Seminars in Fetal and Neonatal Medicine 23 (2018) 321–326

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

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

A new wrinkle: Umbilical cord management (how, when, who)

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ARTICLE INFO

Keywords:
Umbilical cord management
Umbilical cord milking
Delayed cord clamping
Physiologic-based cord clamping
Placental transfusion
Immediate cord clamping
Cord blood

ABSTRACT

In the past five years, umbilical cord management in both term and preterm infants has come full circle, going from the vast majority of infants receiving immediate cord clamping to virtually all governing organizations promoting placental transfusion, mainly in the form of delayed cord clamping (DCC). Placental transfusion refers to the transfer of more blood components to the infant during the first few minutes after birth. The different strategies for ensuring placental transfusion to the baby include delayed (deferred) cord clamping, milking of the attached cord before clamping, and milking of the cut cord. In this review, we address the current evidence to date for providing placental transfusion in different circumstances and the methods for implementation. We also highlight the gaps in knowledge and areas for future research.

1. Introduction

Delayed cord clamping (DCC) ranging from 30 s until the cessation of pulsation of the cord has been endorsed by different governing bodies. The International Liaison Committee on Resuscitation (ILCOR) recommends a ≥30 s delay in cord clamping at all gestations [1]. The Neonatal Resuscitation Program (NRP) [2] and American College of Obstetricians and Gynecologists (ACOG) [3] have similar recommendations whereas the World Health Organization (WHO) [4] strongly recommends DCC for 1–3 min for all births, while initiating simultaneous essential neonatal care. The exception is for cases of interrupted placental circulation and those infants who require resuscitation at birth [3]. Several randomized controlled trials (RCTs), cohort studies, and meta-analyses have been published on DCC in premature newborns. A recent systematic review of 18 RCTs compared DCC (for ≥30 s) with early clamping in 2834 preterm infants [5]. Delayed cord clamping significantly reduced hospital mortality (number needed to benefit 33 in all preterm infants and 20 in 996 infants ≤28 weeks gestation) with high GRADE quality of evidence. Delayed cord clamping increased hematocrit and reduced the number of blood transfusions [5]. Whereas increases in the rates of polycythemia and hyperbilirubinemia were seen, no significantly harmful effects were found, including no increase in the rate of exchange transfusions.

For full-term infants, a Cochrane review of 15 trials involving 3911 women-and-infant pairs showed DCC to improve hemoglobin and hematocrit levels postnatally and reduce iron deficiency at three to six months of age without increasing maternal complication [6]. The only reported drawback was an increased requirement of phototherapy. The reduction of iron deficiency and iron deficiency anemia can have a significant impact on children's health and long-term neurodevelopment, not only for developing countries where iron deficiency is more common but also for high-income countries [7]. A Swedish study noted an improved fine-motor and social development in four-year-old children randomized to DCC for ≥3 min compared with those who received immediate cord clamping (ICC) at birth [8].

Delayed cord clamping at birth is complex, with many factors interacting to determine the net amount of blood transfused and the physiological benefit achieved for the infant. Although a longer duration of DCC increases blood transfer to the infant [9–11], the optimal duration is not known. Other factors, including uterine contractions, type of delivery, gravity and infant's breathing, may also play a determinant role [12–14]. Whereas DCC for ≥1–3 min in spontaneously breathing infants positioned on mother's chest or abdomen after vaginal delivery has been recommended, more evidence is needed for those born by cesarean delivery and those who are not vigorous at birth [15]. We will discuss alternatives to DCC such as cord milking (cut and intact), and ventilation during DCC (see Fig. 1).

