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

Context With few exceptions, the umbilical cord of every newborn is clamped and cut at birth, yet the optimal timing for this intervention remains controversial.

Objective To compare the potential benefits and harms of late vs early cord clamping in term infants.

Data Sources Search of 6 electronic databases (on November 15, 2006, starting from the beginning of each): the Cochrane Pregnancy and Childbirth Group trials register, the Cochrane Neonatal Group trials register, the Cochrane library, MEDLINE, EMBASE, and CINHAL; hand search of secondary references in relevant studies; and contact of investigators about relevant published research.

Study Selection Controlled trials comparing late vs early cord clamping following birth in infants born at 37 or more weeks' gestation.

Data Extraction Two reviewers independently assessed eligibility and quality of trials and extracted data for outcomes of interest: infant hematologic status; iron status; and risk of adverse events such as jaundice, polycythemia, and respiratory distress.

Data Synthesis The meta-analysis included 15 controlled trials (1912 newborns). Late cord clamping was delayed for at least 2 minutes (n=1001 newborns), while early clamping in most trials (n=911 newborns) was performed immediately after birth. Benefits over ages 2 to 6 months associated with late cord clamping include improved hematologic status measured as hematocrit (weighted mean difference [WMD], 3.70%; 95% confidence interval [CI], 2.00%-5.40%); iron status as measured by ferritin concentration (WMD, 17.89; 95% CI, 16.58-19.21) and stored iron (WMD, 19.90; 95% CI, 7.67-32.13); and a clinically important reduction in the risk of anemia (relative risk (RR), 0.53; 95% CI, 0.40-0.70). Neonates with late clamping were at increased risk of experiencing asymptomatic polycythemia (7 studies [403 neonates]: RR, 3.82; 95% CI, 1.11-13.21; 2 high-quality studies only [281 infants]: RR, 3.91; 95% CI, 1.00-15.36).

Conclusions Delaying clamping of the umbilical cord in full-term neonates for a minimum of 2 minutes following birth is beneficial to the newborn, extending into infancy. Although there was an increase in polycythemia among infants in whom cord clamping was delayed, this condition appeared to be benign.

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CLAMPING 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.[1-4] 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.[5,6]

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.[7-10] This blood is also known to be rich in hematopoietic stem cells.[9,11]

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,[3,10,12,13] which would provide the equivalent of 30 to 35 mg of iron.[14,15] 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.[3,16,17] 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

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Author Affiliations: Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario (Dr Hutton); and The Child and Family Research Institute (Dr Hutton), Western Regional Training Centre for Health Services Research (Dr Hassan), and Department of Health Care and Epidemiology (Dr Hassan), University of British Columbia, Vancouver.
Corresponding Author: Eileen K. Hutton, PhD, McMaster University, 1200 Main St W, MDCL-3101, Hamilton, Ontario, Canada L8N 3Z5 (huttone@mcmaster.ca).

during the first 6 months of life.[14,18] Others believe that the increase in blood volume to the neonatal circulation resulting from delays in clamping may be harmful and could result in overloading the neonatal blood volume, thus increasing the likelihood of respiratory distress,[19,20] neonatal jaundice,[21] and polycythemia.[22,23] 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 significantly decrease maternal blood loss following birth.[24]

Several reviews have studied the potential benefits and risks of late vs early clamping of the umbilical cord. In a recent Cochrane review of cord clamping in the preterm population, late clamping showed some potential benefit in terms of decreased need for blood transfusion and lower risk of intraventricular hemorrhage.[25] Reviews to date of studies in term infants provided no strong evidence for the superiority of either clamping strategy.[3,26,27] However, these reviews were based on studies with small numbers of enrolled infants and did not include 2 large, well-designed trials published 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.[28] 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 umbilical cord in term infants. Outcomes of interest were decided a priori and included reported or clinically determined jaundice, use of phototherapy, polycythemia (defined as hematocrit increased to >65%),[29] tachypnea or respiratory grunting, 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%)[30] and iron-deficiency anemia (defined as hemoglobin concentration <11 g/dL and ferritin concentration <10 µg/L).[31] 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 absolute values of hemoglobin, hematocrit, blood volume and viscosity, and bilirubin, as well as iron status measured by levels of ferritin and stored iron.[32]

Inclusion and Exclusion Criteria

The review included controlled trials (both randomized and nonrandomized) comparing late vs early cord clamping following birth in infants born vaginally 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-birthweight infants, because the potential effects of early vs late clamping are expected to be different in these 2 groups.

