
<thead>
<tr>
<th>Variables</th>
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<th>More than 15 s Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord time cut</td>
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<tr>
<td>Mean±SD</td>
<td>14.5±1.04</td>
<td>28.4±7.5</td>
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</tr>
<tr>
<td>Range</td>
<td>10–15</td>
<td>16–50</td>
<td></td>
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<tr>
<td>Newborn Hgb</td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>14.5±2.4</td>
<td>16.08±1.9</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>11–18.6</td>
<td>12–19</td>
<td></td>
</tr>
<tr>
<td>Newborn Hct</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>42.8±7.1</td>
<td>47.6±5.6</td>
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</tr>
<tr>
<td>Range</td>
<td>33–56.7</td>
<td>36–59</td>
<td></td>
</tr>
<tr>
<td>Newborn ferritin</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>173.6±91.7</td>
<td>214.7±124.3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>29–400</td>
<td>20–713</td>
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</tr>
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</table>

Table 2. Infants hematological outcome measures
Discussion

Based on the cord clamping time, this study showed a significant difference between newborn Hgb and Hct (≤15 s and >15 s) 48 hours after birth. The equivalence of the groups at baseline (maternal age, weight, Hgb, number of live children, neonatal birth weight and gestational age) support the conclusion that the effect may be causal.

Significant higher ferritin levels and Hgb concentrations have been reported in newborns born with the Leboyer method of delivery (neonates placed on their mothers’ abdomens, whose cords where clamped once pulsation ceased).18 Studies in India and Guatemala in addition to other well-designed, well-executed randomized trials have shown higher venous Hct levels six hours after birth and the sustained effect of late clamping has been demonstrated by other indicators of infant hematologic status (iron stores and ferritin) at age six months.19 – 21 This investigation was not undertaken in our study. Similarly, in the preterm population, late clamping has shown some potential benefits in terms of the decreased need for blood transfusion and lower risk of intraventricular hemorrhage as well as a reduced need for packed red cell transfusion 24 hours to 6 weeks after birth.22–24

Other uncontrolled studies, particularly in India and China, have shown no significant hematological differences between groups three to six months after birth.25–26 The majority of trials did not adequately address the hematologic status of recruited mothers as a potential confounder in the relationship between clamping interval and risk of anemia during infancy.21 We assessed mothers’ Hgb levels in the two groups. The complications of late cord clamping, such as the increase in hyperviscosity, stroke volume, heart rate, cardiac output, and left to right shunt across the ductus arteriosus are still controversial.18 Accordingly, there is no evidence of any significant harm as measured by the need for phototherapy to treat jaundice or by admission to the NICU.27

Among different studies, early cord clamping has been described as cord clamping that occurred immediately to 10 s after birth whereas late cord clamping could be prolonged until the time of placental delivery.21 The volume of placental blood transfusion depends on the time of clamping and the position in which the infant is held prior to clamping and is estimated at approximately 35 mL/kg of birth weight or 32% of blood volume in a term infant kept at vaginal level with the cord clamped three minutes after birth or once pulsation ceased (Leboyer delivery).28–29 One important issue is the possibility of overlap between the timing definitions of late and early cord clamping. The majority of trials did not provide data about the mean clamping time for the compared groups (Table 2). In this study, the mean difference in cord clamping was 13.9 s and no additional practices, such as neonatal positioning, were concomitantly used.

With multivariate-regression analyses, the differences among the early and late groups in Hct and Hgb levels 48 hours postpartum remained significant. (P<0.01). There was no significant difference in ferritin levels between the two groups (Table 2). Simple linear regression analysis between the time of cutting the cord and newborn Hct and Hgb levels 48 hours following delivery showed no statistical significance regarding the effect of these variables and cord time cut (Figure 1). Thus the effects of cord clamp time on neonate Hgb are shown at the lowest and highest time measurements, therefore a linear effect cannot be maintained. As such, the recommendation regarding the optimal time to clamp the umbilical cord for all infants (approximately three or more minutes after birth), is completely logical.30

The majority of randomized and unrandomized trials that have researched cord clamping divide
vaginally delivered births into two groups with the exception of two recent trials in 2006 that choose to include infants delivered by cesarean section.\textsuperscript{28,30} In this study, 50 cases, each, of infants delivered vaginally and by cesarean section were enrolled. Most infants in cesarean section group had delayed cord clamping (\(P<0.05\)). Delivery type can affect the time for cord clamping. Cesarean sections are performed in an operating room and the duration of cord clamp depends on the surgical procedure and cannot be delayed because of surgical complications to the mother (hemorrhage and infection). Elimination of this limitation gives permission to prolong this time manually in vaginal delivery; this can be another benefit of vaginal delivery as opposed to a cesarean section.\textsuperscript{31}

Perhaps the most important finding is that the beneficial effects of late cord clamping appear to extend beyond the early neonatal period. Documented results estimated a significant (47\%) reduction in the risk of anemia and a 33\% reduction in the risk of having deficient iron stores at ages two to three months that occur with late clamping. Although this is of particular importance for developing countries in which anemia during infancy and childhood is highly prevalent, it is likely to have an important impact on all newborns, regardless of birth setting.\textsuperscript{29}

**Acknowledgements**

It’s our great pleasure to thank the staff and the Chief of the Delivery Center of Imam Hossein Hospital, Dr. Z. Shahverdi and Laboratory personnel and Faezeh Maryam Tajali for their assistance in this study.

**References**

19. Grajeda R, Perez-Escamilla R, Dewey KG. Delayed clamping of the umbilical cord improves hematologic status of Guatemalan infants at 2 mo of...


Late vs Early Clamping of the Umbilical Cord in Full-term Neonates
Systematic Review and Meta-analysis of Controlled Trials

Eileen K. Hutton, PhD
Eman S. Hassan, MBBCh

CAMPING AND CUTTING OF THE umbilical cord at birth is by far the oldest and most prevalent intervention in humans. In spite of that, the optimal timing of cord clamping has been a controversial issue for decades. There are no formal practice guidelines, but most practitioners in western countries clamp and cut the cord immediately after birth, while the practice worldwide is variable.

Earlier physiological studies have shown that, of the total blood volume in the combined fetal-placental circulation at full gestation, approximately 25% to 60% (54-160 mL) is found in the placental circulation and that as many as 60% of the fetal red blood cells are found therein. This blood is also known to be rich in hematopoietic stem cells.

Previous research has suggested that early clamping of the cord (within the first 5 to 10 seconds of birth), compared with later clamping, results in a decrease to the neonate of 20 to 40 mL of blood per kilogram of body weight, which would provide the equivalent of 30 to 35 mg of iron. It has been argued that early cord clamping puts the newborn at increased risk of hypovolemic damage and iron loss, as well as of several blood disorders and type 2 diabetes, as a consequence of loss of hematopoietic stem cells. Early cord clamping has been postulated as a major cause of anemia in infancy, and this has led some investigators to recommend late clamping as a low-cost intervention to reduce anemia.
late blood volume, thus increas-
ing harmful and could result in overloading
the neonatal blood volume, thus increas-
ing the likelihood of respiratory dis-
tress, neonatal jaundice, and polycy-
temia. In addition, early clamping
is part of active management of the third
stage of labor to assist with delivery of
the placenta, and this management has
been shown in a Cochrane review to sig-
nificantly decrease maternal blood loss
following birth. Several reviews have studied the poten-
tial benefits and risks of late vs early clamping of the umbilical cord. In a
recent Cochrane review of cord clamp-
ing in the preterm population, late clamp-
ing showed some potential benefit in
terms of decreased need for blood trans-
fusion and lower risk of intraventricu-
lar hemorrhage. Reviews to date of stud-
ies in term infants provided no strong
evidence for the superiority of either
clamping strategy. However, these
reviews were based on studies with small
numbers of enrolled infants and did not
include large, well-designed trials pub-
lished in 2006. One additional review
combined studies of preterm and term
infants in a meta-analysis and focused the
discussion on practice in developing
countries. Thus, we believed that an
updated rigorous review and meta-
analysis of the timing of cord clamping
in term infants was needed.

