Seminars in Fetal and Neonatal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Delayed cord clamping in healthy term infants: More harm or good?

Marlies Bruckner [a,b,c], Anup C. Katheria [d,*], Georg M. Schmölzer [a,b,c]

[a] Centre for the Studies of Asphyxia and Resuscitation, Neonatal Research Unit, Royal Alexandra Hospital, Edmonton, Alberta, Canada
[b] Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[c] Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria
[d] Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, San Diego, CA, United States

ARTICLE INFO

Keywords:
Newborn infants
Delivery room
Cord management

ABSTRACT

It is recommended to delay cord clamping in healthy term infants for at least 60- and 180-s in high- and limited-resource environments, as delayed cord clamping lowers the incidence of anemia and iron deficiency and improves neurodevelopment. There are improvements in hemodynamic parameters such as peripheral arterial oxygen saturation, heart rate, cardiac output, and cerebral oxygenation. Historically, delayed cord clamping caused a higher rate of hyperbilirubinemia and phototherapy, but more recent evidence suggests this may no longer be the case. In limited-resource environments delayed cord clamping may reduce anemia and iron deficiency potentially improving neurodevelopmental outcomes. The use of delayed cord clamping in newborn infants with intrauterine growth restriction or monochorionic twins is limited and further evidence is needed before it can be formally recommended.

1. Introduction

In 2010, the International Liaison Committee on Resuscitation recommended that cord clamping be delayed for at least 60 s in term infants that did not require resuscitation [1]. Since then, there have been no updated recommendations regarding cord clamping in healthy term infants. Similarly, the American College of Obstetricians and Gynecologists currently recommend delayed cord clamping in vigorous term infants for at least 30–60 s [2] but there is no consensus how to define early or immediate cord clamping (ECC) or delayed or deferred clamping (DCC).

At term, the infant-placental blood volume distribution is 1/3 in the placenta and 2/3 in the fetus [3], which would remain in the placenta. In comparison, with DCC for 60sec and 3min the placental residual blood-volume is reduced to 20% and 13%, respectively [3]. Prolonging the clamping and cutting of the cord allows the newborn infant to receive blood that otherwise would remain in the placenta [4]. For non-vigorous infants there may be an even greater benefit of delaying the clamping time due to increase blood remaining in the placenta. Using a strict time period for all infants to define when to clamp the cord potentially could harm the sickest infants. Allowing the newborn infant to transition from fetal to neonatal life before clamping the cord might be a more logical approach. While there are some potential benefits to placental transfusion including reduced prevalence of anemia or iron deficiency, there are some theoretical risks including over-transfusion, symptomatic polycythemia, jaundice, hypothermia, persistent pulmonary hypertension and delayed resuscitation [5]. The aim of this review was to summarize and discuss available evidence describing risks and benefits of DCC in healthy term born infants.

1.1. Delaying cord clamping in all healthy term newborns?

While current most governing bodies recommend delaying/deferring cord clamping by 30–60sec, the guidelines are vague on the newborns position, mode of birth, indications such as intra-uterine growth restriction (IUGR), multiple gestations, and maternal factors, or contraindications for prolonged placental transfusion [6] (Fig. 1). Studies have demonstrated that in a vaginal delivery, positioning the newborn either below the perineum or on the mothers abdomen/chest during placental transfusion does not affect the volume transfused, hematocrit, bilirubin concentrations, incidence of polycythemia, need for phototherapy, or admission rate to the neonatal intensive care unit (NICU) [7,8]. This is encouraging as skin-to-skin contact after birth is important for bonding.

In newborn infants born via cesarean section, a higher residual blood volume remains in the placenta, hence infants have lower levels of hematocrit, hemoglobin, and erythrocytes when compared to newborns

* Corresponding author. 3003 Health Center Dr., San Diego, CA, 92123, United States.
E-mail address: anup.katheria@sharp.com (A.C. Katheria).

https://doi.org/10.1016/j.siny.2021.101221

Available online 24 February 2021

born vaginally [9]. A recent observational study compared ECC (<60sec) and DCC (≥60sec) in healthy term infants born via cesarean section and reported no differences in hematocrit at 48 h after birth [10]. Cavallin et al. randomized newborn infants to either ECC or DCC and reported significantly higher hematocrit levels in healthy term infants with DCC compared to ECC (mean difference: 6%, 95%CI (3–8), $p < 0.0001$) [11]. Bilirubin levels and need for phototherapy was similar between the groups [10,11].

While there have not been large studies demonstrating the safety of DCC in newborn infants with IUGR, one substudy demonstrated that it was safe and potentially reduced the incidence of necrotizing enterocolitis [12]. Some guidelines still raise concerns that DCC could worsen polycythemia and hyperviscosity [12] in this population. Recently, Yunis et al. demonstrated in a randomized controlled trial that IUGR preterm infants (<34 weeks' gestation) who received DCC (60sec) had increased stem cell transfusion and significantly lower episodes of anemia at 2 months, red blood cell transfusion, and shorter duration of oxygen therapy compared with those in the ICC (≤10 s) group [13]. There was no difference in the incidence of polycythemia [13]. Cord management in this population should be an interdisciplinary discussion including parents, obstetrics, and neonatology [14].

Dichorionic twins have two placentas and DCC in the first delivering twin should not affect the other twin. Dichorionic twins born either vaginally or via cesarean birth should have DCC for at least 30–60sec. However, monochorionic twins share a placenta and therefore DCC is not recommended (i.e., risk of acute inter-twin transfusion at birth). While studies reported differences in hemoglobin levels between the 1st and 2nd vaginally born twin but not after caesarean birth [15], no difference in hematocrit levels were observed [16].

Infants with red blood cell alloimmunization benefit from DCC due to a decreased postnatal exchange and top-up transfusions [17,18]. Thus, DCC with duration of 30sec in infants at risk for red blood cell alloimmunization neonatal anemia is recommended [17]. Table 1 gives an overview of recommendations, absolute and relative contraindications for DCC in vigorous healthy term born infants. However, it must be considered that there is significant heterogeneity among recommendations about performing DCC [6].