Search Strategy

To identify all relevant studies, we performed a literature search on November 15, 2006, in 6 electronic databases (starting from the beginning of each): the Cochrane Pregnancy and Childbirth Group trials register, the Cochrane Neonatal Group trials register, the Cochrane 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 *delay**) 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 relevant studies. Investigators working in this area were contacted about any relevant 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 rereviewing the corresponding articles, and the final set was agreed on by consensus. The methodological quality of each trial was also independently assessed using a modified version of the Jadad scale.[33] Trials rated 10 or more are considered high quality. No disagreements 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.[34] Double entry of the data into Revman was carried out by the 2 reviewers. For continuous variables, we used the mean and standard deviation reported in the original trials to calculate the weighted mean difference (WMD). We expressed the harmful effects of each clamping practice as the relative risk (RR) of adverse events. Estimates of pooled outcomes with 95% confidence intervals (CIs) were calculated by means of fixed-effects models. We also performed tests of heterogeneity between trials using the χ^2 test for significance. When heterogeneity between studies was found to be significant as indicated by I^2 values greater than 50%, pooled estimates based on random-effects models were reported.[35] For those outcomes with adequate data, we performed a sensitivity analysis by comparing 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 alter the rate of placental transfusion, including mode of delivery (vaginal vs cesarean), 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.[10,36]

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)[32,37-43] and 7 nonrandomized (TABLE 2)[19,44-49] 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 preterm infants (12 trials)[50-61] or low-birthweight 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).[70] 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

Source	Location	Randomization	Quality Score/ Comments*	Participants	Intervention	Outcomes
Ceriani Cernadas et al,[37] 2006	Argentina	Multicenter (computer-generated random numbers in sealed opaque envelopes), stratified by hospital and mode of delivery using variable block sizes	12 Outcome assessors blinded Compliance with allocated intervention: ECC, 94.6%; LCC 1, 91.2%; LCC 2, 90.2%	276 Full-term infants born vaginally or by cesarean delivery Inclusion criteria: uneventful singleton pregnancy at term 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	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 = 92) at 3 min after birth (mean, 169.5 s); newborns placed on mother's abdomen or lap	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
Chaparro et al,[32] 2006	Mexico City, Mexico	Computer-generated random numbers in sealed opaque envelopes	12	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	ECC (n = 239) ≈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	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
Emhamed et al,[38] 2004	Tripoli, Libya	Randomized sealed opaque envelopes	10 1 Lost to follow-up in each group Significantly higher proportion of anemic mothers in the LCC group	104 Singleton term infants (37-42 wk) born vaginally Fetal exclusion criteria: birth weight <2500 g or gestational age <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	ECC (n = 46) within 10 s after birth (mean, 12.8 [SD, 5.5] s) LCC (n = 58) after cessation of cord pulsations (mean, 214.6 [SD, 50.6] s); newborns placed on mother's abdomen In both groups, intramuscular oxytocin given after cord clamping	Primary: hematologic status 24 h after birth Secondary: possible adverse effects
Gupta and Ramji,[39] 2002	India	Computer-generated random-number sequences in sealed opaque envelopes	10 44 Infants lost to follow-up at age 3 mo	102 Singleton term infants born vaginally to anemic mothers (hemoglobin <10 g/dL) Fetal exclusion criteria: major congenital anomalies, needed resuscitation at birth Maternal exclusion criteria: eclampsia, severe heart failure, severe antepartum hemorrhage, Rh isoimmunization	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	Primary: levels of serum ferritin and hemoglobin at age 3 mo Secondary: full breast feeding, adverse events

(continued)