METHODS
We compared the potential benefits and
harms of late vs early clamping of the um-
bilical cord in term infants. Outcomes of
interest were decided a priori and included
reported or clinically determined jaun-
dice, use of phototherapy, polycythemia
(defined as hematocrit increased to
>65%), tachypnea or respiratory grunt-
ing, admission to the neonatal intensive
care unit (NICU), and short- and long-
term risk of anemia (defined as either
hemoglobin concentration <10 g/dL or
hematocrit level <46%) and iron-
deficiency anemia (defined as hemoglo-
bin concentration <11 g/dL and ferritin
center concentration <10 µg/L). We were also
interested in determining the short- and
long-term effects of the timing of cord
clamping on a number of physiological
parameters in infants, including the ab-
solute values of hemoglobin, hematocrit,
blood volume and viscosity, and biliru-
bin, as well as iron status measured by lev-
els of ferritin and stored iron.

Inclusion and Exclusion Criteria
The review included controlled trials
(both randomized and nonrandom-
ized) comparing late vs early cord clamp-
ing following birth in infants born vagi-
nally or by cesarean delivery at 37 or more
weeks’ gestation. We included only those
studies that reported original data on at
least 1 of our outcomes of interest. We
excluded studies that exclusively
involved preterm infants or low-birth-
weight infants, because the potential
effects of early vs late clamping are ex-
pected to be different in these 2 groups.

Search Strategy
To identify all relevant studies, we per-
fomed a literature search on Novem-
ber 15, 2006, in 6 electronic databases
(starting from the beginning of each): the
Cochrane Pregnancy and Childbirth
Groups trials register, the Cochrane Neo-
natal Group trials register, the Cochr
ane library, MEDLINE, EMBASE, and
CINHAL. The search was not restricted
by language. We used both the Medical
Subject Heading terms and text word
search for late, early, umbilical cord
clamping, placental transfusion, and term
infants: (early or immediate or late or de-
lay*) and (umbilical-cord and clamp* or
placental-transfusion) and (term or full-
term or infant). We also performed a hand
search of secondary references in rele-
vant studies. Investigators working in
this area were contacted about any rel-
evant unpublished research.

Data Extraction and
Quality Assessment
Both authors independently assessed
the eligibility of identified studies and
extracted data from included trials using
previously prepared standardized forms.
Differences in data between the
2 sets of forms were resolved by re-
viewing the corresponding articles,
and the final set was agreed on by con-
sensus. The methodological quality of
each trial was also independently as-
sessed using a modified version of the
Jadad scale. Trials rated 10 or more
are considered high quality. No dis-
agreements existed between reviewers
that impacted categorization of trials as
being of low quality vs high quality.

Analysis
For the meta-analysis we used Revman
version 4.2. Double entry of the data
into Revman was carried out by the 2 re-
viewers. For continuous variables, we
used the mean and standard deviation
reported in the original trials to calcu-
late the weighted mean difference
(WMD). We expressed the harmful ef-
fects of each clamping practice as the
relative risk (RR) of adverse events. Es-
timates of pooled outcomes with 95%
confidence intervals (CIs) were calcu-
lated by means of fixed-effects models.
We also performed tests of heteroge-
nity between trials using the χ² test for
significance. When heterogeneity be-
tween studies was found to be signifi-
cant as indicated by F values greater
than 50%, pooled estimates based on random-
effects models were reported. For those
outcomes with adequate data, we per-
fomed a sensitivity analysis by com-
paring the findings of the meta-
analysis of high- and low-quality studies
together with only those studies that had
been ranked as high quality.

Subgroup analyses were planned for
possible confounding birth-related
practices that had the potential to al-
ter the rate of placental transfusion,
including mode of delivery (vaginal vs ces-
arean), height of infant relative to that
of the maternal introitus or placenta
during the cord clamping interval, use
of oxytocic drugs, and milking of the
cord toward the infant.

RESULTS
Search Results
The search identified 37 English-
language studies evaluating the effects
of late vs early clamping of the umbili-
cal cord. Of these, 8 randomized (Table 1)42,37,43 and 7 nonrandomized (Table 2)44,44-49 controlled trials were included in the review. Three of the included trials were conducted by the same research group, but it was clear from the descriptions that they were based on different samples.44,47,48 The remaining 22 studies were excluded because they included exclusively pre-term infants (12 trials)40,41 or low-birth-weight infants (4 trials).62-65 did not include a control group (2 studies),7,66 included data previously published (1 trial),67 did not report gestational age (2 trials),68,69 or did not include any of the outcomes of interest (1 trial).72 No studies including only cesarean births were found, and no additional data were obtained from contacts with authors.

**Description of Included Trials**

Eight trials were conducted in countries with low perinatal mortality rates (<10 per 1000 total births), including Canada, Germany, United Kingdom, Sweden, and the United States; 2 in countries with moderate perinatal mortality rates (10-20), including Argentina and Libya; and 5 in countries with higher perinatal mortality rates (>20), including Egypt, Guatemala, India, and Mexico. Six of the 15 trials were of high quality (Tables 1 and 2). There was no clear evidence of substantial imbalance in the baseline characteristics.

### Table 1. Included Randomized Controlled Trials (N = 8) Comparing Early vs Late Cord Clamping in Term Infants, Listed According to Study Quality Score

