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OPTIMAL TIMING FOR CLAMPING THE UMBILICAL CORD AFTER BIRTH

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Synopsis

This paper provides a brief overview of pros and cons of clamping the cord too early (within seconds) after birth. It also highlights evolving data that suggests that delaying cord clamping for 30–60 seconds after birth is beneficial to the baby and the mother, with no measurable negative effects.

Keywords

early cord clamping; delayed cord clamping; umbilical cord milking

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> *"Another thing very injurious to the child, is the tying and cutting of the navel string too soon; which should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases. As otherwise the child is much weaker than it ought to be, a portion of the blood being left in the placenta, which ought to have been in the child…"*
>
> Erasmus Darwin [quoted in reference 1]

Most mammals in the animal kingdom wait until the expulsion of the placenta to sever the umbilical cord from their newborn after delivery. In humans, the attendant aiding the delivery clamps and severs the umbilical cord, much before the placenta is delivered—often within a few seconds of the infant's birth. Which of these two approaches is optimal is to be shown, since the optimal timing for clamping of the umbilical cord in human infants after birth has remained controversial.

The practice of early cord clamping started in the 20th century with increasing number of women opting for hospital births, and increasing number of obstetricians conducting such deliveries. Prior to the mid 1950s, the term "early clamping" was being loosely defined as cord clamping around 1 minute after birth, and "late clamping," was usually reserved for clamping done more than 5 minutes after birth. In a series of studies on blood volume changes after birth carried out by investigators in Sweden, the United States, and Canada, it

was reported that in healthy term infants, over 90% of blood volume is achieved within the first few breaths the infant takes after birth [reviewed in reference 2]. Because of these findings and the lack of specific recommendations on the optimal timing, the interval between birth and cord clamping began to be shortened.

The Pros and Cons of Early versus Delayed Clamping

At present, in most deliveries, cord clamping is performed soon after birth; often before 10–15 seconds after birth, with the baby maintained at or below the level of the placenta. This practice probably evolved with intent to carryout resuscitation of preterm and depressed term infant as soon after birth as possible. However, the "benefit" of immediate cord clamping after birth has not been demonstrated. In addition to the timing of cord clamping, the location of the baby at or below the level of the introitus affects placental transfusion.

Because of many demonstrated benefits from delaying cord clamping, in recent years several international organizations and entities have recommended this practice (Table 1), albeit with a caveat *"if* (or *whenever*) *possible"* [3–7]. In fact, as per the European consensus, delayed cord clamping is the first step of resuscitation for infants at risk for respiratory distress syndrome [6].

However, there are valid concerns about universally adopting delayed cord clamping. Some of the concerns are that there can be a delay in carrying out timely resuscitation when needed; that the practice may interfere with attempts to collect cord blood for banking purposes; and that it may increase the potential for excessive placental transfusion leading to neonatal polycythemia, especially in pregnancies with risk factors such as maternal diabetes, severe intrauterine growth restriction, and living in high altitudes.

Yet, equally valid counterpoints have been proposed to support delayed cord clamping. Since the placenta continues to perform gas exchange after delivery, sick and preterm infants are likely to benefit most from additional blood volume derived from a delay in cord clamping—echoing the recommendation of the European expert consensus noted above [6]. The American Congress of Obstetricians and Gynecology opined that the routine practice of umbilical cord clamping should not be altered for the collection of cord blood for banking [8]. Neonatal polycythemia has not been observed at higher frequencies among infants in the delayed cord clamping group in several systematic reviews, and in large randomized controlled studies [9– 12].

Physiological Rationale

A series of physiological studies between 1960 and 1980 showed that factors facilitating placental-to-neonatal blood transfusion include initiation of extra-uterine breathing, gravity and the position of the infant relative to the placenta, the time of clamping of the umbilical cord, the patency of the umbilical blood vessels, and uterine contractions [1, 14]. Recent experimental works in pregnant sheep have provided additional insights into the dynamics of transitional circulation following birth, breathing, and cord clamping. Following umbilical cord clamping, the right ventricle (RV) filling volume drops abruptly (due to cessation of umbilical venous blood flow into the RV), leading to a drop in RV output by about 50%. Cord clamping that leads to umbilical arterial occlusion causes a marked increase in left ventricular after-load from a lack of low-resistance placental circulation [15–18] and increased left ventricular diameter at the end of diastole [19], potentially leading to a drop in cardiac output (see below).

