Timing of umbilical cord clamping after birth for optimizing placental transfusion

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Purpose of review
A brief delay in clamping the umbilical cord after birth offers health benefits to the newborn, with no adverse effects to the mother or her infant. Yet, in most obstetric practice, the cord is clamped soon after birth. A summary of the current evidence on delayed cord clamping and some reasons for the disconnect between the evidence and practice are discussed here, along with the recommendations from professional organizations and societies about this practice.

Recent findings
In term infants, umbilical cord clamping between 30 and 180 s after birth results in higher concentrations of hemoglobin and hematocrit during the neonatal period, and increased serum ferritin levels and a lower incidence of iron-deficiency anemia at 4–6 months of age. These are important benefits for children in low and middle income countries where iron-deficiency anemia is highly prevalent. In preterm infants, delayed cord clamping for at least 30 s increases the concentrations of hemoglobin and hematocrit, improves mean systemic blood pressure, urine output, and cardiac function, and decreases the need for vasopressors and blood transfusions during the neonatal period. It also decreases the prevalence of necrotizing enterocolitis, sepsis, and intraventricular hemorrhage (all grades). Milking of the unclamped umbilical cord toward the infant soon after birth also has similar beneficial effects. In some studies, more infants in the delayed cord clamping groups required phototherapy for jaundice.

Summary
Many professional organizations, societies, and experts recommend at least a 30-s delay before clamping the umbilical cord, especially after preterm births. The value of this practice for term births in resource-rich settings has not been evaluated.

Keywords
anemia, intracranial hemorrhage, iron-deficiency anemia, necrotizing enterocolitis, neonatal jaundice, preterm, sepsis, serum ferritin, umbilical cord clamping

INTRODUCTION

The recommendations concerning the optimal time to clamp the umbilical cord after birth have varied since antiquity (Table 1) [1–6,7▪▪], and the topic still remains controversial [8–10]. Although systematic reviews of controlled clinical trials have concluded that cord clamping between 30 and 180 s after birth has significant health benefits, this practice is not widely utilized [8,10], in part because of the concerns that such a delay might prevent timely resuscitation. In this article, I have reviewed the literature on this topic briefly, with an emphasis on the physiological rationale for delayed clamping. I also present an overview of the recommendations from professional organizations on optimal time for cord clamping.

CHANGING PRACTICE OF UMBILICAL CORD CLAMPING AFTER BIRTH

Until the early decades of the 20th century, most pregnant women delivered in their homes, where midwives tended to cut the umbilical cord several minutes after birth or wait until after the cord ceased pulsating. Coinciding with the improvements in obstetric and neonatal care, more women began

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KEY POINTS

- Clamping of the umbilical cord soon after birth has no physiological rationale.
- A delay of at least 30 s and up to 2 min or more to clamp the umbilical cord after birth in term infants increases hematocrit/hemoglobin status in the neonatal period and reduces the frequency of iron-deficiency anemia at 4–6 months of age.
- A delay of at least 30 s (and to 180 s) to clamp the umbilical cord after birth in preterm infants stabilizes the blood pressure, reduces the need for blood transfusions, and reduces the frequency of intraventricular hemorrhage.
- Although there are no major maternal or neonatal adverse effects from delayed cord clamping, the practice seems to increase the likelihood of requiring phototherapy for clinically significant jaundice.

seeking hospital deliveries, and in the 1960s the practice of active management of the third stage of labor was introduced to reduce postpartum hemorrhage and to prevent placental retention [8]. Initially, the components of this practice were to use uterotonic drugs after infant birth and to apply a steady traction on the umbilical cord to deliver the placenta. However, for reasons unknown, immediate cord clamping became one of the steps in the active management of the third stage of labor. The increasing availability of pediatric expertise in the delivery room for neonatal resuscitation might have hastened this addition. Some experts believe that the practice of immediate cord clamping was an unintended addition to the active management of third stage of labor and that it has no physiological rationale, and has not been shown to benefit the infant or the mother [7▪▪,8,11].