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Randomization</th>
<th>Quality Score/Commentsa</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceriani Cernadas et al</td>
<td>Argentina</td>
<td>Multicenter (computer-generated random numbers in sealed opaque envelopes), stratified by hospital and mode of delivery using variable block sizes</td>
<td>12 Outcome assessors blinded Compliance with allocated intervention: ECC, 94.6%; LCC 1, 91.2%; LCC 2, 90.2%</td>
<td>276 Full-term infants born vaginally or by cesareal delivery Inclusion criteria: uneventful singleton Fetal exclusion criteria: congenital malformations or intrauterine growth restriction (estimated fetal weight ≤ 10th percentile) Maternal exclusion criteria: diabetes, (pre)eclampsia, hypertension, or any other complications</td>
<td>ECC (n = 93) within the first 10 s (mean, 12.7 s) LCC 1 (n = 91) excluded at 1 min after birth (mean, 59.8 s) LCC 2 (n = 93) at 3 min after birth (mean, 169.3 s), newborns placed on mother’s abdomen or lap</td>
<td>Primary: venous hematocrit value 6 h after birth Secondary: hematocrit, bilirubin, early morbidity and mortality at age 24 to 48 h, any neonatal disease occurring within the first month of life</td>
</tr>
<tr>
<td>Chaparro et al</td>
<td>Mexico City, Mexico</td>
<td>Computer-generated random numbers in sealed opaque envelopes</td>
<td>12</td>
<td>476 Mother-infant pairs Inclusion criteria: women not in advanced labor when admitted Exclusion criteria: planned cesarean delivery; pregnancy of ≤36 or ≥42 weeks; multiple gestation; (pre)eclampsia; diabetes; hypertension; cardiopathies, chronic renal disease; hemorrhage; placental abnormalities; newborns with low birth weight; or fetal anomalies Women excluded if not planning to breastfeed for at least 6 mo, smoked at all during pregnancy, unwilling to return for follow-up visits at the same hospital, or were participating in another research study at the hospital</td>
<td>ECC (n = 239) at 10 s after delivery of the infant’s shoulders (mean, 16.5 [SD, 6.4] s) LCC (n = 237) at 2 min after delivery of the infant’s shoulders (mean, 99.3 [SD, 44.2] s), with newborns placed at level of uterus</td>
<td>Primary: infant hematologic and iron status at age 6 mo Secondary: estimated maternal blood loss at delivery, newborn hematocrit, and reported clinical jaundice between birth and age 14 d</td>
</tr>
<tr>
<td>Emhamed et al</td>
<td>Tripoli, Libya</td>
<td>Randomized sealed opaque envelopes</td>
<td>10 Lost to follow-up in each group Significantly higher proportion of anemic mothers in the LCC group</td>
<td>104 Singleton term infants (37-42 wk) born vaginally Fetal exclusion criteria: birth weight &lt; 2500 g or gestational age &lt; 37 wk Maternal exclusion criteria: gestational diabetes or (pre)eclampsia, instrument delivery, serious hemorrhage during pregnancy or delivery, major congenital abnormalities, and need for early cord clamping or resuscitation</td>
<td>ECC (n = 46) within 10 s after birth (mean, 12.8 [SD, 6.5] s) LCC (n = 50) after cessation of cord pulsations (mean, 214.6 [SD, 50.6] s), with newborns placed on mother’s abdomen in both groups, intramuscular oxytocin given after cord clamping</td>
<td>Primary: hematologic and iron status at age 24 h after birth Secondary: possible adverse effects</td>
</tr>
<tr>
<td>Gupta and Ramji</td>
<td>India</td>
<td>Computer-generated random-number sequences in sealed opaque envelopes</td>
<td>10 Infants lost to follow-up at age 3 mo</td>
<td>102 Singleton term infants born vaginally to anemic mothers (hemoglobin &lt; 10 g/dL) Fetal exclusion criteria: major congenital anomalies, needed resuscitation at birth Maternal exclusion criteria: eclampsia, severe heart failure, severe antepartum hemorrhage, Rh incompatibility</td>
<td>ECC (n = 53) immediately after birth (mean time unknown) LCC (n = 49) after descent of placenta in the vagina (mean time unknown) Newborns held within 10 cm below the introitus</td>
<td>Primary: levels of serum ferritin and hemoglobin at age 3 mo Secondary: full breast feeding, adverse events</td>
</tr>
</tbody>
</table>

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### Table 1. Included Randomized Controlled Trials (N = 8) Comparing Early vs Late Cord Clamping in Term Infants, Listed According to Study Quality Score (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Randomization</th>
<th>Quality Score/Comments*</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al,43 1997</td>
<td>Canada</td>
<td>Randomization occurred at 36th gestational week, stratified by parity and social class before randomization</td>
<td>10 1 Dropped out after randomization</td>
<td>55 Singleton term infants born vaginally Maternal inclusion criteria: low obstetrical risk (score &lt;3), interested in Leboyer approach to birth, intended to attend prenatal classes Maternal exclusion criteria: expected delivery before 36 wk of gestation or would not be available for the follow-up assessment period</td>
<td>ECC (n = 26) within the first 60 s of delivery (median, 45 [range, 2-80] s) LCC (n = 28) as part of Leboyer method after stopping of cord pulsation (median, 180 [range, 30-375] s); newborns placed on mother’s abdomen</td>
<td>Maternal primary morbidity: postpartum hemorrhage, extension of episiotomy, infected episiotomy, endometritis, and urinary infections Fetal primary morbidity: asphyxia, hypothermia, tachypnea, polycythemia, hyperbilirubinemia Secondary: maternal perception of birth, infant behavior</td>
</tr>
<tr>
<td>Oxford Midwives Research Group,41 1991</td>
<td>United Kingdom</td>
<td>Simple random-number tables in sealed opaque envelopes</td>
<td>10 Outcomes assessors were blinded Oxytocic drugs for third-stage management comparable between groups 2 Women lost to follow-up</td>
<td>554 Singleton term infants, of 37–42 weeks’ gestation, with an expected spontaneous vertex delivery Fetal exclusion criteria: fetal distress, resuscitation during labor, evidence of hypoxia Maternal exclusion criteria: receiving medications other than iron and vitamins, baby to be adopted, specific preference for ECC or LCC</td>
<td>ECC (n = 256) as soon as possible after delivery (mean time unknown) LCC (n = 298) after stopping of cord pulsation or 3 min after delivery, whichever is sooner (mean time unknown) Newborns placed at/above placenta at 30 s</td>
<td>Primary: duration of cord adherence Secondary: birth weight, feeding, fetal jaundice, postpartum hemorrhage, manual removal of placenta</td>
</tr>
<tr>
<td>Geethanath et al,42 1997</td>
<td>New Delhi, India</td>
<td>No description of randomization method, withdrawals, or dropouts</td>
<td>8</td>
<td>107 Singleton term infants, born vaginally of nonanemic mothers (maternal hemoglobin &gt;10 g/dL) Fetal exclusion criteria: birth asphyxia, major congenital anomalies Maternal exclusion criteria: eclampsia, heart failure, severe antepartum hemorrhage, Rh immunization</td>
<td>ECC (n = 48) immediately after birth (mean time unknown) LCC (n = 59) after descent of placenta in vagina (mean time unknown); newborns held within 10 cm below introitus</td>
<td>Primary: serum ferritin level Secondary: hemoglobin level</td>
</tr>
<tr>
<td>Saigal et al,43 1972</td>
<td>Montreal, Quebec</td>
<td></td>
<td>5</td>
<td>45 Term infants (38–42 gestational wk) born vaginally, epidural anesthesia was used in all mothers Fetal exclusion criteria: malformed infants who developed systemic infections, erythroblastotic infants, small for dates Maternal exclusion criteria: diabetes</td>
<td>ECC (n = 15) immediately after birth (within 5 s; mean time unknown) LCC 1 (n = 15; excluded) at 1 min after birth; newborns held 30 cm below level of introitus LCC 2 (n = 15) at 5 min after birth (mean time unknown); newborns held 30 cm below level of introitus in both groups, oxytocic drugs given after cord clamping</td>
<td>Primary: volume of placental transfusion Secondary: bilirubin levels</td>
</tr>
</tbody>
</table>

Abbreviations: ECC, early cord clamping; LCC, late cord clamping.

