

Umbilical cord clamping in preterm infants

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ABSTRACT

For several years now, the survival of preterm infants has been increasing, which has shifted our concern to preterm infants born before 28 weeks of gestation in particular. The timing of umbilical cord clamping may lead to several disorders, especially when done early (10-15 seconds). In the last two decades, several investigations have shown the considerable benefits of delayed cord clamping (2-3 minutes). Delayed cord clamping has been practiced in obstetrics and neonatal care based on the recommendations made by scientific societies and in systematic reviews, which have provided solid evidence to support this practice in preterm infants. This review describes the most relevant articles from the last years, which strongly support the use of delayed cord clamping versus early cord clamping. In addition, this practice reduces the rate of severe disorders in preterm infants.

Key words: *clamping, umbilical cord, placental circulation, premature infant.*

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For centuries now, the timing of umbilical cord clamping has been taken into consideration. Until after the end of the Second World War, births used to take place at home, and the umbilical cord was cut when it stopped pulsating. Some families did not perform cord clamping, and it came out with the placenta. For thousands of centuries, human beings have maintained the pulsation of the umbilical cord, which has been confirmed for *Homo sapiens*. This also happens in mammals, which are very similar to human beings.

In the first years of the 21st century, the frequency of delayed cord clamping has been increasing. This was due to scientific studies conducted in newborn infants.¹⁻¹¹ Most countries started implementing this practice and observed that neonates

with delayed clamping had a better long-term course.²

At the beginning, some studies related to the timing of cord clamping were conducted in a few preterm newborn infants. A pilot study recruited 32 preterm infants born between 24 and 32 weeks, whose cord clamping had been done at 5 to 10 seconds versus 30 to 45 seconds. Its results showed that the delayed cord clamping group had a higher blood pressure and oxygen use was not required.¹²

Other studies included preterm infants born before 37 weeks of gestation, with most of them being born between 34 and 36 weeks, and the result of cord clamping was similar to that of infants born at term.

The evolution of cord clamping improved with the 2007 Cochrane systematic review, which included 7 studies involving 297 preterm infants out of the 16 identified studies. The main objective assessed the timing of placental transfusion, according to the timing of cord clamping. The outcome measures were transfusion, anemia, and intraventricular hemorrhage, with a significantly lower incidence observed among neonates with clamping at 30 to 120 seconds.¹³

After this systematic review, other clinical studies related to delayed clamping, which assessed placental transfusion, were published. One of them found that an increase in red blood cells prevented anemia, a very common disorder. It resulted from the frequent blood sampling in the neonatal intensive care unit (NICU). Most preterm infants born before 32 weeks usually receive several blood transfusions. In addition, anemia affects the course of respiratory diseases (in particular, bronchopulmonary dysplasia) and

bacterial infections due to blood transfusions.⁴⁻¹⁶

Another Cochrane review from June 2012 added 15 studies.¹⁷ It included a study that revealed better outcomes with delayed clamping versus immediate clamping. With delayed clamping, preterm infants required less blood transfusions due to anemia (7 trials, 392 preterm infants). In addition, they had a decreased incidence of intraventricular hemorrhage (10 trials, 539 neonates) and necrotizing enterocolitis (5 trials, 241 neonates).^{18,19}

Another study assessed the relation of immediate and delayed clamping in preterm infants born at ≤ 32 weeks of gestational age. Its results revealed that a delayed clamping was associated with a significant reduction in intraventricular hemorrhage and early transfusions.²⁰

Several studies assessed the outcomes of delayed cord clamping and found neonatal benefits, such as improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis and intraventricular hemorrhage. Bilirubin levels were higher among preterm infants with delayed clamping, without statistically significant differences in phototherapy between both groups. No differences were observed between both groups in relation to other outcomes, including neonatal death, severe intraventricular hemorrhage (grades 3-4), and periventricular leukomalacia. These studies concluded that placental transfusion with delayed clamping improved blood pressure, reduced blood transfusions, and decreased the risk of intraventricular hemorrhage and necrotizing enterocolitis.²¹⁻²³

Both Cochrane reviews, from 2007 and 2012, contributed greatly to broaden knowledge of the effects of cord clamping timing in preterm infants. Results pointed out the benefits of delayed clamping, particularly in physiological placental transfusion. None of the studies assessed in published reviews found adverse events that could be attributed to delayed clamping. This is extremely important in the field of medicine, where all practices should be proven to be safe before being used and implemented.