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https://doi.org/10.1016/j.siny.2018.07.003

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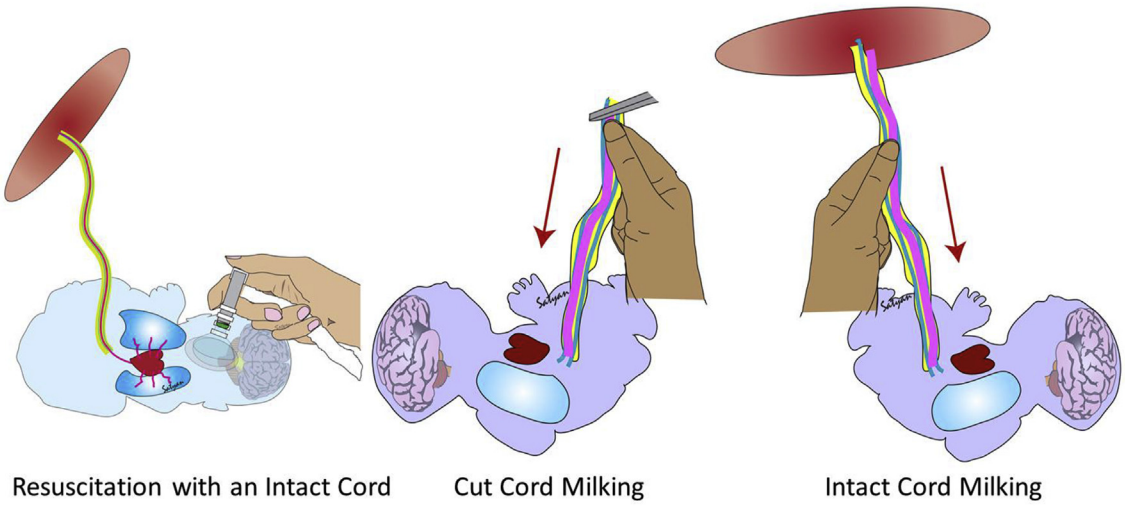

Fig. 1. The three methods of providing placental transfusion at birth. (Drawings courtesy of Dr Satyanarayana Lakshminrusimha, University of California – Davis, CA, USA.)

2. Respirations and DCC

The benefits of DCC might go beyond the addition of blood volume, and could be related to supporting a smooth transition from the fetal to adult circulation while allowing the lung to aerate and pulmonary circulation to be established [16]. A physiologically based approach, rather than a time-dependent concept, for DCC has been proposed based on animal data [17]. Studies on preterm lambs suggest that cord clamping before establishing ventilation exposes the newborn to reduced cerebral blood flow due to a significant reduction in left ventricular output. This reduction occurs due to the elimination of the umbilical venous blood flow before it is replaced by pulmonary venous return as a source of preload to the left ventricle [16]. In addition, swings in heart rate and systemic blood pressure result from elimination of the low-resistance placental circulation, followed by a fall from the reduced left cardiac output and a subsequent rise after an increased left ventricular output is achieved when breathing commenced (Fig. 2). All these factors may contribute to brain injury, especially in the preterm infant with immature myocardium and pressure-passive cerebral circulation [17–19]. Conversely, lung aeration and establishment of pulmonary circulation before cord clamping allowed for better oxygenation and gradual transition of left ventricular preload from umbilical venous blood flow to pulmonary venous blood return, thus minimizing the development of hypoxia and ischemia and mitigating any swings in systemic and cerebral blood flow [20].

In the only published RCT to date, comparing assisted ventilation with no assisted ventilation during a 60 s delay in cord clamping, Katheria et al. found no significant difference in hematocrit levels or short-term outcomes in 150 preterm infants [21]. One potential explanation is that > 90% of the infants began breathing by ≥ 60 s with gentle stimulation. Non-breathing infants may have had a closed glottis, rendering early non-invasive assisted ventilation ineffective. This has been demonstrated in both human [22] and animal trials [23]. The initiation of spontaneous respiration versus actively providing positive pressure ventilation before cord clamping needs further investigation.

Providing ventilation to a newborn still connected to the umbilical cord has technical challenges. Katheria et al. demonstrated the feasibility of providing resuscitation of preterm infants at bedside during DCC despite the finding that 30% of providers had difficulty placing the baby on the resuscitation platform [21]. The same study group has also recently demonstrated the feasibility of providing bedside resuscitation during DCC in term infants, but due to logistical issues they excluded infants born by cesarean delivery [24]. The CORD pilot trial had a similar percentage of infants that required early cord clamping due to a short cord [25]. Training of the obstetrical and neonatal teams could be time consuming and labor intensive, which may limit the generalizability of this approach until further data are available.