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

Source	Location	Randomization	Quality Score/ Comments*	Participants	Intervention	Outcomes
Nelson et al,[40] 1980	Canada	Randomization occurred at 36th gestational week, stratified by parity and social class before randomization	10 1 Dropped out after randomization	55 Singleton term infants born vaginally Maternal inclusion criteria: low obstetrical risk (score <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	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	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
Oxford Midwives Research Group,[41] 1991	United Kingdom	Simple random-number tables in sealed opaque envelopes	10 Outcomes assessors were blinded Oxytocic drugs for third-stage management comparable between groups 2 Women lost to follow-up	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	ECC (n = 256) as soon as possible after delivery (mean time unknown) LCC (n = 296) after stopping of cord pulsation or 3 min after delivery, whichever is sooner (mean time unknown) Newborns placed at/above placenta at 30 s	Primary: duration of cord adherence Secondary: birth weight, feeding, fetal jaundice, postpartum hemorrhage, manual removal of placenta
Geethanath et al,[42] 1997	New Delhi, India	No description of randomization method, withdrawals, or dropouts	8	107 Singleton term infants, born vaginally of nonanemic mothers (maternal hemoglobin >10 g/dL) Fetal exclusion criteria: birth asphyxia, major congenital anomalies Maternal exclusion criteria: eclampsia, heart failure, severe antepartum hemorrhage, Rh isoimmunization	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	Primary: serum ferritin level Secondary: hemoglobin level
Saigal et al,[43] 1972	Montreal, Quebec		5	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	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	Primary: volume of placental transfusion Secondary: bilirubin levels

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.[19,32,37,38,44,45,47,48] Six trials described early clamping as immediate clamping.[39,41-43,46,49] The trial by Nelson et al[40] 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.[37,43] 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.[19,39,41-45,47,48]

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.[44,48] Two of the 4 trials that provided information regarding the use of oxytocic drugs limited administration to the period after the cord was clamped.[38,40] The other 2 trials reported use of oxytocic drugs at different stages of labor, including delivery of the placenta.[41,43] Milking of the umbilical cord was not tested in any of the trials. The majority of trials did not adequately address the hematologic status of the recruited mothers as a potential confounder in the relationship between clamping interval and risk of anemia during infancy.

Meta-analysis Findings

Among the 15 studies, a total of 1912 newborns underwent a trial of late (n=1001) or early (n=911) clamping of the umbilical cord. Tests of heterogeneity were statistically significant in 4 of the comparisons performed in this

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

Source	Location	Quality Score*	Participants	Intervention	Outcomes
Nelle et al,[44] 1996	Germany	8	30 Singleton term infants born vaginally at 39-40 wk Inclusion criteria: uneventful full-term pregnancy Fetal exclusion criteria: malformations, high risk of infections, intrauterine asphyxia Maternal exclusion criteria: high-risk pregnancies, diabetes, twin pregnancies	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	Primary: postnatal changes in left and right systolic time intervals Secondary: adverse events
Abdel Aziz et al,[45] 1999	Cairo, Egypt	7	30 Full-term infants born vaginally at 39-40 wk Inclusion criteria: singleton healthy full-term pregnancy Exclusion criteria: unspecified	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	Primary: determinants of blood viscosity Secondary: jaundice, polycythemia
Grajeda et al,[46] 1997	Guatemala	7	89 Singleton term infants (37 wk or older), birth weight more than 2000 g, born vaginally Fetal exclusion criteria: major congenital abnormalities and need for early cord clamping or resuscitation Maternal exclusion criteria: gestational diabetes or pre(eclampsia), previous cesarean delivery, serious hemorrhage during pregnancy or delivery, cephalopelvic disproportion during delivery	ECC (n = 29) immediately after birth (mean, 18 [SD, 18] s) LCC 1 (n = 30) after stopping of cord pulsation (mean, 84 [SD, 48] s) LCC 2 (n = 30) after stopping of cord pulsation (mean, 84 [SD, 48] s); newborns placed below level of placenta	Primary: fetal hematologic status Secondary: adverse health effects
Linderkamp et al,[47] 1992	Germany	7	30 Singleton term infants born vaginally at 39-40 wk Inclusion criteria: uneventful full-term pregnancy Exclusion criteria: unspecified	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	Primary: determinants of blood viscosity (hematocrit, plasma viscosity, RBC aggregation, and RBC deformity) Secondary: bilirubin measurements in jaundiced infants
Nelle et al,[48] 1993	Germany	7	30 Singleton term infants born vaginally at 39-40 wk Inclusion criteria: uneventful full-term pregnancy Exclusion criteria: unspecified	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	Primary: postnatal changes in blood viscosity and its determinants Secondary: adverse events
Yao et al,[19] 1971	New York State	6	57 Normal full-term infants born vaginally without any perinatal complications	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)	Primary: respiratory frequency, pattern, and occurrence of expiratory grunting from birth through the first hours of life
Oh and Lind,[49] 1967	Sweden	5	36 Singleton term infants born vaginally at 38-42 wk Inclusion criteria: uncomplicated full-term pregnancy Exclusion criteria: unspecified	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	Primary: infant body temperature from 5 min to 5 d of life Secondary: hematocrit at 0.5 h after birth

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.