The greatest challenge in the last years was to know what happened with cord clamping timing in extremely preterm infants. It was observed that blood transfer after the first minute contributed to an improved resuscitation in preterm infants with

a very low Apgar score at birth. These aspects are important given that extremely preterm infants have a higher morbidity and mortality in their first year of life and frequently suffer from neurodevelopmental sequelae, which persist in the long term and may last for life.

The American College of Obstetricians and Gynecologists (ACOG) has issued recommendations on the timing of cord clamping. The ACOG pointed out that delayed cord clamping was associated with significant benefits in preterm infants, improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis and intraventricular hemorrhage. It suggested that clamping may be performed 2-5 minutes after birth, and indicated that blood transfer after the first minute may contribute to an improved resuscitation in preterm infants with low Apgar scores.²⁴

Several aspects are present in preterm infants, particularly hypothermia, which may have severe consequences and, therefore, should be avoided in extremely preterm infants. Hypothermia may occur when waiting for delayed cord clamping and during resuscitation. In order to prevent it, it is critical to wrap the preterm infant in a plastic bag immediately after birth without drying them and place a fabric hat on their head. These measures are effective to keep temperature within normal ranges and offer an improved airway access.

Breathing is weak in extremely preterm infants, and it is necessary to apply bag-mask positive pressure ventilation for an adequate recovery. At certain times, endotracheal intubation may be performed in the delivery room, although this is uncommon. In addition, delayed clamping increases placental transfusion and helps arterial and venous umbilical blood flow to produce greater lung expansion by increasing pulmonary vasculature, which favors neonatal recovery.^{25,26}

Another study assessed the effect of delayed clamping on breathing, through a transition at birth in preterm infants ≤ 29 weeks. There were 62 neonates in the delayed clamping group, and 62, in the immediate clamping group. When comparing them, in the early clamping group, some infants were not able to breathe spontaneously and required intubation ($p = 0.01$); there was a higher frequency of chronic lung disease ($p = 0.02$) and severe intraventricular hemorrhage ($p = 0.02$).²⁷

A study conducted in Australia found no significant differences between early and delayed clamping, except for mortality, which was significantly higher among neonates with early clamping.²⁸ Another study assessed the clinical consequences of delayed clamping in moderate and late preterm infants. Its results indicated that hematocrit levels at birth were significantly higher in delayed clamping compared with early clamping. In addition, fewer preterm infants with delayed clamping were admitted to the NICU compared with the early clamping cohort ($p = 0.04$). The incidence of respiratory distress syndrome was significantly lower in the delayed clamping group compared with the early clamping cohort ($p = 0.002$).²⁹

Another study compared preterm infants with delayed clamping and immediate clamping. Its results showed a decrease in intraventricular hemorrhage and an adequate axillary temperature, which was significantly higher in preterm infants with delayed clamping. There were no differences in 1- and 5-minute Apgar scores, 24-hour bilirubin levels, and hematocrit levels.³⁰

Another study showed that delayed clamping made it easier to detect red blood cell alloimmunization, which resulted from the immune hemolytic disease of the newborn, responsible for neonatal anemia and jaundice. Two groups were compared: one with early clamping during the first period of the study (January 2001-June 2009) and one with delayed clamping (June 2009-December 2014). The primary outcome was the need of blood transfusion after birth. Hemoglobin at birth was significantly higher in the delayed clamping group ($p = 0.0003$), which did not have anemia at birth ($p = 0.004$). Moreover, delayed cord clamping showed a considerable improvement in hemoglobin levels, reducing the risk for red blood cell alloimmunization, with a better hemoglobin rate and less need for transfusions.³¹

An appropriate systematic review and meta-analysis detected 18 randomized controlled trials and compared delayed and early cord clamping in 2834 preterm infants. Delayed clamping significantly reduced mortality, which was similar in preterm infants born ≤ 28 weeks of gestation.³²