*Quality score determined using the Jadad scale.

between the late- and early-clamping groups. Small yet similar percentages (approximately 2.7%) of infants in the late- and early-clamping groups were delivered by cesarean. Outcome data for infants delivered by cesarean were not reported separately from those delivered vaginally.31 The majority of trials (n=8) defined early cord clamping as clamping within the first 10 seconds.10,32,37,38,44,45,47,48 Six trials described early clamping as immediate clamping.10,41,43,46,48,49 The trial by Nelson et al43 was the only trial that extended the early cord clamping definition to be as long as 60 seconds. Most of the trials defined late cord clamping as clamping either after cessation of cord pulsation or at 3 minutes. Two studies included an additional study group, with an intermediary clamping...
time at 1 minute. To minimize the chance of overlapping between the timing definitions of late and early clamping in this review, data for infants included in these 2 intermediary groups were excluded from the meta-analysis. As a result, the earliest time at which cord clamping was defined as “late” in this review was 2 minutes. The majority of trials did not provide any data about the mean clamping time for the compared groups.

Our outcomes of interest were not consistently reported by all trials, resulting in several outcomes being reported in only 1 or a small number of the trials. There was variation in the level at which the newborn was kept in relation to the level of placenta or introitus during the clamping interval. In 2 trials, compared with conventional delivery including early cord clamping, late clamping was performed as part of an evaluation of the Leboyer method of labor, which required putting the neonate on the mother’s abdomen after birth while waiting for the cord to stop pulsating before clamping it. Two of the 4 trials that provided information regarding the use of oxytocic drugs limited administration to the period after the cord was clamped. The other 2 trials reported use of oxytocic drugs at different stages of labor, including delivery of the placenta.

### Table 2. Included Nonrandomized Controlled Trials (N = 7) Comparing Early vs Late Cord Clamping in Term Infants, Listed According to Study Quality Score

<table>
<thead>
<tr>
<th>Source</th>
<th>Location</th>
<th>Quality Score*</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelle et al, 1996</td>
<td>Germany</td>
<td>8</td>
<td>30 singleton term infants born vaginally at 39–40 wk</td>
<td>ECC (n = 15) within first 10 s of delivery (mean time unknown) LCC (n = 15) as part of Leboyer method at 3 min (mean time unknown); newborns placed on mother’s abdomen</td>
<td>Primary: postnatal changes in left and right systolic time intervals Secondary: adverse events</td>
</tr>
<tr>
<td>Abdel Aziz et al, 1999</td>
<td>Cairo, Egypt</td>
<td>7</td>
<td>30 Full-term infants born vaginally at 39–40 wk</td>
<td>ECC (n = 15) within the first 10 s of delivery (mean time unknown) LCC (n = 15) at 3 min (mean time unknown); newborns kept at level of introitus</td>
<td>Primary: determinants of blood viscosity Secondary: jaundice, polycythemia</td>
</tr>
<tr>
<td>Grajeda et al, 1997</td>
<td>Guatemala</td>
<td>7</td>
<td>89 singleton term infants (37 wk or older), birth weight more than 2000 g born vaginally</td>
<td>ECC (n = 29) immediately after birth (mean, 18 [SD, 18] s) LCC 1 (n = 30) after stopping of cord pulsation (mean, 64 [SD, 48] s) LCC 2 (n = 30) after stopping of cord pulsation (mean, 84 [SD, 48] s); newborns placed below level of placenta</td>
<td>Primary: fetal hematologic status Secondary: adverse health effects</td>
</tr>
<tr>
<td>Lindkamp et al, 1992</td>
<td>Germany</td>
<td>7</td>
<td>30 singleton term infants born vaginally at 39–40 wk</td>
<td>ECC (n = 15) within the first 10 s of delivery (mean time unknown) LCC (n = 15) at 3 min (mean time unknown); newborns held at level of introitus</td>
<td>Primary: determinants of blood viscosity (hematocrit, plasma viscosity, RBC aggregation, and RBC deformity) Secondary: bilirubin measurements in jaundiced infants</td>
</tr>
<tr>
<td>Nelle et al, 1993</td>
<td>Germany</td>
<td>7</td>
<td>30 singleton term infants born vaginally at 39–40 wk</td>
<td>ECC (n = 15) within the first 10 s of delivery (mean time unknown) LCC (n = 15) as part of Leboyer method at 3 min (mean time unknown); newborns placed on mother’s abdomen</td>
<td>Primary: postnatal changes in blood viscosity and its determinants Secondary: adverse events</td>
</tr>
<tr>
<td>Yao et al, 1971</td>
<td>New York State</td>
<td>6</td>
<td>57 Normal full-term infants born vaginally without any perinatal complications</td>
<td>ECC (n = 24) within the first 10 s of delivery (mean time unknown) LCC (n = 33) after 3–5 min after birth (mean time unknown)</td>
<td>Primary: respiratory frequency, pattern, and occurrence of expiratory grunting from birth through the first hours of life</td>
</tr>
<tr>
<td>Oh and Lind, 1967</td>
<td>Sweden</td>
<td>5</td>
<td>36 Singleton term infants born vaginally at 38–42 wk</td>
<td>ECC (n = 22) immediately after birth (mean, 9 [range, 2–20] s) LCC (n = 14) after stopping of cord pulsation (mean, 3 min 48 s [range, 2.5–5 min]; newborns placed 10 cm below level of introitus</td>
<td>Primary: infant body temperature from 5 min to 5 d of life Secondary: hematocrit at 0.5 h after birth</td>
</tr>
</tbody>
</table>

Abbreviations: ECC, early cord clamping; LCC, late cord clamping; RBC, red blood cell.

*Quality score determined using the Jadad scale.
meta-analysis (hematocrit at 24-48 hours and at 5 days, bilirubin at 24 hours, and risk of grunting or tachypnea). However, power to detect heterogeneity was low because of the relatively small number of available trials.

Physiological Parameters

Mean Hematocrit. Mean neonatal hematocrit measured in capillary or venous blood samples collected from the newborns at around 6 hours after birth was higher for those allocated to late vs early cord clamping (2 trials, 494 infants)32,37 (WMD, 4.16%; 95% CI, 0.83% to 7.49%) (Figure 1). Similarly, 4 trials evaluating 341 infants37,38,45,48 found significantly higher levels of neonatal hematocrit at 24 to 48 hours after the time of delivery with late clamping (WMD, 10.01%; 95% CI, 4.10% to 15.92%). This significant effect was further demonstrated at age 5 days (4 trials, 120 infants)44,45,47,48 (WMD, 11.97%; 95% CI, 8.50% to 15.45%) and at age 2 months (1 trial, 47 infants)46 (WMD, 3.70%; 95% CI, 2.00% to 5.40%). However, no significant differences were found in hematocrit at age 6 months (1 trial, 305 infants)39,40 (WMD, 0.10%; 95% CI, −0.62% to 0.82%). A sensitivity analysis for hematocrit at 24 to 48 hours after delivery comparing high-quality studies with all studies showed no substantial changes in the observed differences (2 trials, 279 infants)37,38 (WMD, 4.54%; 95% CI, 2.98% to 6.10%).