CARDIOVASCULAR CONSEQUENCES OF DELAYED CORD CLAMPING

Increasing the infant's blood volume is the immediate consequence of delayed cord clamping. In a set of landmark studies, Yao *et al.* [12,13] recruited over 300 healthy mothers at term gestation, and studied the effects of cord clamping times and of maternal administration of a uterotonic drug (methylergonovine or Methergine) on infant blood volume and placental residual blood volume. They found that the placental blood is rapidly transferred into the newborn via the uninterrupted umbilical cord in a stepwise fashion over the initial seconds after birth, accelerated by the administration of the uterotonic drug. A 60-s delay increased infants' blood volume by about 16 ml/kg and a 180-s delay by about 23 ml/kg body weight, respectively (Fig. 1). Other studies and systematic reviews have confirmed similar values for blood volume changes with delayed cord clamping in both term and preterm infants [7▪▪,11,14–16].

However, there are some legitimate arguments for clamping the cord soon after birth, one of which is that delayed clamping could hinder the timely initiation of neonatal resuscitation of asphyxiated infants or those with cardiopulmonary failure. Others include potential for polycythemia, jaundice, and concerns that it might interfere with umbilical cord blood banking practice. However, collective evidence suggests that such concerns may not be warranted (Table 2); and the American College of Obstetricians and Gynecologists specifically advises that cord clamping time should not be influenced by the need or desire for umbilical cord blood banking [17].

As immediate cord clamping leads to a significant drop in blood volume, there is a potential to harm infants with an already compromised cardiovascular system, such as those with fetal distress because of a nuchal cord, or those with ineffective pulmonary ventilation.

Table 1. Changing recommendations on the timing of cord clamping

Author (year)	Recommendation
Soranus of Ephesus (c 98–138 AD) [1]	*... When the infant has rested a little after the shaking caused by the birth, one should...* [perform] *omphalotomy...*
Charles White (1728–1813) [2]	*The common method of tying and cutting the navel string in the instant the child is born, is likewise one of those errors in practice that has nothing to plead in its favour but custom...*
Erasmus Darwin (1794) [2]	*... the tying and cutting of the navel string too... should always be left till the child has not only repeatedly breathed but till all pulsation in the cord ceases.*
Various authors [3–6] (1997–2006)	Early: soon after birth to 10 s; late: 30 s to 3 min
Rabe *et al.* (2012) [7▪▪]	For the Cochrane systematic review: early: <20 s; late: >30 s