Many physiological benefits have been documented in clinical studies, too, from delayed cord clamping. Preterm infants in the delayed cord clamping group had significantly higher

superior vena cava blood flow and greater right ventricular output and stroke volumes that persisted up to 48 hours after birth [19]. Baenziger et al showed higher values for mean regional cerebral tissue oxygenation in the delayed cord clamping group at 4 hours of age (69.9% vs 65.5%), which, too, persisted at 24 hours of age (71.3% vs 68.1%) [20].

Another concern often expressed is that the potential delay in resuscitating an infant born after emergency instrument delivery due to fetal distress and/or perinatal asphyxia. In fact, it is precisely in such situations, delayed cord clamping has a potential to be beneficial. Fetal distress, secondary to intrauterine cord compression, leads to selective clamping of the thinwalled umbilical vein carrying oxygenated blood from the placenta to the fetus, without occluding the thicker-walled umbilical arteries carrying de-oxygenated blood from the fetus to the placenta. [21] Since *the latter* blood has no chance of returning to the fetus, fetal oxygenated blood volume gets depleted. According to Hutchon, a delayed cord clamping (40 seconds has been a standard in their unit) and additional placental transfusion can be immensely beneficial for infant born with a history of fetal distress from umbilical cord compression; this should be deemed as the first step of neonatal resuscitation [21].

An additional issue to be considered is the immediate establishment of pulmonary ventilation. Based on fetal/neonatal lamb experiments, Hooper proposes the following three scenarios one might encounter in clinical settings.

1. The best scenario would be: the infant starts breathing soon after birth, and the umbilical cord is clamped at least 30—60 seconds after establishing pulmonary ventilation. The importance of pulmonary ventilation is that it stimulates a decrease in pulmonary vascular resistance and increase in pulmonary blood flow after birth. This is necessary to replace the venous return to the left ventricle that is lost following cord occlusion. During fetal life, umbilical venous blood flow via the foramen ovale had been an important factor contributing to the filling of left atrium and left ventricle, and thus maintaining optimal cardiac output. Thus, the sequence of events described above postnatally facilitate increase in pulmonary venous return carrying oxygenated blood, establish adequate left atrial and left ventricular filling and cardiac output, leading to a smooth cardiovascular transition.
2. Although not ideal, an acceptable scenario would be: the infant breathes and cries soon after birth, and the cord is also clamped right at that time. Here, too, the cardiovascular transition may proceeds seemingly smoothly (as it happens in most term infants), despite a diminished blood volume and a fall in right ventricular filling due to immediate cord clamping. However because of lung aeration, and possibly the existence of adequate capacitance in a healthy term infant, the left ventricular output may not be affected.
3. The worst scenario would be: the infant does NOT breathe immediately after birth, *and* the umbilical cord is occluded soon after birth. The extent of adverse events would then depend upon, among other things, the effectiveness of the bag and mask ventilation. Since the umbilical venous flow into the right heart (containing oxygenated blood from the placenta) drops by ~50% upon cord occlusion and flow through the foramen ovale into the left heart must also drop proportionately. If assisted ventilation does not establish proper aeration of the lungs for whatever reason, pulmonary vascular resistance remains high, preventing the normal increase of pulmonary blood flow and return of oxygenated blood via the pulmonary veins into the left atrium. These events lead to a significant drop in left ventricular output. Then, if the caregivers opt to administer fluid boluses in rapid sequence, a stage may be set to increase the likelihood of intraventricular hemorrhage, especially in very preterm infants, with an already maximally vasodilated cerebral

vascular bed, superimposed upon an immature cerebral autoregulatory systems. (Hooper SB, Personal communications, 2012).

Term Newborns

It is estimated that 3.6 billion people in the world are iron deficient and 2 billion of them have overt iron deficiency anemia [22]. Iron deficiency anemia is also highly prevalent in women of reproductive age group and children under 5 years of age in low and middle-income countries. In areas of the world where maternal iron deficiency anemia is common, up to 30% of infants have iron deficiency anemia. In the industrialized countries, iron deficiency is prevented by iron supplementation, a practice that is difficult to implement in low-resources settings. Numerous studies dating back to several decades have confirmed that delayed umbilical cord clamping at birth enhances red cell mass and improves iron status during infancy [9, 23–29]. In term infants, one-minute delay in cord clamping after birth leads to an additional 80 mL of blood from the placenta to the infant's circulation, which increases to about 100 mL by 3 minutes after birth. This additional blood (plasma and the red cell mass) adds to extra iron, amounting to 40–50 mg/kg of body weight. Such supplemental iron from placental transfusion combined with the approximately 75 mg/kg of body iron present at birth in a full-term newborn, may help prevent iron deficiency during the first year of life [30].