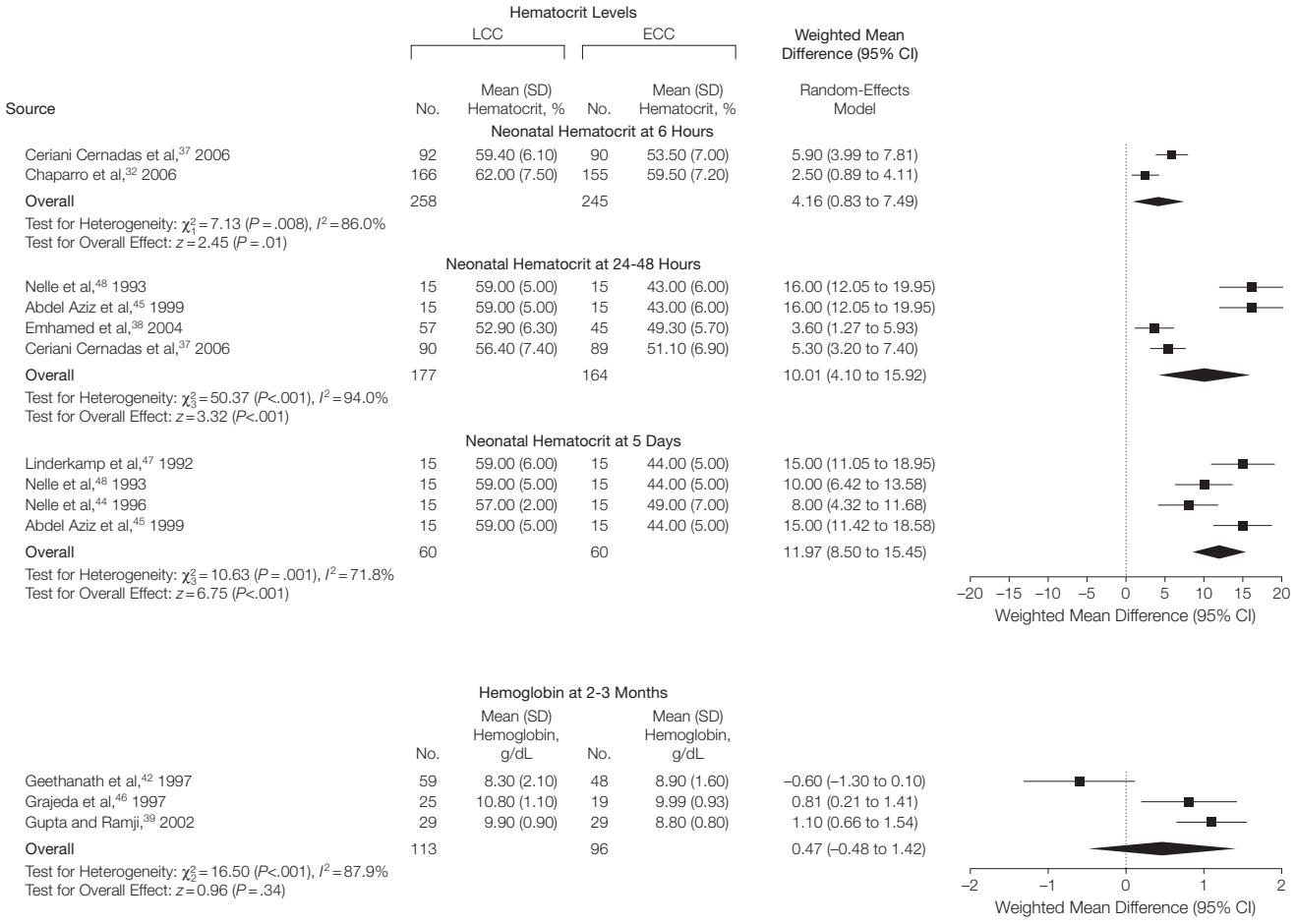
Physiological Parameters

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 infants[37,38,45,48] 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)[32] (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)