Another study assessed differences between clamping within the first seconds and delayed clamping. It was conducted at 8 tertiary maternity units from the United Kingdom. A total of 276 preterm infants born before 32 weeks were included. The study found superior evidence for

clamping at 2 minutes, with improved outcomes.³³

Another study identified data on the effects of umbilical cord interventions among mothers undergoing C-section. There were no significant differences in mortality; however, severe intraventricular hemorrhage was significantly higher in the early cord clamping group. The interaction analysis between gestational age and treatment group was significant for severe intraventricular hemorrhage ($p = 0.003$).³⁴

In asphyxiated newborn infants, it is critical that placental transfusion leads to a quick recovery, which could be observed in a study in preterm and term neonates. Those with early clamping suffered from heart conditions and had very low oxygen saturation levels; they therefore required more oxygen in the first 5 minutes of life. Compared to that result, delayed clamping demonstrated improvements in systemic and brain perfusion, suggesting neuroprotective benefits. There was also an improvement in heart rate, blood pressure, cerebral oxygenation, increased hemoglobin levels, and prediction of anemia.³⁵

There is another common condition in preterm infants due to low iron stores, and this occurs more frequently among those with immediate cord clamping. However, increased iron levels were associated with delayed clamping, and iron stores increased with a greater placental transfusion. Several studies published in recent years have shown evidence of iron stores in preterm infants.

One of them estimated the effect of placental transfusion in 2 groups: early clamping (10 seconds) versus delayed clamping (60 seconds) in preterm infants of 30 to 33 weeks. According to its results, median serum ferritin was significantly higher in the placental transfusion group with delayed clamping.³⁶

Others detected the incidence of anemia at 3 months of age, which was significantly lower in the placental transfusion group with delayed clamping, according to the results.³⁷ Another study, conducted in infants born after elective C-section, found that those with delayed clamping had higher iron stores at 4 months of age compared with the early clamping group.³⁸

Another research assessed the effects of cord clamping on iron stores of infants born to anemic mothers at 3 months of age. Neonates born to mothers with hemoglobin levels < 100 g/L were randomized at delivery to either immediate cord clamping or delayed cord clamping. According

to the outcome measures, hemoglobin and serum ferritin levels at 3 months were significantly higher in the delayed clamping group. In addition, the odds for anemia (< 100 g/L) at 3 months were 7.7 times higher in the early clamping group compared to the delayed clamping group.³⁹

In another study, the objective was to analyze, in a high-risk population, the effects of delayed cord clamping versus early cord clamping, and hemoglobin and ferritin levels at 8 and 12 months of age. According to its results in 540 infants, those undergoing delayed clamping had higher levels of hemoglobin, reducing the prevalence of anemia at 8 and 12 months of age. This resulted in major positive effects on infants' health and development.⁴⁰ Based on these interesting studies, it is possible to conclude that physiologically low iron stores in extremely preterm infants may be compensated.

Several studies published in recent years estimated the relation between umbilical cord milking and usual delayed and early clamping. The results of a study pointed out that umbilical cord milking offered advantages with delayed clamping.⁴¹ However, another study, with a higher number of preterm infants, found no statistically significant differences in outcomes between the cord milking and delayed clamping groups, in relation to placental transfusions, necrotizing enterocolitis, and intraventricular hemorrhage.⁴²

A non-inferiority, randomized clinical trial determined whether there was a difference in the rates of death or severe intraventricular hemorrhage among preterm infants who received placental transfusion with umbilical cord milking versus delayed umbilical cord clamping. Preterm infants born at 23-31 weeks of gestation from 9 university medical centers in 4 countries were recruited between June 2017 and September 2018. The primary outcome was a composite of death or severe intraventricular hemorrhage to determine non-inferiority of umbilical cord milking. No differences were observed in relation to mortality, but severe intraventricular hemorrhage was significantly more common with umbilical cord milking compared to delayed clamping.⁴³

A systematic review and meta-analysis was published in 2020, which addressed extremely interesting aspects by increasing placental transfusion as a transfer of blood from the placenta to the newborn infant. A total of 19 studies were included (2014 preterm infants).