3. Concerns related to DCC

Although DCC has decreased the overall incidence of intraventricular hemorrhage (IVH) in previous studies, enthusiasm for DCC was tempered by the small numbers of very preterm infants included in these trials and by the concerns of reporting bias [26]. Recently, the large (n = 1566) multicenter Australian Placental Transfusion Trial compared a 1 min DCC to ICC and did not show significant differences in IVH or other major morbidities [27]. Similarly, the most recent systematic review did not detect significant improvement of any of the major morbidities, although the mortality was reduced [5]. The efficiency of DCC for placental transfusion in cesarean deliveries has been questioned. Prior trials of DCC vs ICC stratified by mode of delivery found no significant improvement in hematocrit levels or tagged red blood cell volume in newborns delivered by cesarean deliveries [13,28]. The American College of Obstetricians and Gynecologists (ACOG) acknowledged that there are limited data indicating whether DCC performed during cesarean deliveries can improve placental transfusion [3,29].

Another concern with DCC is the potential delay to perform the intervention in infants needing resuscitation (non-vigorous). Infants needing extensive resuscitation are more likely to die or to have IVH but are currently being excluded from a potentially life-saving intervention. This has been borne out in research trials which had significant non-compliance, with up to 26% of newborns randomized to DCC actually receiving ICC [27].

There have been concerns with placental transfusion, such as overtransfusion resulting in symptomatic polycythemia or significant jaundice in both preterm and full-term infants. In a meta-analysis of 15 trials involving 3911 women and term infant pairs, there were no concerns regarding maternal or neonatal outcomes except for the finding of fewer infants in the early clamping group receiving phototherapy (relative risk: 0.62; 95% confidence interval (CI): 0.41–0.96). The authors recommended DCC for term infants if access to treatment for jaundice requiring phototherapy is available [6]. The increased provision of phototherapy with DCC should be weighed against the reduced incidence of iron deficiency and iron deficiency anemia, which may impact the long-term neurodevelopmental outcomes [7,8]. Even using DCC in infants with alloimmunization requiring intrauterine transfusion, Garabedian et al. [29] found no increase in jaundice. It is