Mean Hemoglobin Level. At ≈7 hours after birth, the mean neonatal hemoglobin level measured in capillary blood was higher in newborns with late cord clamping (1 trial, 354 infants)32 (WMD, 0.60 g/dL; 95% CI, 0.11 to 1.09). No significant differences in mean levels were found at ages 2 to 3 months (3 trials, 209 infants)39,42,46 (WMD, 0.47 g/dL; 95% CI, −0.48 to 1.42) (Figure 1) or 6 months (1 trial, 356 infants)32 (WMD, 0.00 g/dL; 95% CI, −0.21 to 0.21). Of the 3 trials assessing hemoglobin levels at 2 to 3 months, only 1 was of high quality.39 In this small trial of 58 infants, levels were higher in newborns who had late clamping (WMD, 1.10 g/dL; 95% CI, 0.66 to 1.54).

Blood Volume and Plasma and Blood Viscosity. Blood volume during the first 2 to 4 hours of life was higher in infants who had late cord clamping (2

---

**Figure 1. Mean Hematocrit and Hemoglobin Levels Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)**

<table>
<thead>
<tr>
<th>Hematocrit Levels</th>
<th>LCC</th>
<th>ECC</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
<td>Random-Effects Model</td>
</tr>
<tr>
<td>Neonatal Hematocrit at 6 Hours</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Ceriani Cernadas et al,37 2006</td>
<td>92 59.40 (6.10)</td>
<td>90 53.50 (7.00)</td>
<td>5.90 (3.99 to 7.81)</td>
</tr>
<tr>
<td>Chaparro et al,37 2006</td>
<td>166 62.00 (7.50)</td>
<td>155 59.50 (7.20)</td>
<td>2.50 (0.89 to 4.11)</td>
</tr>
<tr>
<td>Overall</td>
<td>258</td>
<td>245</td>
<td>4.16 (0.83 to 7.49)</td>
</tr>
<tr>
<td>Test for Heterogeneity: $\chi^2 = 7.13 (P = 0.008), I^2 = 86.0%$</td>
<td>Test for Overall Effect: $z = 2.45 (P = 0.01)$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Neonatal Hematocrit at 24-48 Hours | Mean (SD) | Mean (SD) |                          |
| Neile et al,41 1993 | 15 59.00 (5.00) | 15 43.00 (6.00) | 16.00 (12.05 to 19.95) |
| Abdel Aziz et al,45 1999 | 15 59.00 (5.00) | 15 43.00 (6.00) | 16.00 (12.05 to 19.95) |
| Emhamed et al,38 2004 | 57 52.80 (6.30) | 45 49.30 (5.70) | 3.60 (1.27 to 5.90) |
| Ceriani Cernadas et al,37 2006 | 90 56.40 (7.40) | 89 51.10 (6.90) | 5.30 (2.20 to 7.40) |
| Overall | 177 | 164 | 10.01 (4.10 to 15.90) |
| Test for Heterogeneity: $\chi^2 = 50.37 (P < 0.001), I^2 = 94.0\%$ | Test for Overall Effect: $z = 3.32 (P < 0.001)$ |

| Neonatal Hematocrit at 5 Days | Mean (SD) | Mean (SD) |                          |
| Neile et al,41 1993 | 15 59.00 (6.00) | 15 44.00 (5.00) | 15.00 (11.05 to 18.95) |
| Abdel Aziz et al,45 1999 | 15 59.00 (5.00) | 15 44.00 (5.00) | 10.00 (6.42 to 13.58) |
| Abdel Aziz et al,45 1996 | 15 57.00 (2.00) | 15 49.00 (7.00) | 8.00 (4.32 to 11.68) |
| Overall | 60 | 60 | 11.97 (6.50 to 15.45) |
| Test for Heterogeneity: $\chi^2 = 10.63 (P = 0.001), I^2 = 71.8\%$ | Test for Overall Effect: $z = 6.75 (P < 0.001)$ |

<table>
<thead>
<tr>
<th>Hemoglobin at 2-3 Months</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Hemoglobin, g/dL</td>
<td>Hemoglobin, g/dL</td>
<td></td>
</tr>
<tr>
<td>Geethanath et al,46 1997</td>
<td>59</td>
<td>8.30 (2.0)</td>
<td>48</td>
</tr>
<tr>
<td>Gojeda et al,46 1997</td>
<td>25</td>
<td>10.80 (1.10)</td>
<td>19</td>
</tr>
<tr>
<td>Gupta and Ramji,47 2002</td>
<td>29</td>
<td>9.90 (0.96)</td>
<td>29</td>
</tr>
<tr>
<td>Overall</td>
<td>113</td>
<td>96</td>
<td>0.47 (−0.48 to 1.42)</td>
</tr>
<tr>
<td>Test for Heterogeneity: $\chi^2 = 18.50 (P &lt; 0.001), I^2 = 87.9%$</td>
<td>Test for Overall Effect: $z = 0.96 (P = 0.34)$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
trials, 60 infants)\textsuperscript{35.48} (WMD, 9.07 mL/kg; 95% CI, 5.81 to 12.32). Three trials (90 neonates)\textsuperscript{15.47.48} found no significant differences with respect to values of plasma viscosity at 24 hours after birth (WMD, 0.01 mPa.s; 95% CI, −0.03 to 0.05) and at age 5 days in the same population (WMD, −0.02 mPa.s; 95% CI, −0.07 to 0.02). Three trials (90 infants)\textsuperscript{44.45.47} reported that values of blood viscosity during the first 2 to 4 hours of life and again at age 5 days were significantly higher in neonates allocated to late clamping (2-4 hours: WMD, 1.39 mPa.s; 95% CI, 1.19 to 1.59; 5 days: WMD, 0.94 mPa.s; 95% CI, 0.72 to 1.16) (Figure 2).

**Bilirubin Level.** As shown in Figure 3, there was no significant difference in mean serum bilirubin levels within the first 24 hours of life (2 trials, 163 infants)\textsuperscript{38.41} (WMD, 3.81 mmol/L; 95% CI, −17.55 to 25.18). Similarly, no significant differences in levels were noted between late and early cord clamping at or after 72 hours following birth (2 trials, 91 infants)\textsuperscript{41.43} (WMD, 18.27 mmol/L; 95% CI, −2.47 to 39.00).

**Iron Status.** Iron status was assessed in terms of mean ferritin level and stored iron level. Ferritin levels at ages 2 to 3 months were higher for infants allocated to late vs early cord clamping (2 trials, 144 infants)\textsuperscript{12.46} (WMD, 17.89 µg/L; 95% CI, 16.58 to 19.21) (Figure 4). Two trials that included a total of 165 infants\textsuperscript{19.42} compared the effects of late vs early clamping on having ferritin levels less than 50 µg/L at age 3 months as an indicator for deficient iron stores. Fewer infants allocated to late clamping had ferritin levels less than 50 µg/L (RR, 0.67; 95% CI, 0.47 to 0.96). At age 6 months, ferritin levels were also higher with late clamping (1 trial, 315 infants)\textsuperscript{32} (WMD, 11.80 µg/L; 95% CI, 4.07 to 19.53).