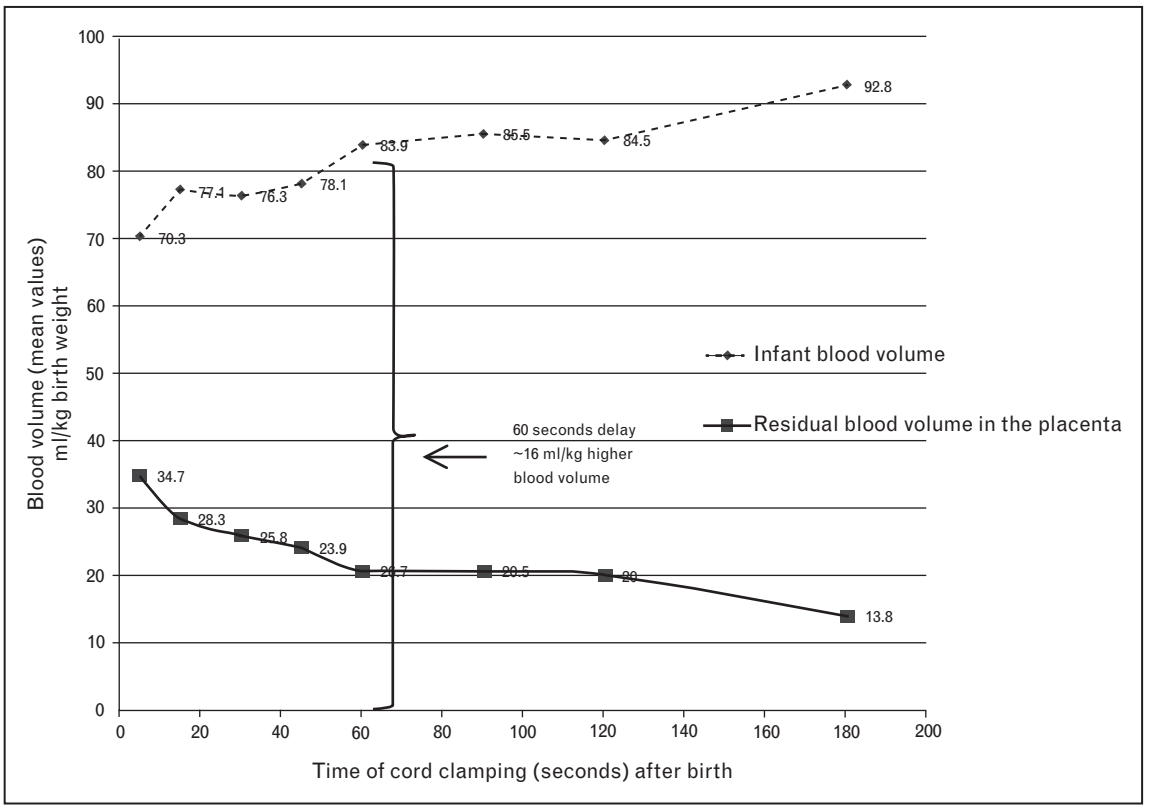

FIGURE 1. Effect of delaying cord clamping on calculated blood volume in the infant and the residual blood volume in the placenta. Adapted and reproduced with permission from Table 1 by Yao *et al.* [12].

Nuchal cord can cause selective intermittent occlusion of the thin-walled umbilical vein, while not occluding the thicker-walled umbilical arteries, thus reducing the inflow of oxygenated blood while maintaining 'bleeding' via the umbilical arteries into the low resistance placental circulation

Table 2. Concerns for delaying cord clamping

Concerns	Potential justification/solutions
Delay in initiating resuscitation in depressed asphyxiated term infants (abruption and uterine rupture)	Maternal emergency is a valid reason for immediate cord clamping; consider cord milking in such cases. In situations where there are no maternal issues, infants with fetal distress (such as those because of nuchal cord) may benefit from improved placental transfusion, as they are likely to be anemic, and hypovolemic, and in shock.
Delay in initiating resuscitation in preterm infants with apnea	Reduced umbilical venous return and inefficient pulmonary ventilation are the worst combination. Consider either resuscitation with an intact cord or milking of the cord. Placental transfusion is the first step in the resuscitation of preterm infants at risk for respiratory distress syndrome.
Polycythemia, jaundice, and need for prolonged phototherapy	No evidence of increased polycythemia; however, as one should in all infants, serum bilirubin needs to be monitored closely; infants discharged home early (<48 h) should be reassessed on follow-up for jaundice.
Assigning the time of birth, and reconciling with step-by-step resuscitation efforts	Time of cord clamping should not affect the assignment of time of birth. Steps of resuscitation should be recorded in relation to the time of birth.
Might affect umbilical cord blood banking	The American College of Obstetricians and Gynecologists recommends that timing of umbilical cord clamping should not be altered for the purpose of collecting cord blood for banking [17].

[8] – blood that has no chance to return to the baby. In such infants, if the cord is clamped immediately after birth, there is a potential to aggravate the already reduced circulating blood volume, especially if the fetus with nuchal cord is asphyxiated, setting the stage for shock.

Similarly, the onset of breathing in relation to clamping of the cord is one of the most important variables that facilitate a smooth transition from fetal to postnatal adaptation [18]. Because cord clamping blocks both umbilical vein and arteries simultaneously, right ventricular preload decreases by about 40%, simultaneously increasing the left ventricular afterload. As most healthy infants cry soon after birth, establishing pulmonary ventilation quickly, pulmonary arterial flow into the lungs increases, as does pulmonary venous flow (oxygenated blood) back into the left heart. Therefore, in such infants, postnatal circulatory status transitions smoothly, despite early cord clamping.