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

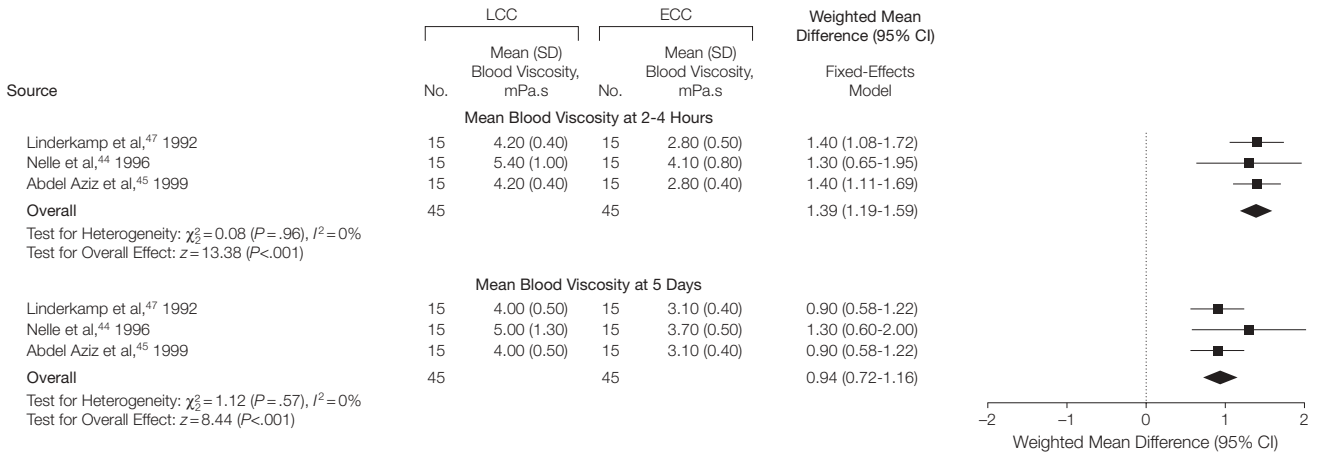
trials, 60 infants)[43,48] (WMD, 9.07 mL/kg; 95% CI, 5.81 to 12.32). Three trials (90 neonates)[45,47,48] found no significant differences with respect to values of plasma viscosity at 24 hours after birth (WMD, 0.01 mPa.s; 95% CI, –0.03 to 0.05) and at age 5 days in the same population (WMD, –0.02 mPa.s; 95% CI, –0.07 to 0.02). Three trials (90 infants)[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)[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)[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)[42,46] (WMD, 17.89 µg/L; 95% CI, 16.58 to 19.21) (FIGURE 4). Two trials that included a total of 165 infants[39,42] 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)[32] (WMD, 11.80 µg/L; 95% CI, 4.07 to 19.53).

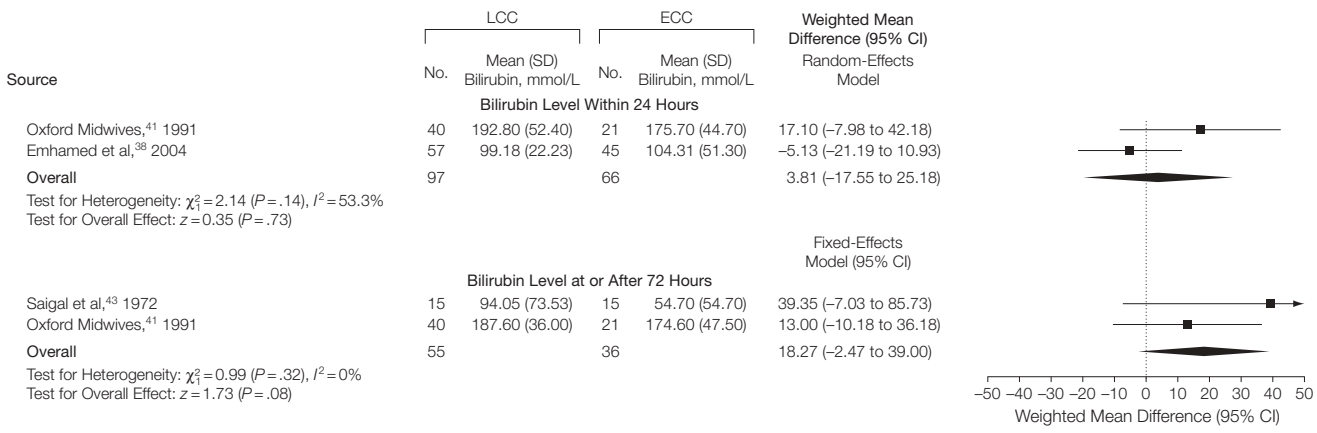
One trial (315 infants)[32] that evaluated stored iron at age 6 months found

