Cord clamping in term and pre-term infants: how should clinicians proceed?

Evidence favours delayed cord clamping in most newborns, but further studies are needed

**Recommendation** For pre-term and term infants who do not require respiratory support, it is advisable to delay umbilical cord clamping for at least 60 seconds

The first minutes of life are the critical stage in the successful transition from a fetus to a newborn. During this period, the newborn infant will undergo one of the greatest physiological changes humans face. The lungs change from liquid to air filled, taking over the role of gas exchange from the placenta, and the cardiovascular system rapidly transitions from a fetal to a newborn circulation, facilitating oxygen delivery throughout the body. Despite significant improvements in delivery room care, the World Health Organization estimates that one million neonatal deaths occur annually on the first day of life, making the immediate care of infants in the delivery room of critical importance.

A significant focus of delivery room care in recent years has been the management of the umbilical cord. The International Liaison Committee on Resuscitation recommends delaying cord clamping by 30–60 seconds in term and pre-term infants not requiring resuscitation, but the recommendation in pre-term infants was based on weak, low quality evidence. A recent systematic review and meta-analysis has provided the first high quality evidence that delayed cord clamping (DCC) reduces hospital mortality in pre-term infants compared with immediate cord clamping (ICC). These findings were largely driven by the recently completed Australian Placental Transfusion Study (APTS), which showed a significant reduction in mortality in the DCC group than in the ICC group (6.4% vs 9.0%), a difference that was not significant in post hoc adjustment for secondary outcomes (P = 0.39). Further, there was an overall reduction in red cell transfusions in the DCC group compared with the ICC group (52.1% vs 60.5%; P = 0.001), which was also shown in the systematic review. The only potential harm identified was an increased incidence of polycythemia, with an increased risk difference of 3%, although this was not associated with morbidity. It is interesting that the only difference in significant morbidity that could explain the difference in mortality rate was a higher incidence of sepsicaemia, with no other differences in morbidities shown either in the APTS or subsequent reviews. It is also worth noting that the previously indicated significant reduction in intraventricular haemorrhage with DCC was no longer statistically significant with the inclusion of the APTS data.

So where does this leave the clinician in determining whether to delay clamping or to immediately clamp the cord? Improved scores in fine motor and social domains at 4 years of age have been shown in term newborns undergoing DCC compared with ICC, but these infants represent a low risk population. Neurodevelopmental outcomes in pre-term infants are poorly described, and no evidence was cited in the International Liaison Committee on Resuscitation recommendations. The reduction in mortality during primary hospital admission in pre-term infants is tantalising, but the underlying mechanism is not immediately obvious. Indeed, it may be linked to reduced interventions in the neonatal intensive care unit rather than any immediate benefit of DCC, as highlighted by the subset analysis of cardiovascular stability. Perhaps the real problem with the current trials is the lack of physiological information whereby a mechanism of benefit may be elucidated.

Animal and human studies have shown the importance of breathing and lung aeration before cord clamping for improving cardiovascular stability and oxygenation and reducing infant mortality, severe bronchopulmonary dysplasia and intraventricular haemorrhage. In a study investigating whether the provision of ventilation during DCC increased placental transfusion compared with DCC alone, over 90% of infants aged under 32 weeks in both groups were reported to make breathing efforts in the first 60 seconds. However, those infants who did not breathe during this time had higher rates of delivery room positive pressure ventilation and intubation. The rates of spontaneous onset of infant breathing before DCC were not reported in the APTS trial, nor were the rates of stimulation (shown to improve early breathing rates) or requirement of respiratory support. The relationship between breathing and cord clamping needs to be further investigated in appropriately designed clinical trials.

In the intervention group in the APTS trial, the duration of DCC was 60 seconds or more (mean, 94 seconds). In the DCC group, 26% of infants did not receive the full 60 seconds, mostly due to clinical concerns about infant wellbeing. The rationale for 60 seconds was not included; professional guidelines recommend DCC in pre-term infants for anywhere between 30–180 seconds if resuscitation is unnecessary. The premise for the delay of 60 seconds was for a blood transfusion to occur, and while not directly measured, the higher peak haematocrit during the first week of life may suggest a transfusion. However, the need to rely on a specific time is counterproductive. The newborn does not know they have 60 seconds to transition, and while many will transition within this time, as indicated by breathing, crying and vigorous movements, some may take longer. Indeed, the infant taking longer to transition may be the one who benefits most from DCC, or may be most at risk if DCC does not provide respiratory support. The proviso is that the
placental circulation is still intact and providing oxygen or circulatory stability during this time. Recent studies in depressed newborns highlighted the need for positive pressure ventilation as early as possible as opposed to cord management. Future trials should consider physiological measures indicative of successful transition which may include breathing stability, end-tidal carbon dioxide, heart rate, arterial saturation, blood pressure or a combination of these.

Antenatal information was not provided on the APTS population, including the incidence of fetal growth restriction (determined by adverse Doppler ultrasound), chorioamnionitis or sepsis, or asphyxia. This information is important as, in some of these populations, DCC may be detrimental to the newborn. Animal and human studies have shown that newborns exposed to intra-uterine inflammation have higher cerebral metabolic load and are more prone to hypoxic-ischaemic injury and periventricular or intraventricular haemorrhage. While DCC in newborns exposed to chorioamnionitis may not be harmful if the placenta is functioning and the infant is breathing, in an infant with apnoea with a suboptimal placenta it may be deleterious.

Moderate to severe fetal growth restriction resulting from placental insufficiency causes the fetus to redistribute its cardiovascular output to sustain oxygen delivery to critical organs, such as the heart, brain and adrenals, at the expense of the periphery, which results in the brain-sparing phenomenon. Animal and human studies have shown altered cardiovascular and vascular function immediately after birth and within the first weeks of life, yet the effect of DCC on this population remains unknown.

Likewise, asphyxia, and subsequent cardiovascular redistribution, results in a newborn with very high systemic vascular resistance, which would favour blood distribution towards the placenta. In this case, ventilation and oxygenation are a key priority and DCC alone may be harmful. The current recommendation for this subgroup is for ICC. However, recent animal and human studies indicate that initial respiratory support for up to 5 minutes before cord clamping results in improved blood pressure and cerebral oxygenation and reduced cerebrovascular injury compared with ICC. Again, studies need to be conducted to fully elucidate the benefits.

The findings suggest that in otherwise healthy pre-term and term infants, there is no harm of DCC, and potentially some benefits. The recommendation is, therefore, to delay cord clamping in pre-term and term infants who are vigorous and making breathing efforts, and to monitor the infant’s wellbeing during DCC. Nevertheless, the critical aspect moving forward is to determine whether DCC is beneficial or harmful to subgroups. If the umbilical cord or placenta is compromised, then there may not be any benefit in DCC and it may potentially be harmful. Similarly, infants born with asphyxia, atony or sepsis may not benefit from DCC if it means delay of respiratory support. Future studies must focus on whether the pathophysiology of the newborn should be guiding the timing of cord clamping or additional interventions before cord clamping, such as stimulation, respiratory support or caffeine administration. This personalised approach to medicine in the delivery room may show the considerable benefits of DCC in particular subgroups, and would thus alleviate clinicians’ fears for delaying cord clamping for up to 60 seconds, would identify optimal physiological markers rather than an arbitrary time to clamp the cord, and would also identify populations in which interventions such as initiating respiratory support will take greater priority than umbilical cord management.

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