1.2. *Umbilical blood gases*

Routine cord blood gas analysis are used to diagnose and treat infants who are acidemic after birth [19,20]. However, the current cord blood gas reference ranges were defined when ECC was routinely practiced, hence blood sampling on the pulsating intact cord needed to be evaluated [19]. Studies demonstrated that cord blood sampling and umbilical gas analysis during DCC is feasible, safe and accurate [21,22]. A recent systematic review, describing umbilical blood gas values of vaginally delivered healthy term singletons reported higher arterial pO_2, pCO_2, base deficit, and lactate values while pH and HCO_3 were lower in the DCC compared to the ECC [19]. Giovannini et al. described that after 3min DCC, pCO_2 and lactate were higher after caesarean section compared to vaginal delivery [23]. Blood gas values obtained after DCC are slightly more acidemic but still within normal reference ranges, therefore this effect is probably clinically insignificant in healthy, term delivered newborns [19]. Furthermore, DCC leads to a decreased transfer of cord blood lipids [24] and a higher supply of hemoglobin [23,25,26], antioxidants [24,27,28], inflammatory mediators [28], and stem cells [29] immediately after birth.

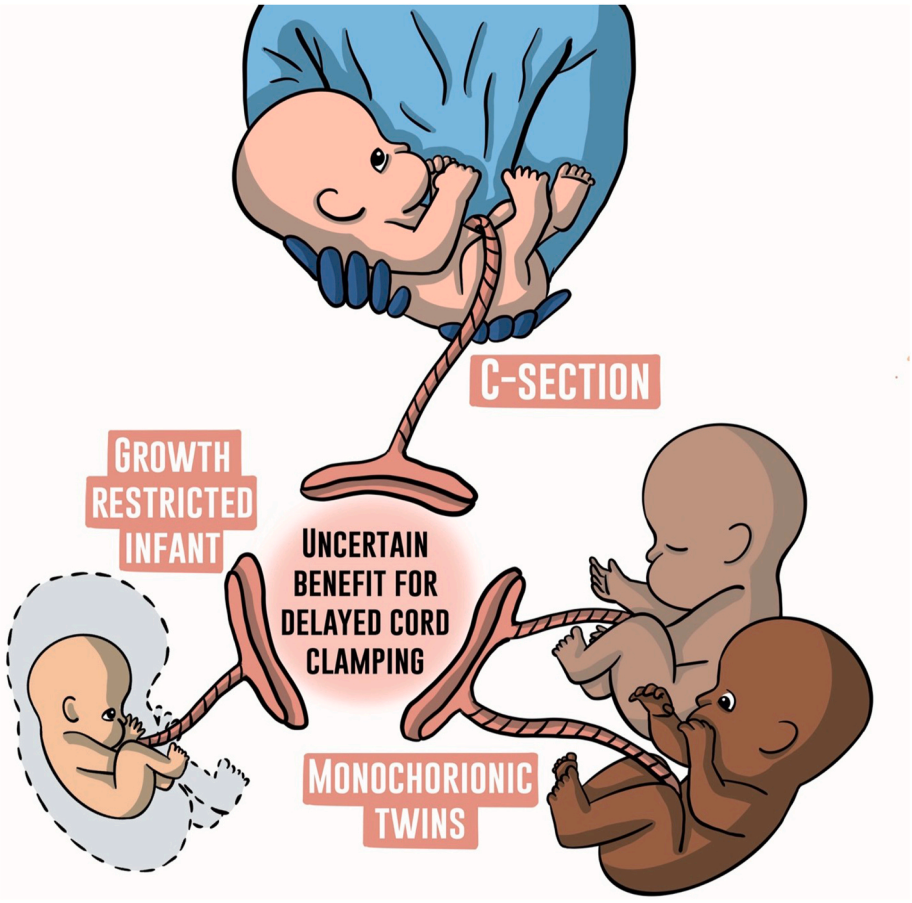

Fig. 1. Scenarios where benefits of delayed cord clamping are uncertain/limited. (growth restricted infant (a very small baby), monochorionic twins (two babies sharing a placenta), cesarean section (a baby being delivered by C-section and held up); with permission from Dr. Cathy Cichon, Twitter handle: @DocScribbles.

Table 1
Overview of recommendations and contraindications for delayed cord clamping (DCC) in vigorous healthy term newborn infants.

Indication for DCC	Relative indication for DCC	Contraindication for DCC
Healthy newborn infants in high-resource environment independent of birth mode (DCC for at least 60sec) [1]	Limited data and inconsistent recommendations about dichorionic twins [2,6,14]. The authors suggest it might be reasonable to perform DCC in the 2nd but not in the 1st dichorionic twin.	Infants contraindication: Need for immediate neonatal resuscitation [2,6,14], monochorionic twins [6,14], birth asphyxia secondary to hypoxic-ischemic events [6,14], shoulder dystocia [14]
Healthy newborn infants in low-resource environment (DCC for 180sec) [61–63]	Consider the mother's choice if she asks for a longer DCC [14]	Maternal contraindications: Healthy newborns from HIV-positive mothers in other cases than mentioned in "indication for DCC" [14], Rhesus disease [6,14], Cesarean delivery under general anesthesia [6,14], massive uterine bleeding, collapse, cardiac arrest [6,14], amniotic embolism [6]
Healthy newborns born via Caesarean Section from HIV-positive mothers with HIV-RNA ≤1000 copies/mL and adequate antiretroviral therapy during pregnancy (DCC between 1 and 2min) [14]	In cases of fetal growth restriction with abnormal umbilical artery Doppler studies or other situations in which uteroplacental perfusion or umbilical cord flow may be compromised, a discussion between neonatal and obstetric teams can help weigh the relative risks and benefits of immediate or delayed umbilical cord clamping [2]	Uteroplacental contraindications: fetal hydrops [6,14], doubts about the integrity of the umbilical cord [6,14], placental detachment [6,14], cord prolapse [6,14], vasa previa rupture [6]
In the case of altruistic (private) cord blood donation [14]		In the case of dedicated (public) cord blood donation [14]

1.3. Medico-legal problems

Umbilical blood gas sampling in healthy vigorous infants after uncomplicated birth is not the standard of care in all hospitals. Analysis of paired arterial and venous specimens might provide some insights into the etiology of acidosis in the newborn infants. When combined with other clinical information, a normal paired arterial and venous cord blood gas result might suggest against an intrapartum hypoxic-ischemic event [30].