Several studies have documented that in term infants, delaying cord clamping leads to higher hemoglobin/hematocrit soon after birth, which persists up to 4 to 6 months of age [29–40]. The mean hemoglobin advantage was between 2–3 g/DL. In another study, the circulating ferritin levels remained higher in infants in the late clamping group until 6 months: weighted mean difference, +11.8 μg/L (95% CI, 4.07 to 19.53) [30].

Although none of the studies of delayed cord clamping have reported an increased risk of clinically significant polycythemia due to delayed cord clamping, the relationship between delayed cord clamping and polycythemia, hyperbilirubinemia and phototherapy requirements have not been consistent. The authors of a meta-analysis of 1762 infants concluded a significantly higher rates of phototherapy (RR, 1.69; 95% CI, 1.08 to 2.63) and clinical jaundice [9] in infants in the delayed cord clamping group. However, indications for phototherapy in different reports were not described. Moreover, the studies that reported polycythemia did not report increased need for phototherapy. The studies that reported increased need of phototherapy also reported similar levels of bilirubin in the early and delayed cord clamping group. Table 2 provides a list of reported benefits from delayed cord clamping in term infants.

Preterm Newborns

In a systematic review of 10 trials of early versus delayed cord clamping in 454 preterm infants under < 37 weeks' gestation, no statistically significant differences were found between the groups in cord blood pH (weighted mean difference, 0.01; 95% CI, −0.03 to 0.05), Apgar scores (relative risk for 5 min Apgar < 8, 1.17; 95% CI, 0.62 to 2.20), and temperature on admission (weighted mean difference, 0.14°C; 95% CI, −0.31 to 0.03)[8].

The only study to our knowledge that evaluated the feasibility of neonatal resuscitation with the cord still attached to the placenta, also measured infant blood volume and concluded that delayed cord clamping resulted in higher blood volumes [42]. Several studies have documented higher blood pressure and higher RBC volume and hemoglobin[10, 18, 42–49]. The benefits of delayed cord clamping included a reduced need for blood transfusions for treating low blood pressure (relative risk, 0.39; 95% CI, 0.18 to 0.85) and anemia (relative risk, 0.49; 95% CI, 0.31 to 0.81)[48].

In their systematic review, Rabe et al [9] reported that in 7/10 trials, the incidence of any grade of intraventricular hemorrhage was significantly lower in the delayed cord clamping groups ($p<0.002$). The incidence of intraventricular hemorrhage was 47/164 (28.7%) in the *early* cord clamping groups, compared to 27/165 (16.4%) in the delayed cord clamping groups, for an increased relative risk of 1.90 (95% CI, 1.27 to 2.84) with early cord clamping. Considering that the infant death rate was similar between two groups (relative risk 1.40, 95% CI, 0.59 and 3.32 between early versus late cord clamping groups), a nearly two-fold reduced risk of for intraventricular hemorrhage with delayed cord clamping should be deemed as a very important benefit. In none of the reports was there an increased need for exchange transfusion for polycythemia, hyperbilirubinemia.

Rabe et al have recently updated their systematic review on cord clamping in 738 preterm infants born between 24 and 36 weeks of gestation among the 15 eligible studies for review [50]. The maximum delay in cord clamping was 180 seconds. The authors concluded that delaying cord clamping was associated with fewer infants requiring transfusions for anemia (seven trials, 392 infants; risk ratio 0.61, and 95% CI 0.46 to 0.81) and for low blood pressure (four trials with estimable data for 90 infants; risk ratio 0.52, and 95% CI 0.28 to 0.94); and reduced frequency of *any* (all grades) of intraventricular hemorrhage diagnosed by cranial ultrasound (ten trials, 539 infants; risk ration, 0.59, and 95% CI 0.41 to 0.85) compared with immediate clamping groups. There were no clear differences among the groups for infant death, severe [grade 3 to 4] intraventricular haemorrhage and periventricular leukomalacia. However, for several of these outcomes, reporting was incomplete, and the estimates provided wide confidence intervals. Outcomes after discharge from the hospital was reported in only one small study; no significant differences between the groups (n=58) in mean Bayley II scores at 7 months of age corrected for prematurity [50]. Table 3 provides a list of reported benefits from delayed cord clamping in preterm infants.