One trial (315 infants)\textsuperscript{32} that evaluated stored iron at age 6 months found

---

**Figure 2. Mean Blood Viscosity Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)**

<table>
<thead>
<tr>
<th>Source</th>
<th>LCC</th>
<th>ECC</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Blood Viscosity, mPa.s</td>
<td>Mean (SD) Blood Viscosity, mPa.s</td>
<td>Fixed-Effects Model</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Linderkamp et al,\textsuperscript{47} 1992</td>
<td>15 4.20 (0.40)</td>
<td>15 2.80 (0.50)</td>
<td>1.40 (1.08-1.72)</td>
</tr>
<tr>
<td>Nelle et al,\textsuperscript{41} 1996</td>
<td>15 5.40 (1.00)</td>
<td>15 4.10 (0.80)</td>
<td>1.30 (0.65-1.95)</td>
</tr>
<tr>
<td>Abdel Aziz et al,\textsuperscript{45} 1999</td>
<td>15 4.20 (0.40)</td>
<td>15 2.80 (0.40)</td>
<td>1.40 (1.11-1.69)</td>
</tr>
<tr>
<td>Overall</td>
<td>45 45</td>
<td></td>
<td>1.39 (1.19-1.59)</td>
</tr>
<tr>
<td>Test for Heterogeneity:</td>
<td>χ²=0.08 (P&lt;0.96), I²=0%</td>
<td>Test for Overall Effect:</td>
<td>z=13.38 (P&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>LCC</th>
<th>ECC</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Blood Viscosity, mPa.s</td>
<td>Mean (SD) Blood Viscosity, mPa.s</td>
<td>Fixed-Effects Model</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Linderkamp et al,\textsuperscript{47} 1992</td>
<td>15 4.00 (0.50)</td>
<td>15 3.10 (0.40)</td>
<td>0.90 (0.58-1.22)</td>
</tr>
<tr>
<td>Nelle et al,\textsuperscript{41} 1996</td>
<td>15 5.00 (1.30)</td>
<td>15 3.70 (0.50)</td>
<td>1.30 (0.60-2.00)</td>
</tr>
<tr>
<td>Abdel Aziz et al,\textsuperscript{45} 1999</td>
<td>15 4.00 (0.50)</td>
<td>15 3.10 (0.40)</td>
<td>0.90 (0.58-1.22)</td>
</tr>
<tr>
<td>Overall</td>
<td>45 45</td>
<td></td>
<td>0.94 (0.72-1.16)</td>
</tr>
<tr>
<td>Test for Heterogeneity:</td>
<td>χ²=1.12 (P=0.57), I²=0%</td>
<td>Test for Overall Effect:</td>
<td>z=8.44 (P&lt;0.001)</td>
</tr>
</tbody>
</table>

Sizes of data markers indicate the weight of each study in the analysis. CI indicates confidence interval.

**Figure 3. Mean Bilirubin Levels Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)**

<table>
<thead>
<tr>
<th>Source</th>
<th>LCC</th>
<th>ECC</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Bilirubin, mmol/L</td>
<td>Mean (SD) Bilirubin, mmol/L</td>
<td>Random-Effects Model</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Oxford Midwives,\textsuperscript{41} 1991</td>
<td>40 192.80 (52.43)</td>
<td>21 175.70 (44.70)</td>
<td>17.10 (&lt;7.98 to 42.18)</td>
</tr>
<tr>
<td>Emhamed et al,\textsuperscript{38} 2004</td>
<td>57 99.18 (22.23)</td>
<td>45 104.31 (51.30)</td>
<td>−5.13 (−21.19 to 10.93)</td>
</tr>
<tr>
<td>Overall</td>
<td>97 66</td>
<td></td>
<td>3.81 (&lt;17.55 to 25.18)</td>
</tr>
<tr>
<td>Test for Heterogeneity:</td>
<td>χ²=2.14 (P=0.14), I²=53.3%</td>
<td>Test for Overall Effect:</td>
<td>z=0.35 (P=0.73)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>LCC</th>
<th>ECC</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Bilirubin, mmol/L</td>
<td>Mean (SD) Bilirubin, mmol/L</td>
<td>Fixed-Effects Model (95% CI)</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Saigal et al,\textsuperscript{45} 1972</td>
<td>15 94.05 (73.53)</td>
<td>15 54.70 (64.70)</td>
<td>39.35 (37.03 to 85.73)</td>
</tr>
<tr>
<td>Oxford Midwives,\textsuperscript{41} 1991</td>
<td>40 187.60 (56.00)</td>
<td>21 174.60 (47.50)</td>
<td>13.00 (&lt;10.18 to 36.18)</td>
</tr>
<tr>
<td>Overall</td>
<td>55 36</td>
<td></td>
<td>18.27 (&lt;2.47 to 39.00)</td>
</tr>
<tr>
<td>Test for Heterogeneity:</td>
<td>χ²=0.99 (P=0.32), I²=0%</td>
<td>Test for Overall Effect:</td>
<td>z=1.73 (P=0.08)</td>
</tr>
</tbody>
</table>

Sizes of data markers indicate the weight of each study in the analysis. CI indicates confidence interval. To convert bilirubin values to mg/dL, divide by 17.1.

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that infants with late cord clamping at birth had higher levels of stored iron vs those with early clamping (WMD, 19.90 mg; 95% CI, 7.67 to 32.13).

**Clinical Outcomes**

**Risk of Anemia.** Compared with early cord clamping, the risk of anemia was decreased with late clamping at 24 to 48 hours after birth (1 study, 179 infants) (RR, 0.20; 95% CI, 0.06 to 0.66) and at ages 2 to 3 months (2 trials, 119 infants) (RR, 0.53; 95% CI, 0.40 to 0.70) (Figure 5). At 6 months, similar proportions of infants in the late- and early-clamping groups were anemic (1 trial, 356 infants) (RR, 0.85; 95% CI, 0.51 to 1.43). However, in the same trial, 315 infants were evaluated for risk of iron deficiency anemia at age 6 months by considering their levels of ferritin as well. None in the late-clamping group (n=161) vs 6 in the early-clamping group (n=161) were diagnosed with the deficiency (RR, 0.07; 95% CI, 0.00 to 1.30).

**Risk of Clinical Jaundice and Use of Phototherapy.** A pooled analysis of data from 8 trials (1009 infants) (RR, 1.16; 95% CI, 0.85 to 1.58). Similarly, no significant differences were noted between late and early clamping in risk of jaundice at 3 to 14 days after birth (1 trial, 332 infants) (RR, 1.27; 95% CI, 0.76 to 2.10). In addition, no significant differences were found between groups in the proportions of infants who had elevated bilirubin levels (>256.5 mmol/L [15 g/dL]) that necessitated use of phototherapy (3 trials, 699 infants) (RR, 1.78; 95% CI, 0.71 to 4.46) (Figure 6).

**Risk of Polycythemia.** Risk of polycythemia after birth was more common in neonates allocated to late rather than early cord clamping at 7 hours (2 trials, 236 neonates) (RR, 3.44; 95% CI, 1.25 to 9.52) and at 24 to 48 hours (7 trials, 403 neonates) (RR, 3.82; 95% CI, 1.11 to 13.21) (Figure 7). A sensitivity analysis that included only high-quality studies provided a similar estimate for risk of polycythemia at 24 to 48 hours (2 studies, 281 infants) (RR, 3.91; 95% CI, 1.00 to 15.36), although statistical significance was lost (Figure 7).