Goodlin et al. analyzed retrospectively 11,203 deliveries and reported that in 96% and 84% of cases with unexpected and expected acidemia (pH < 7.13) newborn infants were discharged together with their mothers [31]. The register of the National Patient Insurance Association in Finland reported 683 obstetric claims during delivery, with the highest amount of compensation paid as a result of delay in the diagnosis of fetal asphyxia from 1987 to 1995 [32]. However, routine umbilical blood gas sampling on all newborn infants does not have any clinical or legal benefits [31].

1.4. Arterial oxygen saturation and heart rate

Peripheral oxygen saturation (SpO_2) and heart rate (HR) of newborn infants during immediate transition are affected by cord clamping time. Smit et al. recorded SpO_2 and HR from vaginally born healthy term infants with DCC compared to the reference ranges from Dawson et al., which were generated when ECC was standard of care [33,34]. Infants with DCC had higher SpO_2 and lower HR values along with a slower HR increase the first minutes after birth [33]. In addition, infants who received DCC have significantly higher minute-by-minute SpO_2 values in the first 5 min after birth compared to the target saturations recommended by the current neonatal resuscitation guidelines [35]. Furthermore, HR was significantly higher and stabilized sooner after birth compared to the reference range by Dawson [35]. However, in infants born via caesarean section no differences in SpO_2 and HR in the first 10 min after birth was observed [11,36]. Katheria et al. randomized term newborn infants at risk for resuscitation to 60sec or 5min of DCC and reported a trend to less resuscitation interventions and improved Apgar scores in the 5min DCC group [37]. A recent Cochrane review reported no difference in Apgar score <7 at 5min (n = 1399; Risk ratio(RR) [95% CI] 1.23 [0.73, 2.07], p = 0.43), admission rate to NICU (n = 1675; RR [95%CI] 0.79 [0.48, 1.31], p = 0.36), and respiratory distress (n = 835, Risk ratio [95%CI] 0.70 [0.22, 2.19], p = 0.53) in term newborn infants who received either ECC or DCC [38].

While several studies reported SpO_2 and HR changes during the immediate transition during ECC or DCC, data about SpO_2 and HR changes within the first 48 h after birth in term newborn infants are lacking. Katheria et al. reported no differences in SpO_2 or HR rate 12 h after birth [37]. There are no studies reporting on further changes of SpO_2 or HR past 12 h in term infants who received either DCC or ECC.

1.5. Hemodynamic parameters and cerebral oxygenation

Animal studies suggest that DCC improves hemodynamic parameters including blood pressure, cardiac output and cerebral oxygenation [39] (Fig. 2). Katheria et al. reported increase in stroke volume and cardiac output increased by a mean(SD) 13.1(12.3)% and 12.6(6.3)% (p < 0.001) for every minute the cord was unclamped in healthy vaginally delivered term infants using electrical impedance [4]. Similar, van Vonderen et al. observed an increased left ventricular output between 2min and 5min after birth in term infants delivered by caesarean section with 30–60sec DCC [40]. In term infants at risk for resuscitation a 5min DCC resulted in greater mean arterial blood pressure and cerebral tissue oxygenation compared to a 1min DCC in the first 12 h after birth [37].

While infants with longer cord clamping duration have a greater

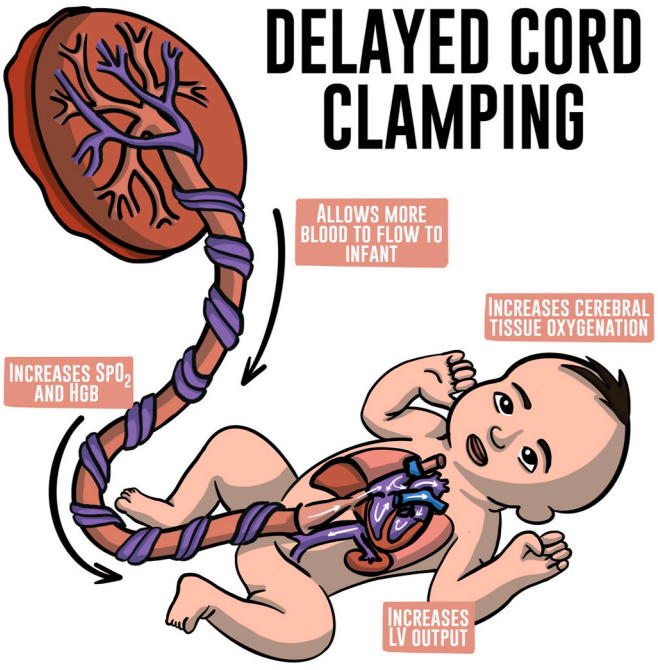

Fig. 2. Benefits of delayed cord clamping, with permission from Dr. Cathy Cichon, Twitter handle: @DocScribbles.

mean blood pressure in the first hours after birth, this disappears during the first days after birth [11]. Cavallin et al. described an increase of systolic and diastolic blood pressure over time, however, blood pressure was similar between ECC (≤10sec) and DCC (>60sec) during the first three days after birth [11]. Similar, no differences in mean blood pressure in infants who received either DCC or umbilical cord milking were described within the first 24–48 h after birth [41]. DCC seems beneficial regarding hypovolemia and hypotension, which might affect cerebral blood flow dynamics [41]. However, there are very limited data on how DCC affects cerebral hemodynamics in term infants. Jaiswal et al. demonstrated that neither DCC nor umbilical cord milking did not result in differences in cranial Doppler indices during the first 24–48 h after birth and they were similar values of healthy newborns with ECC [41].

