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Educational Gaps

1. Clinicians should have an understanding of the currently available evidence about timing of umbilical cord clamping in both preterm and term infants.
2. Umbilical cord milking may provide a safe and effective alternative to delayed cord clamping.

Abstract

In the middle of the 20th century, practices regarding the timing of umbilical cord clamping changed from delaying cord clamping to clamping the umbilical cord soon after delivery of the infant. In the last several years, interest in reviving delayed cord clamping has led to an abundance of literature on the subject. On the basis of recent research, many professional organizations in the fields of obstetrics, midwifery, and pediatrics have started to recommend the use of delayed cord clamping for at least a subset of infants. In part 1 of this 2-part review, we presented the history of the delayed cord clamping debate, discussed the rationale behind the use of delayed cord clamping from a physiologic standpoint, detailed the factors that affect transfusion volume during a delay in cord clamping, and examined the concerns that exist regarding the use of delayed cord clamping. In part 2, we present the evidence surrounding timing of cord clamping for the preterm and term infant and maternal outcomes. Finally, we discuss alternatives to delayed cord clamping and present a summary of unanswered questions on the subject.

Objectives

After completing this article, readers should be able to:
1. Describe the available evidence about timing of umbilical cord clamping for preterm and term infants.
2. Discuss umbilical cord milking as an alternative to delayed cord clamping.
3. Identify future areas of research on the subject of delayed cord clamping.

Introduction

At one time the standard in the medical community, delayed cord clamping (DCC) gave way to early cord clamping (ECC) in the middle of the 20th century. In the last several years, interest in reviving DCC has led to an abundance of literature on the subject. In part 1 of this 2-part review, we presented the history of the DCC debate, discussed the rationale behind the use of DCC from a physiologic standpoint, factors that affect transfusion volume during DCC, and concerns that exist regarding the use of DCC. In part 2 of the review, we examine the evidence comparing DCC to ECC in the preterm infant, term infant, and mother. We also discuss umbilical cord milking (UCM) as an alternative to DCC and present a summary of unanswered questions on the subject of DCC.

Review of the Evidence: Timing of Cord Clamping and the Preterm Neonate

Hematologic Outcomes

Although there is an abundance of literature supporting the practice of DCC in premature deliveries, the area of most clear benefit in preterm infants is in the hematologic realm. Most of the

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randomized clinical trials (RCTs) of DCC in preterm infants have evaluated blood volume, red blood cell volume, hemoglobin and hematocrit, or rates of postnatal blood transfusions rather than reporting on iron stores (as is done in the term population). A study of preterm infants born between 24 and 33 weeks’ gestation in the United Kingdom found a significant increase in blood volume for vaginally delivered infants randomized to DCC (80.5 vs 61 mL/kg). (1) A number of RCTs have found significant improvements in early neonatal hemoglobin or hematocrit. (2)(3)(4)(5)(6)

(7) Other studies have found a nonsignificant trend toward higher hematocrits in premature infants receiving DCC compared with their ECC counterparts. (8) One group reported on outcomes before and after implementing a DCC protocol for preterm infants delivered at their institution. Among very low-birth-weight (VLBW) and low-birth-weight neonates, the cohorts receiving DCC had higher hematocrits after delivery. (9) None of the studies that reported on polycythemia found an increased risk in preterm neonates who received DCC. (4)(5)(10)

Perhaps the most appealing outcome related to increased red blood cell volume after DCC is the effect on rates of postnatal blood transfusions. A prospective study of 32 extremely preterm infants found a significant decrease in rates of blood transfusions (P < .001) during the first month after birth for the DCC group. (7) An earlier trial of preterm infants in the United Kingdom delivered vaginally and randomized to 30 seconds of DCC or conventional cord clamping resulted in increased neonatal red blood cell volumes and significantly lower median blood transfusion volumes during the hospital course. (10) Among 40 VLBW neonates randomized to DCC or ECC in another study, 50% in the DCC group and 85% in the ECC group had received a transfusion by age 6 weeks. (11) However, some individual reports found no difference in the number of transfusions between infants receiving DCC and those receiving ECC. (3)(8)(9) A multicenter RCT of extremely premature infants found a nonsignificant trend toward fewer transfusions. (2) To our knowledge, there is no evidence in the literature that DCC has a negative effect on rates of transfusions among preterm infants. The most recent Cochrane review of DCC in preterm infants validated the positive results of most of these smaller studies; the pooled results of 7 trials (n = 392) revealed that fewer infants received transfusions (relative risk [RR], 0.61; 95% confidence interval [CI], 0.46-0.81) and the overall number of transfusions was less in the DCC groups. (12)