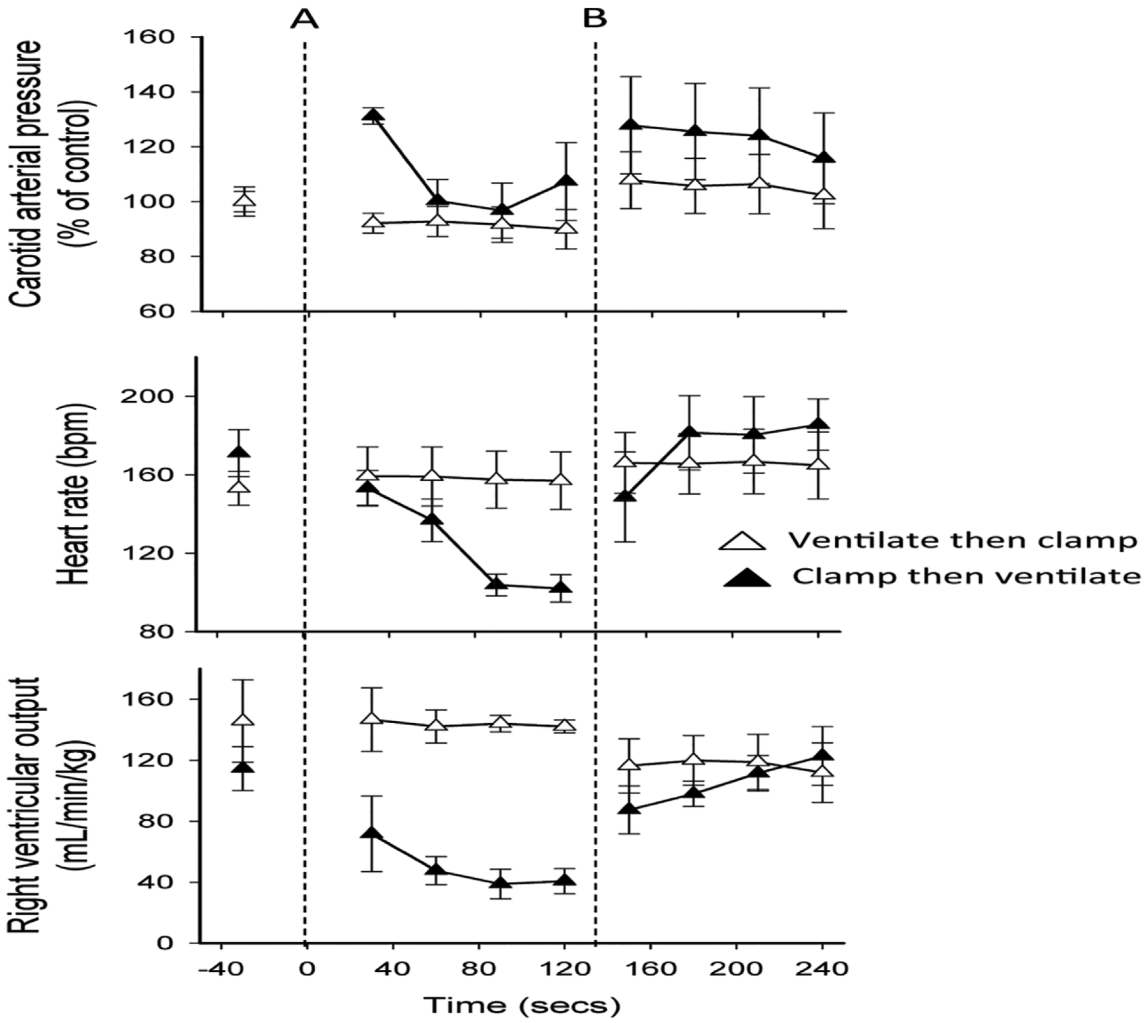

Fig. 2. Delaying cord clamping until ventilation onset improves cardiovascular transition at birth in preterm lambs. Reproduced from Bhatt et al. [16] (courtesy of S. Hooper).

important that pediatric providers be blinded to the randomization of infants in studies examining jaundice and polycythemia as beliefs are widespread and do influence practice [28]. In preterm infants, the most recent systematic review identified an increased incidence of polycythemia (risk difference: 3%; 95% CI: 1–4%), and an increase in hyperbilirubinemia (mean difference in peak bilirubin: +4 mmol/L) in the DCC group. However, there was no difference in partial exchange transfusions for polycythemia or in the exchange transfusions for hyperbilirubinemia [5].

4. Umbilical cord milking

Intact umbilical cord milking (UCM) or milking of the attached cord refers to gentle grasping of the uncut umbilical cord and squeezing it toward the infant, usually for three or four times. The cord refills quickly (in about 2 s) and can be milked again. After three or four milkings of the cord, an infant receives about 17 mL/kg [30]. UCM provides a similar blood volume to a 2 min delay in cord clamping in term infants as measured by residual placental blood volume [31].

Many premature infants require delivery by cesarean section. During cesarean section when the uterus is cut open, the infant may not receive much placental transfusion even if a delay of clamping is possible. DCC at cesarean section may not provide a sufficient placental transfusion compared with vaginal delivery. A recent study demonstrated that UCM at cesarean section improved blood flow and organ perfusion by providing a greater placental transfusion, as measured by improved superior vena cava flow (by echocardiography) and higher admission hemoglobin compared to DCC [32].