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



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)



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.

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)[37] (RR, 0.20; 95% CI, 0.06 to 0.66) and at ages 2 to 3 months (2 trials, 119 infants)[39,46] (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)[32] (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=154) 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)[37,38,40,41,44,45,47,48] did not show an increased risk of developing neonatal jaundice within the first 24 to 48 hours of life associated with late cord clamping (RR, 1.35; 95% CI, 1.00 to 1.81) (FIGURE 6). When low-quality trials were excluded, findings still showed no significant difference between groups in the risk of jaundice (4 trials, 889 infants)[37,38,40,41] (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)[32] (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 mmo/L [15 g/dL]) that necessitated use of phototherapy (3 trials, 699 infants)[38,40,41] (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)[32,37] (RR, 3.44; 95% CI, 1.25 to 9.52) and at 24 to 48 hours (7 trials, 403 neonates)[37,38,42,44,46-48] (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)[37,38] (RR, 3.91; 95% CI, 1.00 to 15.36), although statistical significance was lost (Figure 7).

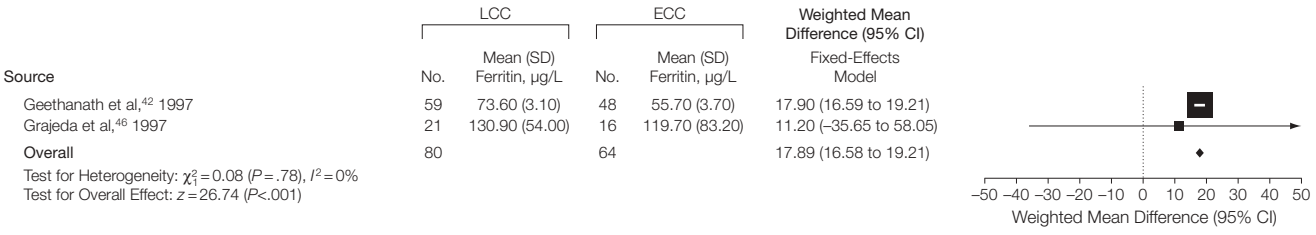
Risk of Tachypnea or Respiratory Grunting. No significant difference was observed between late and early cord clamping in terms of the risk of developing either tachypnea or respiratory grunting (3 trials, 296 infants)[19,37,40] (RR, 2.48; 95% CI, 0.34 to 17.89) (FIGURE 8). The estimate for risk remained nonsignificant when the single low-quality trial was removed from the analysis (2 trials, 239 infants)[37,40] (RR, 1.24; 95 CI, 0.49 to 1.37).

Risk of Admission to the NICU. Only 1 trial (185 infants)[37] 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

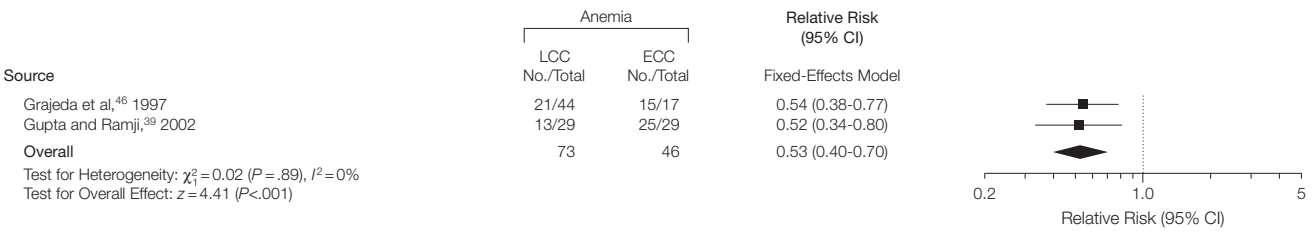
To determine whether the extreme definition of early (up to 1 minute) cord clamping used by Nelson et al[40] had an impact on the overall findings, a sensitivity analysis was undertaken. The results of the meta-analyses with and without these results did not show any significant changes.