**Hyperbilirubinemia**

If DCC increases red blood cell volume, then it follows that there may be increased bilirubin levels. An RCT evaluating effects of DCC in neonates born at 30 to 36 weeks found that an increased proportion of infants were treated with phototherapy (53 vs 73%, P = .03); initial bilirubin level, age at onset of phototherapy, duration of phototherapy, and number of phototherapy courses were not different between the DCC and ECC groups of infants who required treatment. (3) However, most individual studies have not found significant differences in bilirubin levels or phototherapy rates among preterm infants receiving DCC. (4) The potential for a rapid change in circulating blood volume at the time of delivery in very preterm infants receiving DCC initially raised concerns for an increased risk of intraventricular hemorrhage (IVH). However, clinical trials have found either decreased risk or no change in the risk of IVH (all grades). An RCT of 72 premature infants born before 32 weeks and randomized to ECC vs DCC found a significant decrease in rates of IVH among infants in the DCC group with an odds ratio of 3.5 (95% CI, 1.1-11). The difference was most pronounced among male infants. (8) Hofmeyr et al reported on rates of IVH among 38 infants younger than 35 weeks’ gestation randomized to DCC vs ECC. (13) Ultrasonography was performed at approximately 24 hours after birth (range, 6-72 hours), and the results, which were read masked to treatment group, revealed a significantly reduced rate of IVH among infants in the DCC group. (13) A more recent single-center report found no difference in incidence of IVH after implementing a DCC protocol for preterm deliveries. (9) In addition, Ibrahim et al found no difference in the incidence of IVH between infants receiving DCC and ECC. (7) The recent Cochrane review meta-analysis concluded that there was a decreased risk of IVH with data from 10 trials and 539 infants (RR, 0.59; 95% CI, 0.41-0.85). (12) Important to note, however, is the lack of power to determine differences in rates of severe (grade III or IV) IVH among infants randomized to DCC vs ECC.

**Intraventricular Hemorrhage**

The mechanism by which DCC may reduce the risk of IVH in preterm infants probably lies in the effect on hemodynamics and cerebral blood flow. An animal study using preterm catheterized lambs compared a group that
had their cords clamped after the onset of respiration (approximately 3–4 minutes; the DCC group) with a group that had their cords clamped before the onset of ventilation (the ECC group). The DCC lambs exhibited no significant change in heart rate after delivery and had a less severe decrease in right ventricular output. In contrast, carotid and pulmonary blood flows and heart rate underwent rapid fluctuations in ECC lambs, whereas these parameters remained stable in DCC lambs. (14) As described previously, the improved hemodynamic measurements may be attributed to the improved pulmonary blood flow with establishment of ventilation and subsequent improvement in preload for the left ventricle. In support of this statement, Zaramella et al used echocardiography to reveal that infants who received DCC of 4 minutes exhibited larger left ventricular end-diastolic diameters on day 3 after birth compared with infants who underwent ECC. (15) A prospective trial of 51 premature infants (24e31 weeks’ gestation) randomized to 45 seconds of DCC vs ECC evaluated multiple hemodynamic parameters at a series of time points during the first 5 days after birth. Using serial Doppler evaluations, the investigators found that infants in the DCC group had increased superior vena cava blood flow at each time point and greater right ventricular output and stroke volume at 48 hours compared with infants in the ECC group. No significant differences were found in middle cerebral artery or superior mesenteric artery Doppler flows, ventricular shortening fraction, or incidence of patent ductus arteriosus between the groups. (16)