For cord milking in preterm infants, there are multiple systematic reviews [33–36] showing increased blood pressure, hemoglobin level, urine output, cerebral oxygenation, decreased risk of all grades IVH, lower incidence of bronchopulmonary dysplasia and necrotizing enterocolitis, and reduced need for blood transfusions. In late preterm infants, UCM resulted in higher ferritin levels at six weeks of age [37]. None of the studies demonstrated harm from cord milking in these vulnerable infants. Thus, cord milking effectively accelerates placental transfusion at the time of birth, resulting in benefits that may be similar to DCC and far superior to ICC.

Cut-cord milking involves clamping and cutting of a long segment of the umbilical cord attached to the baby at birth before passing the baby with the long cord segment to the pediatric provider who then untwists the cord and milks the entire contents into the baby [38,39]. To date, there are no prospective trials comparing the two methods of cord milking. A retrospective review of the need for blood transfusions in preterm infants with intact versus cut-cord milking demonstrated no difference [38]. A study of blood volumes in term infants demonstrated higher blood volumes transfused with repeated cord milking compared to one-time cut-cord milking [40].

The literature so far has shown that UCM does have many merits and may prove to be a good alternative to DCC in different situations.

Although the physiological rationale may be problematic in light of recent animal and human reports of adverse outcomes of clamping the cord before the onset of respiration [16,41], improved short-term clinical outcomes and long-term neurodevelopmental outcomes have been recently reported in premature infants receiving UCM compared with ICC.

5. Concerns related to UCM

All available clinical data from different trials on humans comparing UCM to ICC or to DCC report no adverse effect. However, these trials were limited by small sample size, especially of extremely preterm infants, and lack of sufficient data on long-term neurodevelopmental outcomes.

The exact physiological impact of UCM on neonatal adaptation still needs more clarification. Recent animal data from preterm lambs demonstrate swings in carotid artery pressure and flow with UCM [42]. This suggests that UCM may have a negative impact, particularly in the extremely preterm infants who may be prone to intraventricular hemorrhage as a result. However, extrapolating these findings to human neonates may not be accurate as the studied preterm lambs were all delivered without administration of antenatal steroids. In addition, the animals were anesthetized and instrumented prior to delivery.

The International Liaison Committee on Resuscitation (ILCOR) in 2015 highlighted this concern, stating that the long-term safety profile is still unknown, and the Committee recommends against the routine use of UCM in newborns < 29 weeks gestation [43]. Some centers continue to use cord milking as their exclusive standard of care, based on reduction in morbidities such as death and IVH after implementation of cord milking [44,45]. Thus, there is an urgent need for high-quality evidence comparing UCM with DCC. Large clinical trials should provide more data about long-term outcomes and areas where the evidence for using DCC is not very clear, as in cases of cesarean delivery and when there is a need for neonatal resuscitation. If UCM provides a superior placental transfusion or improves neonatal outcomes, then a large impact on the burden of disability could be realized. An ongoing trial (PREMOD2, Principal Investigator: A. Katheria; $N = 1500$) will attempt to determine whether UCM is non-inferior or superior to DCC in preterm infants.

6. Neurodevelopmental outcomes with DCC and UCM

The currently available data on long-term neurodevelopmental outcomes is not robust because of the small trials comparing DCC and UCM to ICC or with each other. We have summarized these and other studies in Table 1. Larger trials including long-term neurodevelopmental outcome data are needed to better evaluate the benefits of DCC and UCM.

7. Cord management strategies for non-vigorous babies

Management of the cord in apneic newborns or in those perceived to be non-vigorous and thus in need of resuscitation at birth is still controversial. Whereas ICC allows for earlier resuscitation, it deprives the baby from possible benefits of placental transfusion [36,49]. These non-vigorous infants may be the ones who would benefit most from placental transfusion, not only because the placenta may continue to help with the gas exchange, but also because the added blood volume to the neonatal circulation may improve their oxygenation and cardiovascular adaptation [16,24,36]. Furthermore, the transfused autologous stem cells may mitigate and repair any possible consequent brain injury [50]. Unfortunately, published data about these infants is limited due to exclusion from trials, lack of compliance and/or failure to specify their outcomes in the available clinical trials [1,27]. The current statements from the different governing bodies exclude these infants from the recommended DCC approach due to insufficient evidence [1,3,4]. The Neonatal Resuscitation Program (NRP) guidelines recommend 30 s of DCC in these infants while performing the initial steps of stimulation and suctioning of the airways. This compromise may provide the child with some benefits of a brief DCC while not delaying/compromising the needed resuscitation [2]. Nevertheless, it is unclear whether DCC for 30 s would be of any value in an apneic infant.