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



Sizes of data markers indicate the weight of each study in the analysis. CI indicates confidence interval. To convert values to pmol/L, multiply by 2.247.

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



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

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[31] or placed on the mother's abdomen.[37] 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, 6.08%; 95% CI, 4.63% to 7.54%; in infants kept at level of placenta [1 trial, 30 infants][45]: WMD, 16.00%; 95% CI, 12.05% to 19.05%. Hematocrit at 5 days in infants kept above level of placenta [2 trials, 60 infants][44,48]: WMD, 9.03%; 95% CI, 6.46% to 11.60%; in infants kept at level of placenta [2 trials, 60 infants][45,47]: WMD, 15.00%; 95% CI, 12.35% to 17.65%).

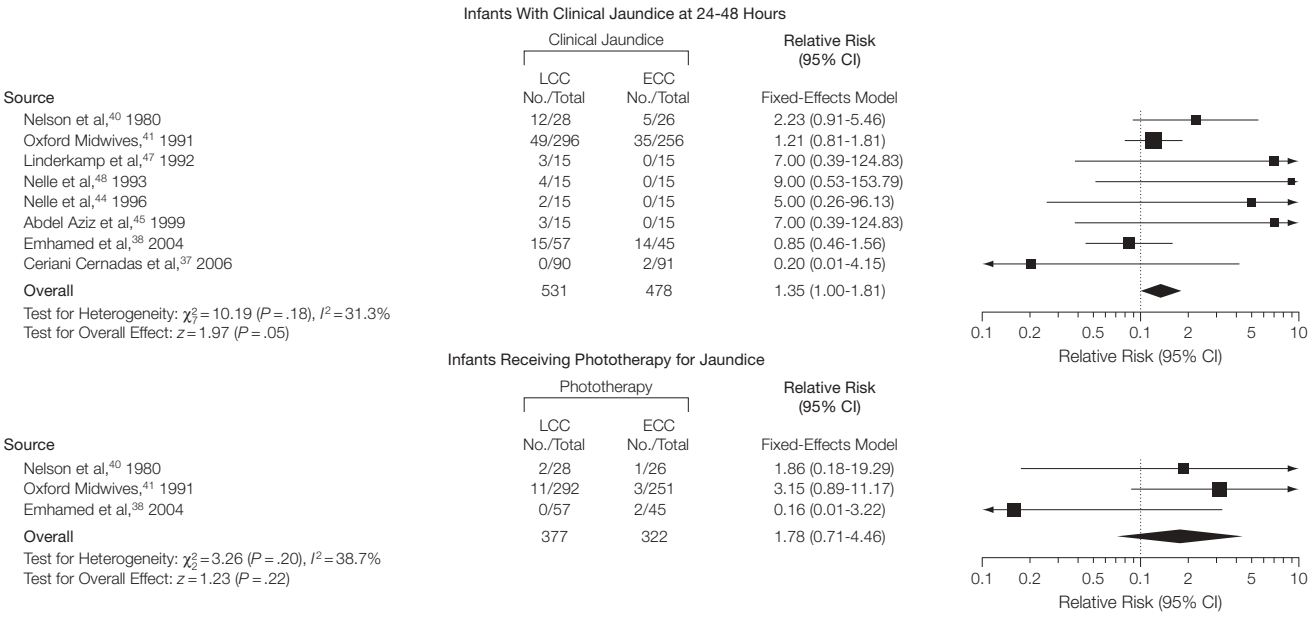
The reducing effect of late clamping on risk of anemia at different points within the first 6 months of life appeared to be sustained irrespective of the level of the newborn after delivery. This was demonstrated by the comparable results of the trial by Ceriani Cernadas et al,[37] in which newborns 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)