Differences in blood pressure with cord clamping timing were measured in a study in the late 1990s, with higher mean blood pressure (P < .01) through the first 4 hours after delivery reported among infants in the DCC group compared with the ECC group. (7) An RCT with 65 premature infants randomized to DCC of 30 to 45 seconds vs ECC found overall higher diastolic blood pressure in infants receiving DCC and higher mean blood pressure among VLBW infants. (4) Baenziger et al evaluated cerebral oxygenation in preterm infants randomized to 60 to 90 seconds of DCC vs ECC. (6) They found that although cerebral blood volume was no different, cerebral regional tissue oxygenation was better at both 4 and 24 hours after delivery in infants receiving DCC. The infants receiving DCC also had a higher mean blood pressure at 4 hours but not at 24 hours; there was no significant difference in heart rate at any study time point. (6) Other studies have found no change in measured blood pressures after delivery. (2) (11) In the 2012 Cochrane review of DCC in preterm infants, Rabe et al found a nonsignificant trend toward higher mean arterial blood pressure at birth and significantly less need for inotropic support after delivery. (12) In summary, DCC appears to provide hemodynamic stability that may reduce fluctuations in cerebral blood flow and blood pressure that contribute to IVH.

Resuscitation

There is concern that use of DCC will delay necessary resuscitation or stabilization for preterm infants. However, no increased need for intubation or mechanical ventilation and no reports of decreased 5-minute Apgar scores among preterm infants receiving DCC have been found in clinical trials. (3)(7)(9)(11)

Mortality and Other Morbidities

Studies evaluating outcomes after DCC have not found any difference in mortality rates among preterm or VLBW infants, although these were not sufficiently powered to detect a difference. (8)(12) DCC has been associated with decreased risk of other major neonatal morbidities. Mercer et al found in their RCT of 72 premature infants born before 32 weeks that when compared with infants in the ECC group, infants in the DCC group were significantly less likely to have birth culture–proven late-onset sepsis during their neonatal intensive care unit stay (P = .03). (8) Among pooled data from 5 trials (n=241), Rabe et al found a decreased risk of necrotizing enterocolitis (RR, 0.62; 95% CI, 0.43-0.9). (12) An earlier study found that preterm infants who received 60 to 90 seconds of DCC had lower risk of respiratory distress syndrome compared with those receiving ECC. (17)

Long-term Neurodevelopment

Little is known about the effect DCC may have on long-term outcomes in preterm infants. Mercer et al performed developmental testing at 7 months’ corrected gestation among former preterm infants as a follow-up from their trial that reported decreased rates of IVH and late-onset sepsis among infants randomized to DCC. They found no significant difference in the Bayley Scales of Infant Development scores between infants receiving DCC and ECC, although there was a trend toward better motor scores in boys who received DCC. (18) It is notable that the infants who were available for follow-up in that study did not exhibit a difference in their rates of IVH, which may have accounted for the findings.

Review of the Evidence: Timing of Cord Clamping and the Full-Term Neonate

Hematologic Outcomes and Iron Deficiency Anemia

Much of the recent clinical research evaluating the effects of DCC in term infants has been performed in the developing world. Grajeda et al performed an RCT of DCC vs...
ECC in Guatemala, finding no difference in hemoglobin levels at birth but a significantly greater hematocrit and hemoglobin level and significantly less frequent anemia at 2 months in the DCC group. (19) A large RCT in Mexico of 476 infants randomized to 2 minutes of DCC or ECC had a 75% follow-up rate at 6 months. Among infants who were followed up, those in the DCC group had increased mean corpuscular volume, increased ferritin levels (50.7 vs 34.4 ng/mL [113.9 vs 77.3 pmol/L] \( P < .001 \)), and increased total body iron with improved iron stores by 27 to 47 mg compared with infants who received ECC. The benefit was most pronounced in exclusively breastfed infants not receiving iron supplementation and in infants born to mothers with low ferritin levels at delivery. (20) An Argentinean study of 276 infants had 92% follow-up \( (n=255) \) at 6 months for iron and hematologic studies. The investigators found that the serum ferritin level was significantly higher in infants who received 3 minutes of DCC compared with ECC \( (33.2 \text{ vs } 20.9 \text{ ng/mL [74.6 vs 47.0 pmol/L]} \) ), but there was no difference in ferritin levels between infants with 60 seconds of DCC vs ECC.