1.6. Anemia and polycythemia

The higher mean blood pressure might contribute to improved hemodynamics and organ perfusion due to effective placental transfusion and extra blood volume from DCC [17]. Ceriani et al. reported that hematocrit levels in healthy term newborn infants who received ECC (15sec), 1min or 3min DCC were not significantly different [42]. However, the prevalence of infants with hematocrit level <45% at 6 h of age was significantly higher at 8.9% in the ECC group versus DCC with either 1min or 3min (1% and 0%, respectively; $p < 0.03$) [42]. In another study was shown that hemoglobin levels of healthy term newborn infants who received DCC (90sec) compared with ECC (30sec) were higher 12 h after of birth. Katheria et al. measured hemoglobin noninvasively with an oximeter 12 h after birth and reported mean(SD) 14.1(1.8) vs. 15.4(2.7) g/dL ($p = 0.06$) in term newborn infants receiving 5min vs. 1min DCC [37].

Hypervolemia, polycythemia, and hyperviscosity syndrome in the first days after birth are frequently mentioned as adverse effects of placental transfusion [17]. Although, several studies reported significantly higher hemoglobin and/or hematocrit values in term infants with DCC none reported long-term complications [11,43–46]. Furthermore, hematocrit levels increased with lengthening time for DCC [11,43–46]. In comparison, Ceriani Cernadas et al. reported no differences in hemoglobin and hematocrit with cord clamping duration of 15sec, 1min, and 3min [42]. Studies have also reported that higher hemoglobin and hematocrit values in healthy term infants who received DCC did not result in an increased incidence of polycythemia [25,26,42,43,47]. Qian et al. reported on a higher rate of polycythemia in those infants only on the 1st day after birth [46]. There is inconsistent data regarding prevalence of anemia during the first days after birth. Ceriani Cernadas et al. reported a higher prevalence of infants with anemia in the first two days after birth with ECC compared DCC (16.8%, 2.2%, and 3,3% with cord clamping duration of 15sec, 1min, and 3min, respectively) [42]. Similar, Askelöf et al. reported a higher prevalence of anemia with ECC compared to DCC with either 60 or 180 s (6.4%, 1.9% and 1.4%, respectively ($p = 0.04$)), however none of the anemic infants required medical treatment [48]. While some studies reported higher rates of anemia with ECC, other studies did not [43,44,49].

A recent systematic review of 20 trials (3733 infants) compared DCC and ECC and reported follow-up data of <6 and ≥ 6 months in term and preterm infants [50]. DCC reduced the incidence of anemia after six months of age (≥6 months group: RR 0.92, 95%CI (0.87–0.99), $p = 0.02$, 5 trials, $n = 1717$ infants) and increased hemoglobin levels after six months of age (≥6 months group: standard mean difference 0.15, 95%CI (0.06–0.25), $p = 0.002$, 5 trials, $n = 1670$ infants) in term infants [50]. A further trial, which was not included in the systematic review by Mercer et al. reported no differences in hemoglobin, hematocrit, or other blood values at four months of age [51]. Similar, Askelöf et al. observed no statistically significant differences in hemoglobin levels, hematocrit levels or prevalence of anemia in 525 term infants who received cord clamping times of 10sec, 60sec, or 180 s at four months of age [48]. Similarly, there was also no significant differences in hemoglobin and hematocrit levels between DCC and umbilical cord milking in healthy term infants at 12 months of age [52]. Although the data about the prevention of anemia with DCC is inconsistent, DCC does not harm the hematological status for healthy term infants at a longer term.

1.7. Hyperbilirubinemia and jaundice

There have been concerns, that DCC causes a higher rate of hyperbilirubinemia and thereby increasing the need for phototherapy. However, studies comparing ECC or DCC (ranging from 30sec up to 5min or until cord pulsation stopped) in term newborns within the first 24 h reported no differences in transcutaneous bilirubin levels in term newborns within the first 24 h (ECC(<30sec) mean(SD) 3.73(2.05) vs. DCC (90sec) 3.48(1.23)mg/dL, $p = 0.40$) ([17,37,53,54]. In 2013, a meta-analysis included 2324 term infants from seven trials reported significantly fewer infants requiring phototherapy for jaundice with ECC compared to DCC (RR 0.62, 95%CI (0.41–0.96), $I^2 = 5\%$). Several studies subsequently reported no differences in either bilirubin levels or need of phototherapy [11,43–47,49]. Yang et al. reported that mean peak of transcutaneous bilirubin levels were significantly higher, while there were no significant differences in mean peak serum bilirubin levels between ECC and DCC [55]. Infants receiving DCC were more likely to have a serum bilirubin measurement (43.7% vs. 29.4%, $p < 0.01$; OR 1.86; 95%CI (1.25–2.78)), and more likely to undergo multiple serum bilirubin measurements [55]. However, this did not result in a higher incidence of phototherapy [55].