However, if the cord is clamped soon after birth and pulmonary ventilation is inadequate, depending upon the severity of the latter, the consequences could be serious. Inadequate ventilation prevents the postnatal drop in pulmonary vascular resistance, preventing the normal increase of pulmonary blood flow, and reducing the return of oxygenated blood into the left side of the heart. Consequent drop in left ventricular output in an asphyxiated infant manifests as hypovolemic shock, often prompting the caregivers to administer fluid boluses in rapid sequence. Rapid volume expansion in a compromised preterm infant with maximally dilated cerebral blood vessels (because of asphyxia), with superimposed immature cerebral autoregulatory controls, could lead to intraventricular hemorrhage [19,20]. Some experts therefore argue that, especially in compromised infants, a delay in cord clamping that improves the infant's blood volume, which may be physiologically, would be beneficial [8].

In a small group of healthy term infants, Zaramella *et al.* [21] reported that delayed cord clamping up to 4 min resulted in a larger end-diastolic left ventricular diameter on day 3 of age, indicating improved venous return and left ventricular function. Such studies have not been reported in asphyxiated term or preterm infants.

OTHER PHYSIOLOGICAL CONSEQUENCES

Several authors have reported cardiovascular, cerebrovascular, and systemic effects because of increased placental transfusion (delayed cord clamping or cord milking, described below), compared with less placental transfusion (immediate cord clamping) in term [21] and in 24–32 weeks of gestation preterm infants [22–25,26▪]. Larger placental transfusions led to greater right ventricular output, right ventricular stroke volume, and superior vena cava blood flow (indicating increased cerebral perfusion because of improved cardiac output) [22]; improved postnatal transition (e.g., Apgar scores, blood pressure, feeding success) [23,24]; increased urine output [24]; and increased mean tissue oxygenation of the brain at 4 and 24 h of age [25,26▪]. These changes have been attributed to higher blood volume, improved cardiac function, and more stable systemic and cerebrovascular circulation.

SYSTEMATIC REVIEWS OF RANDOMIZED CONTROLLED STUDIES

The clinical effects of delayed umbilical cord clamping in term and preterm infants, as well as the effects on maternal outcomes, are summarized in the list below, compiled from the major randomized controlled trials and their systematic reviews [5,6,7▪▪,9,11,15,16,27▪]. Reported findings because of increased placental transfusion are as follows (data from [5,6,7▪▪,9,11,15,16,26▪,27▪,28]):

(1) benefits: term infants
   (a) higher hemoglobin and hematocrit in the early neonatal period;
   (b) higher total body iron stores, 2–4 months of age;
   (c) higher circulating ferritin level, 2–4 months of age;
   (d) lower incidence of iron-deficiency anemia, around 4 months of age;
(2) benefits: preterm infants
   (a) higher hematocrit and hemoglobin during the early neonatal period;
   (b) higher systemic blood pressure between 4 and 24 h of age;
   (c) increased blood volume;
   (d) reduced need for inotropic medications;
   (e) increased urine output during the first 48 h;
   (f) reduced need for blood transfusions for anemia;
   (g) reduced incidence of intraventricular hemorrhage (all grades);
   (h) improved myocardial function (systolic time intervals and cardiac output);
   (i) improved cerebral oxygenation;
   (j) higher transfer of autologous stem cells;
(3) adverse infant outcomes in delayed cord clamping groups:
   (a) increased peak bilirubin values during the first week in preterm infants;

(b) increased need for phototherapy in both preterm and term infants;

(4) unchanged maternal and neonatal outcomes compared with early clamping:
   (a) any or severe postpartum hemorrhage;
   (b) incidence of retained placenta;
   (c) incidence of other obstetric outcomes, such as need for maternal blood transfusions, operative delivery, episiotomy, etc.;
   (d) infant Apgar scores, need for resuscitation, or umbilical cord pH values;
   (e) frequency of respiratory distress in the newborn;
   (f) severe intraventricular hemorrhage or periventricular leukomalacia;
   (g) incidence of polycythemia;
   (h) requirement of exchange transfusions;
   (i) Bayley II Scale of Development at 7 months of age.

A meta-analysis of data from 1762 term infants and their mothers compared the clinical effects of immediate and delayed cord clamping [11]. There were no significant differences in any of the maternal outcomes reported (e.g., postpartum hemorrhage, placental retention, duration of the third stage of labor, and use of uterotonic medications). Infants in the delayed cord clamping group had higher hemoglobin concentrations and higher hematocrits during the neonatal period. At 4 months of age, they had 45% higher mean serum ferritin values and fewer of them suffered from overt iron-deficiency anemia (5.6% in the early clamping group versus 0.6% delayed clamping) [11,27▪]. The above changes were because of added red cell volume and iron-rich plasma at term gestations, which together amounted to an increase in total body iron by 40–75 mg/kg of infant's weight [6,8,11,27▪].