Umbilical Cord Milking

There are only a few reports on “milking” of the umbilical cord, which include one clinical trial and a secondary analysis from the same trial [51,52], a randomized controlled trial [52], and a study assessing cerebral oxygenation [54]. Hosono et al compared “milking” of a 20-cm segment of the umbilical cord 2–3 times, with immediate cord clamping in preterm singleton infants born between 24 and 28 weeks [51,52]. They found significantly higher initial hemoglobin concentrations, higher mean systemic blood pressure, reduced need for blood transfusions, and higher urine output during the first 72 hours in the cord-milked group compared with the immediate cord-clamping group. The milked group also required a shorter duration of supplemental oxygen and mechanical ventilation.

Rabe et al conducted the only randomized controlled trial comparing repeated milking of the umbilical cord (4 times) and 30 seconds delayed cord clamping in 58 preterm infants born between 24 and 32 6/7 weeks of gestation [53]. Infants in both groups had similar concentrations of hemoglobin levels after birth.

In a study involving 50 stable preterm infants <29 weeks of gestation, Takami et al assessed cardiac functions including left ventricular output, and also measured cerebral perfusion and cerebral oxygen extraction at specified intervals between 3 and 72 hours of age, using nearinfrared spectroscopy [54]. In 26 infants, milking of the cord had been carried out according to a preexisting protocol, and in 24, this was not done (the timing of the cord clamping was not provided). The study found that at 24 hours of age, compared to the controls, infants in the umbilical cord milked group had higher left ventricular end-diastolic dimension, left ventricular cardiac output, superior vena cava flow, cerebral tissue

oxygenation index. The authors interpreted these positive benefits as secondary to improved cardiac functions and left ventricular preload. However, more studies are needed to evaluate the potential benefits and risks of umbilical cord milking, especially in comparison with delayed cord clamping.

Maternal Outcomes

A 2008 Cochrane review assessed the effect of cord clamping in term births on maternal and fetal outcomes in 11 clinical trials involving 2,989 mothers and their babies [10]. Reviewers found no significant differences in postpartum hemorrhage between the early cord-clamping (clamping within 1 minute after birth) and late cord-clamping groups (clamping at least 1 minute after birth or after cessation of cord pulsation) in any of the five trials (2,236 women) that measured this outcome (relative risk [RR] for postpartum hemorrhage 500 mL or more, 1.22; 95% confidence interval [CI], 0.96 to 1.55).

Conclusion

As per the WHO recommendation, delayed cord clamping in low and middle-income countries, may be beneficial [3,4], as many studies have documented improved iron stores during the first half of infancy, especially in resources-limited settings where iron deficiency anemia is highly prevalent. However, the benefits of delayed cord clamping in all term infants in industrialized countries need to be weighed against the possible need for more infants developing jaundice and needing phototherapy, especially in settings where “early discharge” is commonly practiced.

In addition, there does not appear to be any difference between infants receiving early versus delayed cord clamping with respect to immediate birth outcomes, such as Apgar scores, umbilical cord pH, or respiratory distress. Although maternal outcomes have not been rigorously studied, the incidence of postpartum hemorrhage is reported to be similar between immediate and late cord clamping groups.

There is evidence, however, to support delayed cord clamping in preterm infants. As with term infants, delaying cord clamping 30–60 seconds after birth with the baby at a level below the placenta is associated with neonatal benefits, including improved transitional circulation, better establishment of red cell volume, and decreased need for blood transfusion. The single most important clinical benefit for preterm infants is the possibility for a nearly 50% reduction in intraventricular hemorrhage. It is also important to note that the timing of umbilical cord clamping should not be altered for the purpose of collecting cord blood for banking [5].

Future Research

Several unresolved issues related to optimal time for cord clamping are listed in Table 4. While many randomized controlled trials have evaluated the benefits of delayed versus immediate cord clamping in term and preterm infants, the *ideal* timing for cord clamping has yet to be established. Further studies are also needed to evaluate the optimal timing of cord clamping, especially in relation to the management of the third stage of labor in relation to cord clamping, and the timing of cord clamping in relation to the initiation of voluntary or assisted ventilation in the neonate. The ideal time for clamping the umbilical cord after cesarean delivery versus vaginal births is also an important area for future research because premature infants, who may benefit most from delayed cord clamping, are more likely to be born via cesarean delivery from a mother who may have other medical and obstetric complications.

Larger clinical trials are needed to investigate the effect of delayed cord clamping on infants delivered at less than 28 weeks' gestation. Further investigation is required to evaluate management of cord clamping in high-risk pregnancies whose infants are prone to develop polycythemia. The risks of umbilical cord milking remain unknown, and more studies are needed to compare milking of the umbilical cord with delayed cord clamping. The value of enhanced stem cell and plasma transfusion due to delayed cord clamping with respect to immediate and long-term immunity, host defense, and repair is another important area for future research.