The mean hemoglobin at follow-up was no different in infants with ECC, 1 minute of DCC, or 3 minutes of DCC. However, the incidence of iron deficiency anemia was 3 times higher among infants receiving ECC compared with infants with 3 minutes of DCC. (21) A group of infants in Zambia randomized to DCC exhibited higher hemoglobin levels at 4 months compared with infants receiving ECC, although this difference did not persist at 6 months. (22) A large RCT in Brazil \( (n=325) \) followed up infants at 3 months (69% follow-up; \( n=224 \)) with hemoglobin and ferritin levels and found a mean improvement of 23.3 ng/mL \( (50.1 \text{ pmol/L]} \) in serum ferritin in infants receiving DCC \( (P = .04) \). (23) Jahazi et al in Iran found no difference in hematocrit at 2 or 18 hours after delivery between term infants born after 30 seconds vs 3 minutes of DCC. (24) However, the measured placental residual blood volume was 39.5% less in the late clamping group, and the neonatal blood volume was increased a mean of 7.1% in the late clamping group \( (P < .001) \). (24) Two separate RCTs from India, both looking at serum ferritin and hemoglobin levels at age 3 months, found conflicting results. Geethanath et al found no difference in serum ferritin or hemoglobin levels at age 3 months. (25) However, Gupta and Ramji found serum ferritin and hemoglobin levels to be significantly higher at age 3 months in the DCC compared with the ECC group, and infants receiving ECC were more than 7 times more likely to be anemic at age 3 months. (26)

Fewer studies on hematologic outcomes in term infants randomized to DCC vs ECC have been published in developed countries. A study from Sweden reported on markers of iron stores in 382 term infants randomized to at least 180 seconds of DCC vs ECC. The primary outcome was serum ferritin level at 4 months. The investigators found no difference between groups in infant hemoglobin levels at 4 months but a 45% higher ferritin level in the DCC group \( (95\% \text{ CI, 23\%-71\% ; } P < .001) \). In addition, the risk of iron deficiency was significantly decreased in infants who received DCC \( (0.6\% \text{ vs } 5.7\% , P = .01) \). (27)

Meta-analyses have found favorable effects of DCC on risk of anemia and improved iron stores in term infants. An analysis of studies including term infants with at least 2 minutes of DCC found significant increases in hematocrit, ferritin, and iron stores and a decreased risk of anemia at 2 to 6 months compared with infants receiving ECC. (28) The 2009 Cochrane review found improved iron stores and less risk of anemia among 3- to 6-month-old infants who had received DCC at delivery. (29)(30) These findings were confirmed in the 2013 updated review.

### Polycythemia and Hyperbilirubinemia

Concern exists for an increased risk of polycythemia with increased placental transfusion at delivery in infants who undergo DCC. However, as with the preterm infant data, this concern has not been supported by results in clinical trials, with a number of studies revealing no difference in incidence of polycythemia between the DCC and ECC groups. (24)(31)(32) One study in Libya, in which infants in the DCC group did not undergo cord clamping until cord pulsation ceased, found that 3 of 50 infants had asymptomatic polycythemia that did not require treatment and no infants had symptomatic polycythemia. (33) A meta-analysis evaluating DCC in term infants found a significantly increased risk of polycythemia (defined as a venous hematocrit of >65%) in the first 48 hours after birth; however, when a sensitivity analysis was performed and only high-quality studies were included, the risk estimate for polycythemia remained similar, but statistical significance was lost \( (RR, 3.91; 95\% \text{ CI, } 1.0-15.3) \). (28)