It is imperative that future research focuses on interventions that evaluate risks and benefits of placental transfusion while supporting physiological transition for non-vigorous newborns. Performing resuscitation with an intact cord could be one possibility. The feasibility of this bedside approach has been demonstrated and a current multicenter study for preterm infants is running [21,24,48]. More studies are needed before this approach can be recommended for standard use. Cord milking could be another option that allows for improving the child's circulatory blood volume, oxygenation, and circulatory transition. It may also help in mitigating or repairing any consequent brain injury through providing the infant with more autologous stem cells [50]. Cord milking may be of particular benefit in conditions where DCC is contraindicated, as in cases of placental abruption. However, as the timing of cord milking may not coincide with the establishment of the infant's pulmonary circulation, it may not be seen as “physiological” as the resuscitation before DCC. So far, the limited data from the few studies that have compared cord milking to DCC, have not concluded any superiority of DCC in terms of reducing brain injuries or improving neurodevelopmental outcomes [32,46]. One-time milking of the cut cord while allowing for resuscitation of the baby away from the mother may also be an option for these infants [38]. Any of these methods, although still not adequately tested, is plausible and has a greater physiological rationale than early cord clamping.

Table 1
Summary of neurodevelopmental outcomes of DCC and UCM in preterm infants.

Study	Control	Intervention	Outcomes	Control	Intervention	*P*-value
Rabe et al. [46] ($N = 39$)	DCC for 30 s	I-UCM four times	Cognitive score[a]	111 ± 26	119 ± 18	0.08
			Language score[a]	95 ± 22	108 ± 18	0.05
			Motor score[a]	102 ± 19	105 ± 15	0.39
Mercer et al. [47] ($N = 161$)	ICC	DCC for 30 s then I-UCM one time	Motor[a]	91.2 ± 12	92.1 ± 15	NS
			Motor < 85[a]	23 (28%)	9 (13%)	0.01
Hosono, J. et al. [unpublished data] ($N = 112$)	ICC	One time C-UCM	Developmental quotient[b]	85.7 ± 16.5	86.8 ± 16.6	0.51
			Cerebral palsy[b]	12 (19%)	2 (3.2%)	0.005
			Normal gross motor function[b]	45 (71.4%)	57 (91.9%)	0.005
Katheria et al. [48] ($N = 135$)	DCC for 45 s	I-UCM four times	Cognitive[a]	95 ± 12	100 ± 13	0.03
			Language[a]	87 ± 13	93 ± 15	0.01
			Motor[a]	97 ± 12	99 ± 12	0.35

N, number of survivors evaluated; DCC, delayed cord clamping; I-UCM, milking of attached cord; ICC, immediate cord clamping; C-UCM, milking of the cut cord.
[a] Bayley Scales of Infant Development, 3rd edn.
[b] Kyoto Scale of Psychological Development.