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Key Points

- As per the WHO recommendation, delayed cord clamping in low and middle-income countries, may be beneficial [3,4], as many studies have documented improved iron stores during the first half of infancy, especially in resources-limited settings where iron deficiency anemia is highly prevalent.
- However, the benefits of delayed cord clamping in all term infants in industrialized countries need to be weighed against the possible need for more infants developing jaundice and needing phototherapy, especially in settings where “early discharge” is commonly practiced.
- In addition, there does not appear to be any difference between infants receiving early versus delayed cord clamping with respect to immediate birth outcomes, such as Apgar scores, umbilical cord pH, or respiratory distress.
- Although maternal outcomes have not been rigorously studied, the incidence of postpartum hemorrhage is reported to be similar between immediate and late cord clamping groups.

Table 1

International Organizations Statements on Optimal Timing for Clamping Umbilical Cord

Organizations and/or Professional Societies and Scientific Groups	Statement	Reference
World Health Organization	*In preterm infants, delaying cord clamping by 30–120 seconds seems to be associated with less need for blood transfusion and less intraventricular haemorrhage. The beneficial effects of delayed cord clamping may yield the greatest benefits in settings where access to health care is limited*" For term infants: "*To reduce the risk of postpartum haemorrhage in the mother, WHO recommends clamping the cord following the observation of uterine contraction at around three minutes after birth. …For the infant, there is growing evidence that delayed cord clamping is beneficial and can improve the iron status for up to six months after birth. This may be particularly relevant for infants living in low-resource settings with less access to iron-rich foods.*	3, and 4
Society of Obstetricians and Gynaecologists of Canada	*Whenever possible, delaying cord clamping by at least 60 seconds is preferred to clamping earlier in premature newborns (< 37 weeks' gestation) since there is less intraventricular hemorrhage and less need for transfusion in those with late clamping*"	5
European Panel of Expert Neonatologist's Consensus Guidelines	*If possible, delay clamping of the umbilical cord for at least 30–45 s with the baby held below the mother to promote placento-fetal transfusion: Evidence grade, A*	6
International Liaison Committee on Resuscitation	*Delay in umbilical cord clamping for at least 1 minute is recommended for newborn infants not requiring resuscitation. There is insufficient evidence to support or refute a recommendation to delay cord clamping in babies requiring resuscitation.*	7

Table 2

Reported Benefits of Delayed Cord Clamping: Term Infants

- Higher hemoglobin @ 4 –12 months of age
- Improved serum ferritin during the first year
- Improved total body iron stores at one year of age
- Improved survival from malaria in endemic regions
- Lower circulating lead levels in regions with high air pollution
  - (competitive effect between iron and lead)

Table 3

Reported Benefits from Delayed Cord Clamping: Preterm infants

- Higher circulating blood volume for 24–48 hours
- Fewer blood transfusions
- Better systemic blood pressure
- Reduced need for inotropic support
- Increased blood flow in the superior venacava
- Increased left ventricular output
- Higher cerebral oxygenation index
- Lower frequency of *any* intracranial hemorrhage
    - No difference in rates of severe IVH

Table 4

Unresolved issues

Maternal care

- What is the best time to clamp the cord in relation to administration of uterotonic drugs in active management of the second stage of labor?
- How best to optimize cord clamping time in cases of maternal hemorrhage?
- Should the cord-clamping time be different in women positive for HIV?

Resuscitation

- How to consistently maintain the infant's position in relation to placenta, especially in cesarean deliveries?
- Can we carryout resuscitation with the umbilical cord still attached to the undelivered placenta?
- How to record the timing of birth, and timing of various steps of neonatal resuscitation, including the recording of the Apgar scores?

Cord Clamping

- How long a delay is ideal? 30 seconds? 60 seconds? Or other durations depending upon the infant condition?
- What should be the location of baby while clamping the cord in relation to the placenta in cesarean sections?
- Should one document the exact time of cord clamping in all births?
- Up to what lower gestational age, benefits from delayed cord clamping can be demonstrated?

Clamping versus Milking of the cord?

- Are there differential benefits between milking and delayed clamping?
- What is the appropriate length of the cord to be milked?
- How "fast" and how many times milking is appropriate?

At Risk Infants

- What should be the standard for cord clamping in births at high altitudes?
- What should be done in infants with a risk for fetal polycythemia (e.g., severe intra uterine growth restriction, infant of diabetic mothers, large and small for gestational age)

Guidelines and education

- Need for developing standardized protocols
- Continued monitoring of outcomes for collective learning
- Periodic reassessment of guidelines