1.8. Iron deficiency and neurodevelopment

Low iron stores could result in a lower intelligent quotient, therefore improving iron storage may be beneficial. DCC improves iron stores in newborn infants due to prolonged placental transfusion of iron-rich blood without adverse effects [25,56]. Zhao et al. reported in a meta-analysis that DCC lowered the incidence of iron deficiency (<6 months and ≥6 months) and iron deficiency anemia (4–12 months) [50]. Furthermore, levels of serum iron (1–5 months), total body iron (4–6 months), serum ferritin (<6 months) and transferrin saturation (2–12 months) were improved with DCC [50]. Ferritin concentration between infants who received 60sec or 180sec of DCC was similar, while 60sec of DCC had higher ferritin concentrations compared to ECC [48]. Mean ferritin was lower in boys compared to girls, and iron deficiency was more prevalent among boys [48]. Recently, Mercer et al. reported greater ferritin levels in healthy term infants with DCC (>5min) compared to ECC (<20sec) [51]. Additionally, they reported that greater ferritin levels were associated with increased brain myelination (evolving brain function and cognitive skills) at four months of age [51]. The authors explain those findings with the assumption iron is involved in myelinogenesis and is a necessary component for maturation and function of the oligodendrocytes [51]. More recently, the same study group reported that in those infants that the iron status was not different anymore at 12 months of age, however, there was still a sustained increase of myelin content in brain regions involving motor pathways and areas responsible for visual/spatial and sensory processing in the infants remained [57]. Furthermore, additional brain regions had higher myelin content after DCC, which were previously not observed at four months of age, but this did not result in improved neurodevelopmental outcomes [57]. A large trial from Sweden compared DCC (≥3min) with ECC (≤60sec) and reported higher scores in “communication” (mean(SD) DCC 59.3(2.0) vs. ECC 58.7(2.6), $p = 0.008$), “gross motor” (mean(SD) DCC 56.1(6.2) vs. ECC 54.7(6.4), $p = 0.02$), and “personal-social” domain (mean(SD) DCC 59.0(2.1) vs. ECC 57.9(3.9), $p = 0.008$) [58]. Similar, low risk term infants had higher scores for parent-reported prosocial behavior (adjusted mean difference (AMD): 0.5; 95%CI: >0.0–0.9; $p = 0.05$), personal-social (AMD: 2.8; 95%CI: 0.8–4.7, $p = 0.006$), and fine-motor development (AMD: 2.1; 95%CI: 0.2–4.0, $p = 0.03$), particularly in boys (DCC vs. ECC at-risk analysis in movement:

3.6% vs. 23.1%; p = 0.008, Ages and Stages Questionnaire: 8.9% vs. 23.6%; p = 0.03, and Wechsler Preschool and Primary Scale of Intelligence: 2.0% vs. 12.5%; p = 0.06) at four years of age after either DCC (≥3min) or ECC (≤10sec) [59]. These studies implicate a minimal effect on neurodevelopmental outcomes in term born infants in a high-income country.

Zhao et al. reported on other clinical pictures (e.g., fever, diarrhoea, crying, tiredness, visit to pediatrician) < 6 months and ≥6 months after birth, however, he only identified three trials and none of these outcomes were statistical significantly improved with ECC or DCC, which could be partly attributed to the small sample sizes or relatively low incidence rates [50].

1.9. Delayed cord clamping in limited resource environments

DCC is an inexpensive and easy to perform intervention in all environments. DCC has many benefits, however DCC could increase the risk of phototherapy and many units continue to perform ECC [25]. Although a systematic review from 2013 reported significantly fewer infants requiring phototherapy for jaundice with ECC, none of the included studies had explicit guidelines to diagnose jaundice, or when to start phototherapy. More recent evidence suggest against the increased risk for phototherapy [11,43–47,49]. Tiemersma et al. randomized newborn infants in a resource-poor setting to either DCC(120–180sec) and ECC(≤30sec) and did not observe an increase in the incidence of neonatal jaundice or hyperviscosity syndrome [60].

The prolonged placental transfusion of iron-rich blood increases iron stores, which might be particularly beneficial in resource-limited settings where severe anaemia is common and associated with increased mortality and impaired mental and motor development [25,61]. In 2006, Van Rheenen et al. published a practical approach to timing of cord clamping in resource poor settings [61]. Normal birthweight infants cord clamping should be delayed for at least 3 min to allow the maximum possible volume of placental transfusion [61]. KC et al. demonstrated that anemia was less prevalent in infants receiving DCC (>3min) compared to ECC(<60sec) (73.0% vs. 82.2%, relative risk (RR) 0.89, 95%CI: 0.81–0.98, p = 0.01) at 8 months of age and 12 months of age (85.9% vs. 77.8%, RR 0.91, 95%CI: 0.84–0.98, p = 0.02, number needed to treat 12) in a low-income country with a high prevalence of anemia [62]. Iron deficiency (22.2% vs. 38.1%, p < 0.001) and iron deficiency anemia (19.3% vs. 33.3%, p < 0.001) were less prevalent in the DCC group at 8 months of age with a number needed to treat of 6 and 7, respectively [62]. Severe jaundice and kernicterus are rare but severe complications; however they have not been reported in any studies. The benefits of reducing anemia and iron deficiency and thereby improving neurodevelopmental outcomes must be considered especially in areas where maternal anemia is prevalent and iron supplementation is limited. Globally DCC has the potential to lead to 5 million fewer infants with anemia at 8 months of age in particular in South-Asia and Sub-Saharan Africa [62]. Therefore DCC should be performed in vigorous healthy term born infants for at least 3 min in resource-limited settings [61–63].

1.10. Research gaps

Studies examining DCC during IUGR, multiple gestations, or infants requiring resuscitation. Currently, there are several ongoing studies examining DCC in healthy term infants (NCT04369313, NCT04632264, NCT04459442, NCT04353544). Most of these studies focus rather on placental transfusion or maternal outcomes than neonatal outcomes. There are no currently studies examining different lengths of DCC in healthy term infants although the optimal cord clamping duration remains unknown. A few studies reported neurodevelopment benefits in healthy term infants with DCC, however further studies are needed. Studies could either examining long-term neurodevelopment outcomes using Ages & Stages Questionnaires or population level data using daycare or school tests.

2. Practice points

- Delay cord clamping in healthy term infants for at least 60- and 180-s in high- and limited-resource environments
- Delayed cord clamping reduces:
  - o Incidence of anemia
  - o Incidence of iron deficiency
  - o Improves hemodynamic parameters (i.e., peripheral arterial oxygen saturation, heart rate, cardiac output, and cerebral oxygenation)
- There is no evidence that delayed cord clamping results in higher rates of phototherapy

3. Conclusion

There is evidence that DCC in healthy term infants might be beneficial regarding prevention of anemia and iron deficiency resulting in improved neurodevelopment up to four years of age. Contrary, higher transcutaneous bilirubin levels might lead to an increased number of blood draws whereas it seems that there is no difference in serum bilirubin or incidence of phototherapy. Further on, it should be differentiated between healthy term infants as there is lack of data regarding birth mode, multiple gestations, infants with IUGR or maternal factors. Serious efforts must be undertaken to conduct studies not only sick infants but in healthy term infants since DCC may have a meaningful impact on important outcomes in those infants later in life.