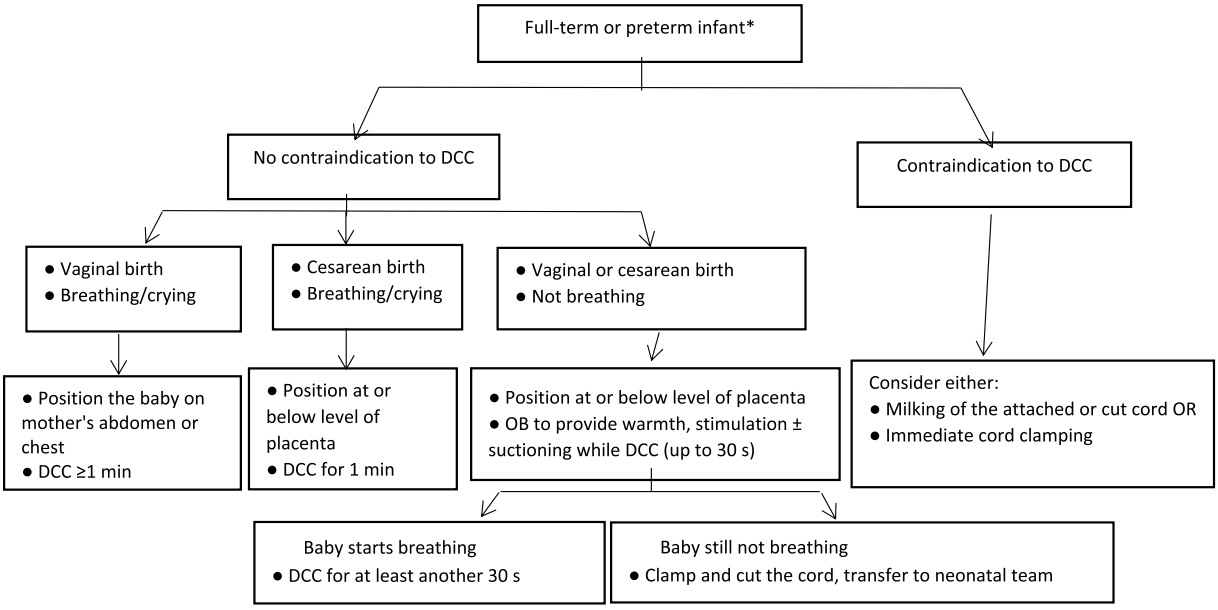

Fig. 3. Flow chart for possible umbilical cord management. DCC, delayed cord clamping; OB, obstetric provider. *Use plastic bags/wrap to maintain normothermia in preterm infants < 32 weeks gestation.

8. Possible approach for term and preterm infants

In stable term infants, DCC for ≥1 min is recommended to improve hemoglobin and hematocrit levels, reduce iron deficiency and possibly iron-deficiency anemia [7]. If these stable term infants are born vaginally, positioning them at mother's abdomen/chest is appropriate [15]. UCM has been shown to provide a superior transfusion in term infants born by cesarean deliveries but more long-term data are needed before it can be recommended for routine use [51]. Until this evidence is available, DCC for 1 min during cesarean deliveries should be performed while positioning the infant at or below level of placenta (Fig. 3). If there is a concern of interrupted placental circulation or cord avulsion, then DCC is contraindicated. In such situations, milking the cord several times or clamping a long segment of the cord and milking it while the infant is being resuscitated could be considered.

For preterm infants, placental transfusion, whether by DCC or UCM, improves hematocrit levels and reduces the need for blood transfusions. DCC reduces hospital mortality. In stable preterm infants, DCC for ≥60 s while positioning the baby at or below the level of placenta and providing warmth may be attempted.

At present, placental transfusion should be considered at every delivery where neonatal resuscitation is not expected as it can have a marked impact on the outcomes of newborns. Immediate cord clamping should not be supported unless both DCC and UCM are contraindicated or not feasible (i.e. cord avulsion or non-reducible nuchal cords) or unless the infant requires resuscitation. Providers may consider UCM in situations where DCC cannot be performed, but it should be viewed with caution in the most immature infants until more data are available.

9. Practice points

- Providing a placental transfusion should be considered in the management of all newborn deliveries.
- The optimal methods of providing a placental transfusion depend on a number of situations such as the presence of breathing, mode of delivery, and the need for immediate resuscitation.

10. Research directions

- Future research studies need to focus on non-breathing preterm infants and asphyxiated term infants to determine the optimal method for providing a placental transfusion.
- Maternal outcomes following extended DCC during cesarean section should be measured.
- Long-term follow-up for DCC and UCM is paramount to ensure the safety of these methods in term and preterm infants.

Conflicts of interest

None declared.

Funding sources

None.

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