**Risk of Tachypnea or Respiratory Grunting.** No significant difference was observed between late and early cord clamping in terms of the risk of developing either tachypnea or respiratory grunting (3 trials, 296 infants) (RR, 2.48; 95% CI, 0.34 to 17.89) (Figure 8). The estimate for risk remained nonsignificant when the single low-quality trial was removed from the analysis (2 trials, 239 infants) (RR, 1.24; 95 CI, 0.49 to 1.37).

**Risk of Admission to the NICU.** Only 1 trial (185 infants) reported on admission to the NICU, and this study observed no significant differences between late and early cord clamping (RR, 2.02; 95% CI, 0.63 to 6.48).

**Sensitivity and Subgroup Analyses**

To determine whether the extreme definition of early (up to 1 minute) cord clamping used by Nelson et al had an impact on the overall findings, a sensitivity analysis was undertaken. The results of the meta-analyses with and without these results did not show any significant changes.

**Figure 4. Mean Ferritin Concentrations at Ages 2 to 3 Months Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)**

<table>
<thead>
<tr>
<th>Source</th>
<th>LCC (Mean ± SD)</th>
<th>ECC (Mean ± SD)</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Ferritin, µg/L</td>
<td>No. Ferritin, µg/L</td>
<td>Model</td>
</tr>
<tr>
<td>Geethanath et al.40</td>
<td>59 (73.60 ± 10)</td>
<td>48 (55.70 ± 13)</td>
<td>17.90 (16.59 to 19.21)</td>
</tr>
<tr>
<td>Grajeda et al.46 1997</td>
<td>21 (130.30 ± 8)</td>
<td>16 (119.70 ± 8)</td>
<td>11.20 (–35.65 to 58.05)</td>
</tr>
<tr>
<td>Overall</td>
<td>80 (117.89 ± 11)</td>
<td>64 (105.70 ± 11)</td>
<td>17.99 (16.58 to 19.21)</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: χ² = 0.08 (P = .78), I² = 0%
Test for Overall Effect: z = 26.74 (P < .001)

**Figure 5. Anemia at Ages 2 to 3 Months Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)**

<table>
<thead>
<tr>
<th>Source</th>
<th>LCC No./Total</th>
<th>ECC No./Total</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grajeda et al.46 1997</td>
<td>21/44</td>
<td>15/17</td>
<td>0.54 (0.38-0.77)</td>
</tr>
<tr>
<td>Gupta and Ramji39 2002</td>
<td>13/29</td>
<td>25/29</td>
<td>0.52 (0.34-0.80)</td>
</tr>
<tr>
<td>Overall</td>
<td>73/46</td>
<td>46/46</td>
<td>0.53 (0.40-0.70)</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: χ² = 0.02 (P = .89), I² = 0%
Test for Overall Effect: z = 4.41 (P < .001)
Due to lack of data in the trials on potential confounders, subgroup analysis was possible only for the variable that represents “height of the newborn after birth in relation to the level of introitus or placenta” for a limited number of the outcomes. Our subgroup analyses are limited to comparing composite data from studies in which the newborn’s level is known, rather than being able to compare data for individual infants. The favorable effect of late clamping on neonatal hematocrit at age 6 hours remained significant whether newborns were kept at the level of the placenta 37 or placed on the mother’s abdomen. The subgroup analyses for data collected for hematocrit at 24 to 48 hours and at age 5 days showed significant differences in favor of late clamping, irrespective of the level of the infant during the delayed time (hematocrit at 24-48 hours in infants kept above level of placenta [3 trials, 311 infants] 37,38,48: WMD, 11.80 µg/L; 95% CI, 6.46% to 17.65%); in infants kept at level of placenta [2 trials, 60 infants] 45,47: WMD, 9.03%; 95% CI, 6.46% to 11.60%; in infants kept at level of introitus [1 trial, 12 infants] 46: WMD, 15.00%; 95% CI, 12.35% to 17.65%).

The reducing effect of late clamping on risk of anemia at different points within the first 6 months of life appeared to be sustained irrespective of the level of the newborn after delivery. This was demonstrated by the comparable results of the trial by Ceriani Cernadas et al. 37 in which newborns were placed on the mother’s abdomen, and the trials by Gupta and Ramji 39 and Grajeda et al. 46 in which newborns were kept at levels lower than that of the introitus. Lower rates of iron deficiency anemia at age 6 months were also reported among infants held at the level of the introitus in the study by Chaparro et al. 32

Values of ferritin during the first 6 months of life were higher in infants allocated to late cord clamping and kept either at the level of the placenta (1 trial, 315 infants) 32 (WMD, 11.80 µg/L; 95% CI, 4.07 to 19.53) or below (2 trials, 144 infants) 39,42 (WMD, 17.89 µg/L; 95% CI, 16.58 to 19.21). Rates of polycythemia during the first 48 hours of life were higher when clamping was delayed, whether infants were held at the level of the introitus 32 or below 46 or placed on the mother’s abdomen. 37,38

Although it was not possible to control for the potential modifying effect of breast feeding or iron-fortified formula on iron stores and risk of anemia, Chaparro et al. 32 reported that late clamping increased body iron stores more in infants who still breastfed at 6 months than in those no longer breastfed. These authors also reported that late clamping had greater effects with respect to stored iron in infants not receiving any iron-fortified formula or milk at 6 months than in those receiving such products (early vs delayed clamping among those receiving formula or milk: WMD, −16.9 mg; 95% CI, −38.60 to 4.90; among those receiving no formula or milk: WMD, −46.80 mg; 95% CI, −77.30 to −16.30).

In 1 large randomized trial, late clamping was found to have a greater effect in reducing the likelihood of anemia in infants born to anemic mothers vs those born to nonanemic mothers. 32

Figure 6. Clinical Jaundice and Need for Phototherapy Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)

<table>
<thead>
<tr>
<th>Infants With Clinical Jaundice at 24-48 Hours</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC</td>
<td>ECO</td>
</tr>
<tr>
<td>No./Total</td>
<td>No./Total</td>
</tr>
<tr>
<td>Nelson et al. 46 1980</td>
<td>12/28</td>
</tr>
<tr>
<td>Oxford Midwives, 41 1991</td>
<td>49/296</td>
</tr>
<tr>
<td>Lindemann et al., 42 1992</td>
<td>3/15</td>
</tr>
<tr>
<td>Nelle et al., 43 1993</td>
<td>4/15</td>
</tr>
<tr>
<td>Nelle et al., 44 1996</td>
<td>2/15</td>
</tr>
<tr>
<td>Abdel Aziz et al., 45 1999</td>
<td>3/15</td>
</tr>
<tr>
<td>Emhamed et al. 47 2004</td>
<td>15/57</td>
</tr>
<tr>
<td>Cresam Cernadas et al., 38 2006</td>
<td>0/90</td>
</tr>
<tr>
<td>Overall</td>
<td>531</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: χ² = 10.19 (P = .18), I² = 31.3%
Test for Overall Effect: z = 1.97 (P = .05)

<table>
<thead>
<tr>
<th>Infants Receiving Phototherapy for Jaundice</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC</td>
<td>ECO</td>
</tr>
<tr>
<td>No./Total</td>
<td>No./Total</td>
</tr>
<tr>
<td>Nelson et al. 46 1980</td>
<td>2/28</td>
</tr>
<tr>
<td>Oxford Midwives, 41 1991</td>
<td>11/292</td>
</tr>
<tr>
<td>Emhamed et al., 44 2004</td>
<td>0/57</td>
</tr>
<tr>
<td>Overall</td>
<td>377</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: χ² = 3.26 (P = .20), I² = 38.7%
Test for Overall Effect: z = 1.23 (P = .22)

Sizes of data markers indicate the weight of each study in the analysis. CI indicates confidence interval.