Acknowledgment

We would like to thank Dr. Cathy Cichon, @DocScribbles for the drawing of the figures. Drs. Schmoelzer and Katheria reports grants from the PREMOD2 (R01HD088646) and MINVI Trial (R01HD096023), mulrandomized controlled trials, which compares delayed cord clamping with umbilical cord milking in preterm infants, and early cord clamping with umbilical cord milking in non-vigorous term infants, from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

References

[1] Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, et al. Part 11: neonatal resuscitation: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 2010;122:S516–38. https://doi.org/10.1161/CIRCULATIONAHA.110.971127.

[2] Committee on Obstetric Practice. Committee opinion No. 684: delayed umbilical cord clamping after birth. Obstet Gynecol 2017;129:e5–10. https://doi.org/10.1097/AOG.0000000000001860.

[3] YAO A. Distribution of blood between infant and placenta after birth. Lancet 1969;294:871–3. https://doi.org/10.1016/S0140-6736(69)92328-9.

[4] Katheria AC, Wozniak M, Harari D, Arnell K, Petruzzelli D, Finer NN. Measuring cardiac changes using electrical impedance during delayed cord clamping: a feasibility trial. Matern Heal Neonatol Perinatol 2015;1:15. https://doi.org/10.1186/s40748-015-0016-3.

[5] Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. J Perinatol 2017;37:105–11. https://doi.org/10.1038/jp.2016.151.

[6] Liyanage SK, Ninan K, McDonald SD. Guidelines on deferred cord clamping and cord milking: a systematic review. Pediatrics 2020;146. https://doi.org/10.1542/peds.2020-1429.

[7] Vain NE, Satragno DS, Gorenstein AN, Gordillo JE, Berazategui JP, Alda MG, et al. Effect of gravity on volume of placental transfusion: a multicentre, randomised, non-inferiority trial. Lancet 2014;384:235–40. https://doi.org/10.1016/S0140-6736(14)60197-5.

[8] Mansaray A, Yetman R, Berens P. Effect of delayed cord clamping above versus below the perineum on neonatal hematocrit: a randomized controlled trial. Breastfeed Med 2015;10:464–7. https://doi.org/10.1089/bfm.2015.0109.

[9] Zhou Y -b, Li H -t, Zhu L -p, Liu J -m. Impact of cesarean section on placental transfusion and iron-related hematological indices in term neonates: a systematic review and meta-analysis. Placenta 2014;35:1–8. https://doi.org/10.1016/j.placenta.2013.10.011.