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

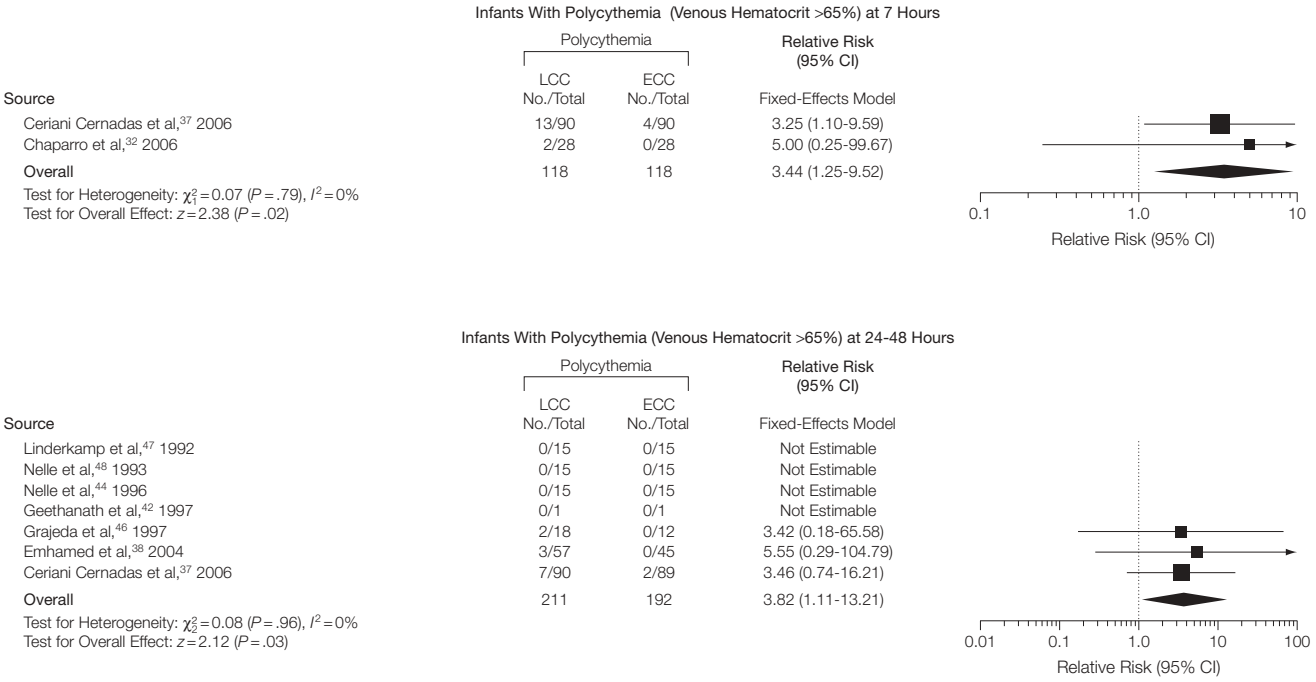
COMMENT

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]

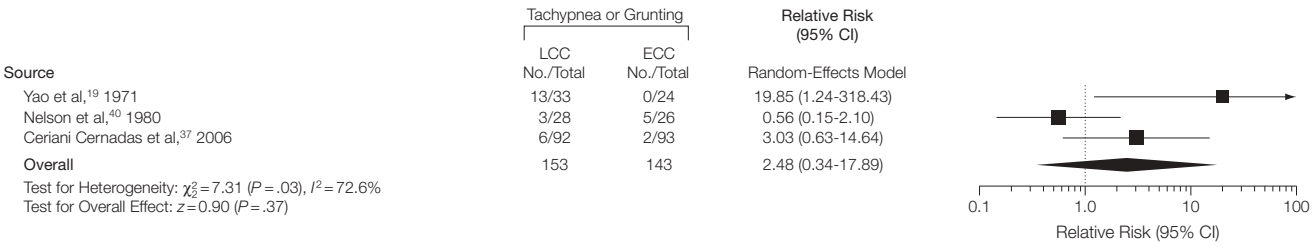
The RRs of some other potential adverse outcomes of late cord clamping (tachypnea or grunting, admission to the NICU) were elevated, although not statistically significant. None of the in-

Figure 7. Polycythemia Among Infants With Late Cord Clamping (LCC) Relative to Early Cord Clamping (ECC)



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)



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%,[39] 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.
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