Although the risk for polycythemia was similar between early and delayed cord clamping groups of term infants, significantly fewer infants in the early cord clamping group required phototherapy for jaundice compared with delayed cord clamping groups [relative risk 0.59; 95% confidence interval (CI) 0.38–0.92]. This equates to a risk difference of 2% more infants in the delayed cord clamping group requiring phototherapy for clinical jaundice (3% in the early clamping group versus 5% in the late clamping group) [11].

In preterm infants, too, there were important measurable benefits from delayed cord clamping. The sizes of the benefits from improved placental transfusion (delayed cord clamping and cord milking, discussed below) are summarized in Table 3, and were mainly drawn from the most recent systematic review of 15 eligible trials that included 738 mothers and their infants born between 24 and 36 weeks of gestation [7▪▪]. The mean effect sizes shown in Table 3 for clinical benefits from increased placental transfusion are impressive, with between six and 15 infants needing to receive more placental transfusion (at least a 30-s delay or cord milking) to result in one extra infant without an important adverse outcome (intraventricular hemorrhage, necrotizing enterocolitis, and sepsis).

However, the rates for other serious adverse outcomes, such as infant mortality, grade III or IV intraventricular hemorrhage, or periventricular leukomalacia, did not differ between the two groups [7▪▪]. The peak bilirubin concentration was higher for infants allocated to more placental transfusion than to less placental transfusion (seven trials, 320 infants, mean difference of 15.01 mmol/l, and 95% CI 5.62–24.40 mmol/l). However, in three studies totaling 180 preterm infants, there was a slight, but statistically nonsignificant, increase in being treated with phototherapy for jaundice (relative risk 1.21; 95% CI 0.94–1.55) among those allocated to more placental transfusion [7▪▪]. In the only follow-up study published thus far, Mercer *et al.* [28] found no significant differences in Bayley II Infant Development Scores at 7 months of age corrected for prematurity ($n = 58$).

UMBILICAL CORD MILKING

Four clinical trials report the findings of 'umbilical cord milking': three were in preterm infants [23,26▪,29] and one in term [30▪]. For this procedure, either the obstetrician or the pediatrician, after infant delivery, 'milks' approximately a 20-cm segment of the umbilical cord two to four times toward the baby.

As the number of infants in the cord milking groups studied has been small (fewer than 100), only general conclusions can be made. Cord milking results in increased placental transfusion and offers benefits of similar magnitude to delayed clamping, summarized in Table 3. The authors of all studies on cord milking conclude that cord milking may be an option in lieu of delayed clamping, especially when the healthcare team deems it necessary to implement immediate resuscitation measures.

There are many unanswered questions about cord milking, some of which are how fast and how often should one milk the cord; what is the optimal length of the cord to be milked and does it vary depending upon infant's gestational age; and, is manual milking of the cord physiologically similar to the pulsatile flow of blood from the placenta? More physiological and clinical studies are needed to address these unresolved issues.

Table 3. Effect size for major benefits from more versus less placental transfusion in preterm infants from randomized controlled trials