[10] Consonni S, Vaglio Tessitore I, Conti C, Plevani C, Condo' M, Torcasio F, et al. Umbilical cord management strategies at cesarean section. J Obstet Gynaecol Res 2020:1–8. https://doi.org/10.1111/jog.14501.
[11] Cavallin F, Galeazzo B, Loretelli V, Madella S, Pizzolato M, Visentin S, et al. Delayed cord clamping versus early cord clamping in elective cesarean section: a randomized controlled trial. Neonatology 2019;116:252–9. https://doi.org/10.1159/000500325.
[12] Wang M, Mercer JS, Padbury JF. Delayed cord clamping in infants with suspected intrauterine growth restriction. J Pediatr 2018;201:264–8. https://doi.org/10.1016/j.jpeds.2018.05.028.
[13] Yunis M, Nour I, Gibreel A, Darwish M, Sarhan M, Shouman B, et al. Effect of delayed cord clamping on stem cell transfusion and hematological parameters in preterm infants with placental insufficiency: a pilot randomized trial. Eur J Pediatr 2020:157–66. https://doi.org/10.1007/s00431-020-03730-4.
[14] Ghirardello S, Di Tommaso M, Fiocchi S, Locatelli A, Perrone B, Pratesi S, et al. Italian recommendations for placental transfusion strategies. Front Pediatr 2018;6:1–16. https://doi.org/10.3389/fped.2018.00372.
[15] Kugelman A, Borenstein-Levin L, Riskin A, Chistyakov I, Ohel G, Gonen R, et al. Immediate versus delayed umbilical cord clamping in premature neonates born < 35 Weeks: a prospective, randomized, controlled study. Am J Perinatol 2007;24:307–15. https://doi.org/10.1055/s-2007-981434.
[16] McDonnell M, Henderson-Smart D. Delayed umbilical cord clamping in preterm infants: a feasibility study. J Paediatr Child Health 1997;33:308–10. https://doi.org/10.1111/j.1440-1754.1997.tb01606.x.
[17] Qian Y, Ying X, Wang P, Lu Z, Hua Y. Early versus delayed umbilical cord clamping on maternal and neonatal outcomes. Arch Gynecol Obstet 2019;300:531–43. https://doi.org/10.1007/s00404-019-05215-8.
[18] Garabedian C, Rakza T, Drumez E, Poleszczuk M, Ghesquiere L, Wibaut B, et al. Benefits of delayed cord clamping in red blood cell alloimmunization. Pediatrics 2016;137:e20153236. https://doi.org/10.1542/peds.2015-3236.
[19] Nudelman MJR, Belogolovsky E, Jegatheesan P, Govindaswami B, Song D. Effect of delayed cord clamping on umbilical blood gas values in term newborns: a systematic review. Obstet Gynecol 2020;135:576–82. https://doi.org/10.1097/AOG.0000000000003663.
[20] Xodo S, Xodo L, Berghella V. Delayed cord clamping and cord gas analysis at birth. Acta Obstet Gynecol Scand 2018;97:7–12. https://doi.org/10.1111/aogs.13233.
[21] Wiberg N, Källén K, Olofsson P. Delayed umbilical cord clamping at birth has effects on arterial and venous blood gases and lactate concentrations. BJOG An Int J Obstet Gynaecol 2008;115:697–703. https://doi.org/10.1111/j.1471-0528.2008.01708.x.
[22] Andersson O, Hellström-Westas L, Andersson D, Clausen J, Domellöf M. Effects of delayed compared with early umbilical cord clamping on maternal postpartum hemorrhage and cord blood gas sampling: a randomized trial. Acta Obstet Gynecol Scand 2013;92:567–74. https://doi.org/10.1111/j.1600-0412.2012.01530.x.
[23] Giovannini N, Crippa BL, Denaro E, Raffaeli G, Cortesi V, Consonni D, et al. The effect of delayed umbilical cord clamping on cord blood gas analysis in vaginal and caesarean-delivered term newborns without fetal distress: a prospective observational study. BJOG An Int J Obstet Gynaecol 2020;127:405–13. https://doi.org/10.1111/1471-0528.16026.
[24] Moustafa AN, Ibrahim MH, Mousa SO, Hassan EE, Mohamed HF, Moness HM. Association between oxidative stress and cord serum lipids in relation to delayed cord clamping in term neonates. Lipids Health Dis 2017;16:210. https://doi.org/10.1186/s12944-017-0599-y.
[25] McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database Syst Rev 2013;2013. https://doi.org/10.1002/14651858.CD004074.pub3.
[26] Van Rheenen P, De Moor L, Eschbach S, De Grooth H, Brabin B. Delayed cord clamping and haemoglobin levels in infancy: a randomised controlled trial in term babies. Trop Med Int Health 2007;12:603–16. https://doi.org/10.1111/j.1365-3156.2007.01835.x.
[27] Vatansever B, Demirel G, Ciler Eren E, Erel O, Neselioglu S, Karavar HN, et al. Is early cord clamping, delayed cord clamping or cord milking best? J Matern Neonatal Med 2018;31:877–80. https://doi.org/10.1080/14767058.2017.1300647.
[28] Diaz-Castro J, Florido J, Kajarabille N, Garrido-Sanchez M, Padilla C, de Paco C, et al. The timing of cord clamping and oxidative stress in term newborns. Pediatrics 2014;134:257–64. https://doi.org/10.1542/peds.2013-3798.
[29] Lawton C, Acosta S, Watson N, Gonzales-Portillo C, Diamandis T, Tajiri N, et al. Enhancing endogenous stem cells in the newborn via delayed umbilical cord clamping. Neural Regen Res 2015;10:1359. https://doi.org/10.4103/1673-5374.165218.
[30] Armstrong L, Stenson BJ. Use of umbilical cord blood gas analysis in the assessment of the newborn. Arch Dis Child - Fetal Neonatal 2007;92:F430–4. https://doi.org/10.1136/adc.2006.099846.
[31] Goodlin RC, Freedman WL, McFee JGWS. The neonate with unexpected acidemia. J Reprod Med 1994;39:97–100.
[32] Kurki T. Analysis of obstetric complications reported to the national patient insurance association in Finland from 1987 to 1995. Acta Obstet Gynecol Scand 1997;76:839–42. https://doi.org/10.3109/00016349709024362.
[33] Smit M, Dawson JA, Ganzeboom A, Hooper SB, van Roosmalen J, te Pas AB. Pulse oximetry in newborns with delayed cord clamping and immediate skin-to-skin contact. Arch Dis Child - Fetal Neonatal 2014;99:F309–14. https://doi.org/10.1136/archdischild-2013-305484.
[34] Dawson JA, Kamlin COF, Wong C, Te Pas AB, Vento M, Cole TJ, et al. Changes in heart rate in the first minutes after birth. Arch Dis Child Fetal Neonatal 2010;95. https://doi.org/10.1136/adc.2009.169102.
[35] Padilla-Sánchez C, Baixauli-Alacreu S, Cañada-Martínez AJ, Solaz-García Á, Alemany-Anchel MJ, Vento M. Delayed vs immediate cord clamping changes oxygen saturation and heart rate patterns in the first minutes after birth. J Pediatr 2020;227:149–56. https://doi.org/10.1016/j.jpeds.2020.07.045. e1.
[36] De Bernardo G, Giordano M, De Santis R, Castelli P, Sordino D, Trevisanuto D, et al. A randomized controlled study of immediate versus delayed umbilical cord clamping in infants born by elective caesarean section. Ital J Pediatr 2020;46:71. https://doi.org/10.1186/s13052-020-00835-2.
[37] Katheria AC, Brown MK, Faksh A, Hassen KO, Rich W, Lazarus D, et al. Delayed cord clamping in newborns born at term at risk for resuscitation: a feasibility randomized clinical trial. J Pediatr 2017;187:313–7. https://doi.org/10.1016/j.jpeds.2017.04.033. e1.
[38] McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Evidence-Based Child Heal A Cochrane Rev J 2014;9:303–97. https://doi.org/10.1002/ebch.1971.
[39] Hooper SB, Crossley KJ, Zahra VA, van Vonderen J, Moxham A, Gill AW, et al. Effect of body position and ventilation on umbilical artery and venous blood flows during delayed umbilical cord clamping in preterm lambs. Arch Dis Child - Fetal Neonatal 2017;102:F312–9. https://doi.org/10.1136/archdischild-2016-311159.
[40] van Vonderen JJ, Roest AAW, Siew ML, Blom NA, van Lith JM, Walther FJ, et al. Noninvasive measurements of hemodynamic transition directly after birth. Pediatr Res 2014;75:448–52. https://doi.org/10.1038/pr.2013.241.
[41] Jaiswal P, Upadhyay A, Gothwal S, Chaudhary H, Tandon A. Comparison of umbilical cord milking and delayed cord clamping on cerebral blood flow in term neonates. Indian J Pediatr 2015;82:890–5. https://doi.org/10.1007/s12098-015-1734-2.
[42] Ceriani Cernadas JM. The effect of timing of cord clamping on neonatal venous hematocrit values and clinical outcome at term: a randomized, controlled trial. Pediatrics 2006;117:e779–86. https://doi.org/10.1542/peds.2005-1156.
[43] Mercer JS, Erickson-Owens DA, Collins J, Barcelos MO, Parker AB, Padbury JF. Effects of delayed cord clamping on residual placental blood volume, hemoglobin and bilirubin levels in term infants: a randomized controlled trial. J Perinatol 2017;37:260–4. https://doi.org/10.1038/jp.2016.222.
[44] Purisch SE, Ananth CV, Arditi B, Mauney L, Ajemian B, Heiderich A, et al. Effect of delayed vs immediate umbilical cord clamping on maternal blood loss in term cesarean delivery. J Am Med Assoc 2019;322:1869. https://doi.org/10.1001/jama.2019.15995.
[45] Chen X, Li X, Chang Y, Li W, Cui H. Effect and safety of timing of cord clamping on neonatal hematocrit values and clinical outcomes in term infants: a randomized controlled trial. J Perinatol 2018;38:251–7. https://doi.org/10.1038/s41372-017-0001-y.
[46] Qian Y, Lu Q, Shao H, Ying X, Huang W, Hua Y. Timing of umbilical cord clamping and neonatal jaundice in singleton term pregnancy. Early Hum Dev 2020;142:104948. https://doi.org/10.1016/j.earlhumdev.2019.104948.
[47] Chantry CJ, Blanton A, Taché V, Finta L, Tancredi D. Delayed cord clamping during elective cesarean deliveries: results of a pilot safety trial. Matern Heal Neonatol Perinatol 2018;4:16. https://doi.org/10.1186/s40748-018-0083-3.
[48] Askelöf U, Andersson O, Domellöf M, Fasth A, Hallberg B, Hellström-Westas L, et al. Wait a minute? An observational cohort study comparing iron stores in healthy Swedish infants at 4 months of age after 10-, 60- and 180-second umbilical cord clamping. BMJ Open 2017;7:e017215. https://doi.org/10.1136/bmjopen-2017-017215.
[49] Rhoades J, Wesevich V, Tuuli M, Macones G, Cahill A. Implementation and outcomes of universal delayed umbilical cord clamping at term. Am J Perinatol 2019;36:233–42. https://doi.org/10.1055/s-0038-1669908.
[50] Zhao Y, Hou R, Zhu X, Ren L, Lu H. Effects of delayed cord clamping on infants after neonatal period: a systematic review and meta-analysis. Int J Nurs Stud 2019;92:97–108. https://doi.org/10.1016/j.ijnurstu.2019.01.012.
[51] Mercer JS, Erickson-Owens DA, Deoni SCL, Dean DC, Collins J, Parker AB, et al. Effects of delayed cord clamping on 4-month ferritin levels, brain myelin content, and neurodevelopment: a randomized controlled trial. J Pediatr 2018;203:266–72. https://doi.org/10.1016/j.jpeds.2018.06.006. e2.
[52] Agarwal S, Jaiswal V, Singh D, Jaiswal P, Garg A, Upadhyay A. Randomised control trial showed that delayed cord clamping and milking resulted in no significant differences in iron stores and physical growth parameters at one year of age. Acta Paediatr 2016;105:e526–30. https://doi.org/10.1111/apa.13559.
[53] Mohammad K, Tailakh S, Fram K, Creedy D. Effects of early umbilical cord clamping versus delayed clamping on maternal and neonatal outcomes: a Jordanian study. J Matern Neonatal Med 2019;34:231–7. https://doi.org/10.1080/14767058.2019.1602603.
[54] Shinohara E, Kataoka Y. Prevalence and risk factors for hyperbilirubinemia among newborns from a low-risk birth setting using delayed cord clamping in Japan. Jpn J Nurs Sci 2020;1–9. https://doi.org/10.1111/jjns.12372.
[55] Yang S, Duffy JY, Johnston R, Fall C, Fitzmaurice LE. Association of a delayed cord-clamping protocol with hyperbilirubinemia in term neonates. Obstet Gynecol 2019;133:754–61. https://doi.org/10.1097/AOG.0000000000003172.
[56] Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates. J Am Med Assoc 2007;297:1241. https://doi.org/10.1001/jama.297.11.1241.
[57] Mercer JS, Erickson-Owens DA, Deoni SCL, Dean III DC, Tucker R, Parker AB, et al. The effects of delayed cord clamping on 12-month brain myelin content and neurodevelopment: a randomized controlled trial. Am J Perinatol 2020;1. https://doi.org/10.1055/s-0040-1714258.