Five of them (n = 922) compared umbilical cord milking with delayed clamping, and the remaining 14 (n = 1092) compared umbilical cord milking with immediate clamping. Umbilical cord milking significantly increased the risk for intraventricular hemorrhage compared to delayed clamping. When compared to immediate clamping, cord milking reduced the need for red blood cell transfusions but did not result in improved clinical outcomes. It was concluded that cord milking could not be considered a placental transfusion strategy in preterm neonates based on the currently available evidence.⁴⁴

Physiological aspects related to umbilical cord clamping in preterm infants

The benefits of delayed clamping result from physiological mechanisms; they are therefore not considered a treatment, since this practice respects natural aspects. Such benefits are the product of allowing the neonate to receive the blood volume that ought to have been in the child. Placental transfusion is an inevitable physiological consequence in the first minutes of life, during the redistribution of blood between the placenta and the neonate.^{45,46} Nature has determined that that blood volume belonged to the newborn infant; so, why deprive them of receiving it?

It is necessary to know that, when fetal distress occurs in advanced stages of labor, less blood is transferred to the fetus in the second stage of labor, making it critical at birth to perform delayed cord clamping and allow the neonate to receive placental blood and recover. As mentioned above, for many years, immediate umbilical cord clamping was the standard of care. Such completely inadequate and arbitrary practice did not take into consideration that the physiological rationale of cord clamping was to wait enough time to allow the circulatory transition from the placenta to the newborn infant. In addition, it improved lung aeration and increased pulmonary blood flow, placing them back at the center of circulatory transition.

Some reviews pointed out the significant benefits of hemodynamic actions with delayed clamping, which was considered a physiological protective effect. Several studies also found that the timing of cord clamping was related to the moment of the first breath, together with other mechanisms.

In 1999, through a UNICEF initiative, a study was conducted in 31 maternity centers across Argentina in order to establish the moment when umbilical cord clamping occurred. The

exact timing of clamping was determined using a stopwatch in 3738 births. The median clamping timing was 35 seconds in the overall population. Based on these data, several measures were taken to promote delayed clamping in Argentina.

Another important topic related to physiology is that of stem cells, which have multiple roles and are involved in maturation aspects, anti-inflammatory action in the central nervous system, and the reduction of disorders or diseases⁴⁷ (Table 1). Moreover, since it was known that umbilical cord blood contains various hematopoietic stem cells, endothelial cell precursors in the mesenchyme, and multipotent lineage stem cells, the merit of delayed cord clamping has been determined. An important benefit of said delay is related to a higher number of stem cells in the umbilical cord blood, particularly in preterm infants born before 28 weeks.

It can be highlighted that, with the delay of cord clamping, the importance of placental transfusion in containing blood together with the stem cells entering the neonate can be noted. This allows for an extremely higher transfer of stem cells, in particular when the delay ranges from 60 to 120 seconds after birth (Table 2).

TABLE 1. Stem cell action in several neonatal disorders⁴⁸

Confirmed benefits	
•	Respiratory distress syndrome
•	Anemia of prematurity
•	Intraventricular hemorrhage
•	Sepsis
•	Periventricular leukomalacia
Benefits not yet confirmed	
•	Chronic lung disease
•	Apnea of prematurity
•	Retinopathy of prematurity
•	Necrotizing enterocolitis
•	Patent ductus arteriosus

TABLE 2. Timing of umbilical cord clamping and stem cells⁴⁷

	Clamping timing (seconds)	Blood volume (mL)	Hematopoietic stem cells received by neonates
Early clamping	5	0	0
Delayed clamping	180	75-80	1100-45 000

Not long ago, mankind's first stem cell transfer and nature's first stem cell transplant were observed, which were published in 2010.⁴⁸ This was possible because, at birth, the placenta and the umbilical cord started contracting and pumping blood toward the newborn.

Those who still perform early clamping are not aware of the physiology of transition at birth, and end up curtailing stem cell transplant and depriving infants of additional stem cells. The actions of stem cells are extremely important: they play a role in multiple risk situations and their beneficial effects persist until older ages and even in adulthood. In addition, the rationale behind their physiological mechanisms is gaining more and more attention as it leads to an increase in the number of cells.

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