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COMMENT

Our results showed that delaying clamping of the umbilical cord for at least 2 minutes after birth consistently improved both the short- and long-term hematologic and iron status of full-term infants. Placental transfusion associated with late compared with early cord clamping resulted in consistently higher hematocrit levels within normal physiologic ranges and in improved markers of iron status over the first months of life without having a significant impact on the absolute values of bilirubin and plasma viscosity during the first week of life. Although late clamping was associated with a moderate increase in blood viscosity and increased rates of polycythemia, there was no evidence of any significant harm as measured by the need for phototherapy to treat jaundice or by admission to the NICU. The risk of polycythemia was not significant when only high-quality studies were considered. In addition, none of the polycythemic infants evaluated in this review were symptomatic (ie, had symptoms of central nervous system, cardiopulmonary, gastrointestinal tract, or renal impairment).71

The presence of polycythemia in both the late- and the early-clamping groups suggests that mild neonatal hyperviscosity with subsequent uncomplicated polycythemia can occur in some normal healthy neonates, regardless of the time at which the cord is clamped. This is the consequence of a rapid change in hematocrit that normally occurs during the first 24 hours of life.72

The RRs of some other potential adverse outcomes of late cord clamping (tachypnea or grunting, admission to the NICU) were elevated, although not statistically significant. None of the infants with late clamping (LCC) relative to early cord clamping (ECC)

<table>
<thead>
<tr>
<th>Source</th>
<th>Polycythemia</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linderkamp et al,47 1992</td>
<td>0/15</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Nele et al,48 1993</td>
<td>0/15</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Nele et al,49 1996</td>
<td>0/15</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Geethanath et al,46 1997</td>
<td>2/18</td>
<td>3.42 (0.18-65.58)</td>
</tr>
<tr>
<td>Grajeda et al,40 2004</td>
<td>3/57</td>
<td>5.55 (0.29-104.79)</td>
</tr>
<tr>
<td>Ceriani Cernadas et al,42 1997</td>
<td>7/90</td>
<td>3.46 (0.74-16.21)</td>
</tr>
<tr>
<td>Overall</td>
<td>211/192</td>
<td>3.82 (1.11-13.21)</td>
</tr>
</tbody>
</table>

Sizes of data markers indicate the weight of each study in the analysis. CI indicates confidence interval.

Figure 8. Tachypnea or Grunting Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)

<table>
<thead>
<tr>
<th>Source</th>
<th>Tachypnea or Grunting</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yao et al,39 1971</td>
<td>13/33/0/24</td>
<td>19.85 (1.24-318.43)</td>
</tr>
<tr>
<td>Nelson et al,41 1980</td>
<td>3/28/5/26</td>
<td>0.56 (0.15-2.10)</td>
</tr>
<tr>
<td>Ceriani Cernadas et al,42 2006</td>
<td>6/92/2/93</td>
<td>3.03 (0.63-14.64)</td>
</tr>
<tr>
<td>Overall</td>
<td>153/143</td>
<td>2.48 (0.34-17.89)</td>
</tr>
</tbody>
</table>

Sizes of data markers indicate the weight of each study in the analysis. CI indicates confidence interval.
fants with tachypnea or grunting after late clamping needed supplementary oxygen beyond 24 hours of life. This suggests that these respiratory signs are not clinically significant but are part of a physiologic compensatory mechanism. However, since these outcomes were based on a small number of trials and infants, further study is warranted.

Perhaps the most important finding was that the beneficial effects of late cord clamping appear to extend beyond the early neonatal period. Our meta-analysis estimated a significant 47% reduction in risk of anemia and 33% reduction in risk of having deficient iron stores at ages 2 to 3 months with late clamping. Although the risk estimate of anemia at ages 2 to 3 months was pooled from 2 small studies,39,46 and the loss to follow-up in 1 of these was 40%, this finding agrees with the results of a large, well-designed and well-executed randomized trial with respect to the sustained effect of late clamping on other indicators of infant hematologic status at age 6 months: iron stores and ferritin concentrations.32

Because of the relatively small number of studies that reported on any single outcome, use of a funnel plot to explore the possibility of publication bias was not possible. We were reassured that not all studies had positive outcomes for all results and that we were unable to find any unpublished results through contacting key researchers.

The strength of evidence may be limited, since not all included trials were randomized. However, we attempted to control for this by stratifying our results by quality of design, and our results did not vary substantially. Not all studies measured the same outcomes at the same points, and, as a result, several outcomes that we studied are reported by 1 or a small number of studies. In addition, although some individual reports addressed possible confounders such as maternal anemia or iron-fortified formula, we were not able to control for them in our analyses. Despite these limitations, however, because of the consistency of findings across trials, we believe our findings are reliable.

Few of the studies we reviewed reported on maternal outcomes, including early postpartum blood loss. This is particularly significant because active management of the third stage of labor includes administration of a uterotonic agent before delivery of the placenta, and early cord clamping and cutting is recognized as a means of minimizing blood loss for women in the early postpartum period. Although conclusions about maternal outcomes cannot be drawn from our research, it is likely that delayed clamping is compatible with active management of the third stage of labor. Uterotonic agents administered following birth and prior to cord clamping have been shown to increase the rate of placental transfusion and are thus likely to enhance the effect of delayed clamping.36 Although this approach has not been studied, a joint statement from the International Federation of Gynaecology and Obstetrics and the International Confederation of Midwives on active management of the third stage of labor already recommends that delayed clamping be incorporated as part of the active management approach to placental delivery.73 In a recent literature review, similar practice recommendations pertaining to third-stage management were made for providing care in resource-poor settings.28

Late clamping of the umbilical cord is a physiological and inexpensive means of enhancing hematologic status, preventing anemia over the first 3 months of life and enriching iron stores and ferritin levels for as long as 6 months. Although this is of particular importance for developing countries in which anemia during infancy and childhood is highly prevalent, it is likely to have an important impact on all newborns, regardless of birth setting. Additional research may be helpful in refining the timing of clamping by determining the minimum time required to provide maximum benefit associated with placental transfusion. Questions remain about whether the optimal time for clamping is affected by the use of oxytocic drugs before the delivery of the placenta or by milking of the umbilical cord. We believe that this meta-analysis supports incorporating into clinical practice a minimum delay of 2 minutes before clamping the umbilical cord following birth for all full-term newborns.

Author Contributions: Dr Hutton had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hutton.

Acquisition of data: Hutton, Hassan.

Analysis and interpretation of data: Hutton, Hassan.

Drafting of the manuscript: Hutton, Hassan.

Critical revision of the manuscript for important intellectual content: Hutton, Hassan.

Statistical analysis: Hutton, Hassan.

Obtained funding: Hutton.

Administrative, technical, or material support: Hutton, Hassan.

Study supervision: Hutton.

Financial Disclosures: None reported.

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