[58] Rana N, Kc A, Målqvist M, Subedi K, Andersson O. Effect of delayed cord clamping of term babies on neurodevelopment at 12 Months: a randomized controlled trial. Neonatology 2019;115:36–42. https://doi.org/10.1159/000491994.

[59] Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L. Effect of delayed cord clamping on neurodevelopment at 4 Years of age. JAMA Pediatr 2015;169:631. https://doi.org/10.1001/jamapediatrics.2015.0358.

[60] Tiemersma S, Heistein J, Ruijne R, Lopez G, van Lobenstein J, van Rheenen P. Delayed cord clamping in South African neonates with expected low birthweight: a randomised controlled trial. Trop Med Int Health 2015;20:177–83. https://doi.org/10.1111/tmi.12419.

[61] Van Rheenen PF, Brabin BJ. A practical approach to timing cord clamping in resource poor settings. Br Med J 2006;333:954–8. https://doi.org/10.1136/bmj.39002.389236.BE.

[62] Kc A, Rana N, Målqvist M, Jarawka Ranneberg L, Subedi K, Andersson O. Effects of delayed umbilical cord clamping vs early clamping on anemia in infants at 8 and 12 months. JAMA Pediatr 2017;171:264. https://doi.org/10.1001/jamapediatrics.2016.3971.

[63] Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations, vol. 132; 2015. https://doi.org/10.1161/CIR.0000000000000276.