Akin to the concern for polycythemia is the understandable fear of an increase in hyperbilirubinemia among term infants who receive DCC. An evaluation of individual RCTs reveals mixed results. Some found no difference in rates of jaundice or use of phototherapy. (22)(31)(33) (34) However, a Cochrane review on the subject in 2009 found an increased risk of hyperbilirubinemia requiring phototherapy when evaluating data on 1,762 infants from 5 RCTs \( (RR, 0.59; 95\% \text{ CI, 0.38-0.92}) \). (29) An update on that review in 2013 continued to reveal an increased risk of jaundice requiring phototherapy. (30) However, a meta-analysis by Hutton and Hassan in 2007 did
not find a difference in mean serum bilirubin levels or an increased risk of clinical jaundice or use of phototherapy in infants receiving DCC compared with infants receiving ECC. (28) Another meta-analysis by Mathew in 2011 confirmed these findings and did not find significant differences in hyperbilirubinemia, jaundice, or an increased need for phototherapy due to DCC. (32)

Additional Outcomes
No studies of DCC have found a difference in admission rates to the neonatal intensive care unit. (30)(32) Likewise, no difference in respiratory distress among term infants receiving DCC vs ECC has been detected. (31)(35) No difference in timing of cord separation was found among 551 term infants randomized to DCC vs ECC. (34)

Aside from evaluating RBC indexes and iron stores, few investigators have researched additional outcomes for term infants beyond the early neonatal period. A large (n=382) follow-up group of term infants randomized at birth to 180 seconds of DCC vs ECC underwent the Ages and Stages Questionnaires at age 4 months. Overall, the scores were no different between the groups. However, among the subsection scores, infants who received DCC had increased problem-solving scores (mean difference of 2 points; \( P = .03 \)) and lower personal-social scores (mean difference of 2 points; \( P = .01 \)) compared with the infants receiving ECC. (31) The same set of infants had serial IgG levels measured at birth, 2 to 3 days, and 4 months, and parents reported on history of infections in the first 4 months after birth. The IgG levels were statistically, but not likely clinically, significantly higher in the infants receiving DCC at 2 to 3 days but not at other time points. There was no difference in reported infections. (31)

Review of the Evidence: Timing of Cord Clamping and Maternal Outcomes
In thinking about the risks and benefits of DCC vs ECC, we must also look at maternal outcomes. Because a main contributor to the evolution in the routine use of ECC was the addition of ECC to the active management of the third stage of labor procedures, the effect of DCC on maternal postpartum hemorrhage (PPH) must be known. The 2013 Cochrane review on maternal outcomes of DCC concluded that with data on 2066 women, no significant differences were apparent between the ECC and DCC groups for severe (≥1,000-mL blood loss) PPH. In terms of PPH with a blood loss of 500 mL or more, data from 2,260 women were analyzed, again revealing no significant differences between deliveries managed with ECC or DCC. No statistically significant differences were found in the need for maternal blood transfusion after ECC or DCC in 1,345 women. No trials in the Cochrane review reported on maternal death or severe maternal morbidity. (30)

Alternatives to DCC: UCM
Because of concerns about the amount of time DCC takes after the birth of an infant, particularly in the extremely premature population or in those infants who require immediate resuscitation, UCM has emerged as a possible alternative to DCC because roughly 15 to 20 mL of cord blood resides in the umbilical vein alone. (36) Research involving UCM at this time is limited to 5 RCTs dating back to 2008. Hosono et al were the first to perform an RCT to compare UCM and ECC in 40 infants born between 24 and 28 weeks’ gestation. (37) UCM was defined as milking 20 cm of umbilical cord 2 to 3 times before clamping at a rate of 20 cm per 2 seconds while the infant was held at or below the level of the placenta. (37) They found that infants in the UCM group were more likely not to have needed red blood cell transfusions and had a decreased number of red blood cell transfusions. The initial hemoglobin level and mean admission blood pressures were significantly higher in the UCM group, and no significant differences were found in major morbidities or mortality between the 2 groups. (37) In a secondary analysis of the same enrolled patients, they found that those infants in the UCM group had significantly higher systolic and diastolic blood pressures in the first 12 hours after birth, as well as significantly higher urine output in the first 72 hours after birth. (38) In a study with a similar patient population, cord milking methods, and size (n=50), Takami et al found that the hemoglobin level was significantly higher, mean arterial blood pressures were higher for the first 12 hours, and urine output was higher for the first 24 hours in the milked group compared with the ECC group. (39) They also found that left ventricular end-diastolic dimension, left ventricular cardiac output, and superior venous cava flow were higher in the milked group compared with the ECC group, thereby stabilizing cerebral oxygenation and perfusion as measured by near-infrared spectroscopy. No differences in morbidities were seen between the 2 groups. (39) Rabe et al (36) compared the use of UCM to a 30-second delay in cord clamping in 58 preterm infants born at less than 33 weeks’ gestation. In this study, UCM was performed while the infant was held 20 cm below the level of the placenta and the cord was milked 4 times at a rate of 20 cm per 2 seconds. The authors concluded that this method of cord milking achieved a similar amount of placenta-fetal blood transfusion compared with a 30-second DCC because no significant differences were found in mean hemoglobin values for the first 42 days and...
no significant differences were found in the number of infants undergoing red blood cell transfusion or the median number of transfusions in the first 42 days. (36) In general, in the preterm infants described in these studies, UCM appears to be safe, leads to higher hemoglobin levels, reduces the need for red blood cell transfusions, and facilitates the stabilization of blood pressure and urine output. (36)(37)(38)(39)