Specific outcomes	Number of trials reporting outcomes (total no. of infants)	Effect size (95% confidence interval)	Mean number needed to treat to reduce one adverse outcome[a]
Intraventricular hemorrhage	10 (539)	Risk ratio 0.59 (0.41–0.85)	15
Number needing inotropic support for low blood pressure	4 (158)	Risk ratio 0.42 (0.23–0.77)	6
Number needing blood transfusion for low blood pressure	4 (130)	Risk ratio 0.52 (0.28–0.94)	7
Number needing blood transfusion for anemia	7 (392)	Risk ratio 0.61 (0.46–0.81)	8
Sepsis (incidence)	2 (137)	Risk ratio 0.29 (0.09–0.99)	10
Necrotizing enterocolitis (incidence)	5 (241)	Risk ratio 0.62 (0.43–0.90)	9
Mean regional tissue oxygenation of the brain at 4 h of age (ml/100 g tissue)[b]	1 (39)	Mean difference 6.4% (5.47–7.41)	NA
Mean regional tissue oxygenation of the brain at 24 h of age (ml/100 g tissue)[b]	1 (38)	Mean difference 4.29% (3.44–5.14)	NA
Mean systolic blood pressure at 4 h of age (mmHg)	2 (111)	Mean difference 2.49 (0.26–4.72)	NA
Hematocrit at 4 h of life (%)	5 (173)	Mean difference 5.40 (3.62–7.17)	NA
Hematocrit at 24 h of life (%)	3 (199)	Mean difference 3.28 (1.34–5.22)	NA
Blood volume after birth (ml/kg)	2 (81)	Mean difference 8.25 (4.39–12.11)	NA
Red cell mass after birth%	1 (35)	Mean difference 5.30 (0.05–10.55)	NA

NA, not applicable.
All data are the summary measures published in the Cochrane Database Systematic Review [7▪▪].
[a]Number needed to treat is the reciprocal of the differences in proportions of outcomes between the two groups, rounded to the nearest integer.
[b]Data on these rows are from [25].

RECOMMENDATIONS AND OPINIONS FROM PROFESSIONAL GROUPS

The World Health Organization was the first to recommend delayed cord clamping as a standard for all infants at birth [31▪▪]. Since then, many organizations, professional societies and their committees have followed suit (Table 4) [32–34,35▪▪]. Although some variations exist in the language of

Table 4. Recommendations from professional organizations

Professional entity (year)	Recommendations
World Health Organization (2006, updated 2012) [31▪▪]	In preterm births, delay cord clamping for 30–120 s after birth; and in term births, up to 3 min after birth; also observe uterine contractions.
Society of Obstetricians and Gynaecologists of Canada (2009) [32]	Delaying cord clamping for at least 60 s for preterm births.
International Liaison Committee on Resuscitation (2010) [33]	Delay umbilical cord clamping for at least 1 min for newborn infants not requiring resuscitation. There is insufficient evidence to support or refute a recommendation to delay cord clamping in babies requiring resuscitation.
European Association of Perinatal Medicine (2010) [34]	If possible, delay clamping of the cord for at least 30–45 s with the baby held below the mother (evidence grade A).
The American College of Obstetricians and Gynecologists (2012) [35▪▪]	Evidence exists to support delayed umbilical cord clamping in preterm infants, when feasible (by 30–60 s). Evidence is insufficient to confirm or refute the potential for benefits from delayed umbilical cord clamping in term infants, especially in settings with rich resources.

the guidelines, all entities recommend that whenever feasible one ought to consider delaying cord clamping, at least for 30 s after birth, as the resultant increase in placental transfusion offers clinically important, measurable benefits to the infant.

KNOWLEDGE GAPS, SUMMARY, AND CONCLUSION

Additional issues need further clarification: the optimal position to hold the infant in relation to the placenta, especially after cesarean birth; the optimal time to clamp the cord for high-risk infants, such as multiple gestations, and in those at risk for fetal polycythemia (e.g., intrauterine growth restriction, large for gestational age infants, and infants of diabetic mothers); the time for cord clamping in high-risk mothers (e.g., positive for human immunodeficiency virus, hepatitis A, B, C; and bleeding from abruption of the placenta, or placenta previa); and the possible effect of delayed cord clamping on umbilical cord blood gases and acid–base status.

As answers to the above issues emerge, it appears prudent to follow the recommendations of one's regional professional society and incorporate the practice of delayed cord clamping for at least 30 s, whenever feasible, especially for preterm infants. The benefits from this practice are robust, with little, if any, adverse effects to the mother or her infant.

One also needs to record the time of clamping the cord, preferably for all births, in the medical records of the mother and her infant. This will alert the caregivers, and could help the pediatric team to monitor infants' bilirubin status and to implement appropriate follow-up plans.

Although delayed cord clamping is beneficial for all infants in low-income and middle-income countries where iron-deficiency anemia is highly prevalent, its benefits for term infants born in industrialized countries need to be weighed against the possible increased need for phototherapy, especially in settings where 'early discharge of term and near-term infants' is a common practice.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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