UCM has also been studied in the term population. Upadhyay et al compared UCM and ECC (<30 seconds) in 200 infants born at greater than 35 weeks’ gestation. (40) In this group, UCM was performed by first cutting the cord at a length of 25 cm from the umbilicus, holding the cord above the level of the infant, then milking the cord 3 times at a rate of 20 cm per 2 seconds, after which time the cord was clamped at 2 to 3 cm from the umbilicus. They found that infants undergoing UCM had significantly higher mean hemoglobin and ferritin levels at age 6 weeks, without increased polycythemia, serum bilirubin, or need for phototherapy. (40) Erickson-Owens et al compared ECC (<10 seconds) to UCM (5 times) and found in 24 term infants delivered by elective cesarean section that those undergoing UCM had smaller placental residual blood volumes and higher hematocrits at 36 to 48 hours after birth. (41) Although questions remain on how best to use UCM, these initial studies on the subject suggest that it may be a safe alternative to DCC, particularly when resuscitation needs to occur. (42)

Conclusions and Future Avenues of Exploration

Despite all the evidence that has been gathered, a great deal of which supports the safety and efficacy of DCC, many questions remain. These questions are summarized beautifully by Raju and Singhal (Table). (43) Although questions remain on how best to use UCM, these initial studies on the subject suggest that it may be a safe alternative to DCC, particularly when resuscitation needs to occur. (42)

Table. Remaining Questions

<table>
<thead>
<tr>
<th>Maternal care</th>
<th>What is the best time to clamp the cord in relation to administration of uterotonic drugs?</th>
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<tr>
<td>Resuscitation</td>
<td>How can the infant’s position in relation to the placenta be maintained, especially in cesarean deliveries?</td>
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<tr>
<td>Cord clamping</td>
<td>How long of a delay is ideal—30 seconds, 60 seconds, other duration?</td>
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<td>Clamping vs milking</td>
<td>Are there differential benefits between milking and DCC?</td>
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<tr>
<td>At-risk infants</td>
<td>What should be done in infants at risk for fetal polycythemia (eg, born at high altitude, severe intrauterine growth restriction, infants of diabetic mothers, infants large or small for gestational age)?</td>
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DCC=delayed cord clamping; HIV=human immunodeficiency virus. Adapted from Raju and Singhal. (43)
American Board of Pediatrics Neonatal–Perinatal Content Specifications

- Know the mechanisms resulting in anemia of prematurity.
- Understand the mechanism and gestational timing of placental transfer of iron to the fetus and its effect on iron stores in newborn infants.
- Recognize the causes of iron deficiency anemia and various prevention measures.
- Know the effects of variations in arterial and venous blood pressure, blood gas tensions, and hemoglobin concentration on cerebral blood flow and cerebral vascular resistance.
- Know the risk factors for development, proposed mechanisms, clinical and laboratory features, and diagnosis of IVH.

References

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