

Long-Term Neurodevelopmental Outcomes of Placental Transfusion (Delayed Cord Clamping or Cord Milking) Compared to Immediate Cord Clamping in Preterm Infants

Stefano Nobile^{1,2*} and Michela Anna Tenace²

¹Department of Woman and Child Health and Public Health, Division of Neonatology, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy

²Department of Mother and Child Health, Salesi Children's Hospital, Ancona, Italy

***Corresponding Author:** Stefano Nobile, Department of Woman and Child Health and Public Health, Division of Neonatology, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, and Department of Mother and Child Health, Salesi Children's Hospital, Ancona, Italy.

Received: April 15, 2019; **Published:** June 17, 2019

Abstract

There is recent evidence that a delay of clamping by 30 to 60 seconds after birth, compared to immediate cord clamping, is associated with increased placental transfusion and better neonatal outcomes. Umbilical cord milking is usually defined as the milking of 20 cm of umbilical cord toward the umbilicus 3 times while the infant was held at the level of the introitus or below the level of the placenta before cord clamping. There is paucity of evidence regarding long-term neurodevelopmental outcomes for delayed cord clamping/cord milking compared with immediate cord clamping (particularly for preterm infants). To date, three randomised controlled trials reported data on neurodevelopment at 1 - 2 years' follow-up. The findings of these studies suggest that placental transfusion compared to early cord clamping might be associated with better neurodevelopment among preterm infants, at least at earlier (< 30 weeks) gestational ages and possibly in some settings. However, available studies were underpowered to detect significant differences between groups. Further studies are needed to confirm these findings and to assess the optimal timing of cord clamping.

Keywords: Placental Transfusion; Cord Clamping; Cord Milking; Preterm Infants

Background

The umbilical cords of babies born preterm have generally been cut immediately to allow the transfer of the newborn to the neonatal team. However, there is recent evidence that a delay of clamping by 30 to 60 seconds after birth is associated with increased placental transfusion and better neonatal outcomes [1]. There is controversy about how long it is appropriate to delay clamping if the baby is perceived to require resuscitation. Umbilical cord milking is usually defined as the milking of 20 cm of umbilical cord toward the umbilicus 3 times while the infant was held at the level of the introitus or below the level of the placenta before cord clamping.

Both interventions are associated with placental transfusion; international panels of experts have made different recommendations about this practice, as summarised below.

The 2015 international guidelines on cardiopulmonary resuscitation of the newborn [2] highlighted the effects of delayed cord clamping (less periventricular haemorrhage, higher blood pressure and blood volume, less need for transfusion, lower incidence of necrotising enterocolitis, higher peak bilirubin value) and cord milking (higher mean blood pressure, lower incidence of intraventricular haemorrhage, higher haemoglobin level with less need for transfusions) in preterm infants during their NICU stay. The treatment recommendations were: 1) to provide delayed cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommen-

Citation: Stefano Nobile and Michela Anna Tenace. "Long-Term Neurodevelopmental Outcomes of Placental Transfusion (Delayed Cord Clamping or Cord Milking) Compared to Immediate Cord Clamping in Preterm Infants". *EC Pulmonology and Respiratory Medicine* 8.7 (2019): 552-555.

dation, very-low-quality evidence); 2) to avoid cord milking for infants born at 28 weeks of gestation or less, because there is insufficient published human evidence of benefit.

Non-uniform guidelines have been published in recent years by medical associations. The World Health Organisation and the International Federation of Gynaecology and Obstetrics suggested delayed cord clamping (1 - 3 minutes) in non-asphyxiated newborns and in those not requiring resuscitation [3]. The American College of Obstetricians and Gynaecologists [1] recommended delayed cord clamping (DCC: > 30 - 60 seconds) for vigorous preterm infants and did not support nor refute cord milking.

The Royal College of Obstetricians and Gynaecologists [4] suggested potential benefit of delayed cord clamping among preterm infants but did not provide clear indications.

The National Institute for Health and Care Excellence [5] recommended delayed cord clamping (30-180 seconds) for stable preterm infants and mothers and cord milking for those requiring resuscitation/medical interventions.

The Italian Association of Obstetrics and Gynaecologists [6] recommended delayed cord clamping (> 60 seconds) for breathing preterm infants (evidence grade IA), cord milking for preterm infants requiring resuscitation (evidence grade IIC) and list contraindications for delayed cord clamping (i.e. placental diseases, multiple birth, IUGR with abnormal Doppler etc).

In some institutions, the provision of placental transfusion at birth may be not codified by an institutional protocol and could depend on various factors, including the attitude of the gynaecologist and the neonatologist present at birth, the maternal and foetal health status, the mode of delivery (personal communications). Most vaginally-born term infants may receive DCC before skin-to-skin care; some preterm infants born by Caesarean section could rather receive cord milking, as it is faster and allows prompt resuscitation and stabilisation. Term infants delivered by Caesarean section can either receive cord milking, immediate cord clamping or DCC. Local guidelines for preterm infants are particularly needed since, at least in some institutions, extremely preterm infants are often delivered by Caesarean section (in an attempt to reduce the occurrence of intraventricular haemorrhage).

The collaboration between neonatologists and gynaecologists is important, and a prenatal plan could be helpful.

Clinical aspects and previous studies

Major knowledge gaps on this topic are multiple and include 1) the lack of evidence regarding neurodevelopmental outcomes for DCC/cord milking compared with immediate cord clamping (particularly for preterm infants) and 2) the comparison of DCC/cord milking versus immediate cord clamping among preterm infants who receive resuscitation. We will try to address the first issue.

To date, three randomised controlled trials reported data on neurodevelopment at 1 - 2 years' follow-up [7-9]. These were randomised trials in the United Kingdom, United States of America and north India involving patients followed between 18 and 30 months' corrected age (overall 315 treated with immediate cord clamping, 264 with delayed cord clamping, 82 with cord milking); 29 of them were followed at 3.5 year corrected age (18 with cord milking and 11 with delayed cord clamping).

Mercer, *et al.* [8] studied 161 preterm infants born < 32 weeks' gestational age, and showed that a brief delay in cord clamping (30 - 45 seconds followed by a single cord milking) was associated with better motor outcomes at 18 - 22 months; however, details about cognitive and language scores were not provided, and post-hoc sensitivity analyses using actual treatment were needed since there was a 12% rate of protocol violations and unequal groups on 2 major confounding variables.

Rabe, *et al.* [7] compared 30 seconds' delayed cord clamping with cord milking and did not include a control group of infants treated with immediate cord clamping due to the institutional protocol of providing delayed cord clamping to all deliveries (i.e. it was deemed unethical to provide immediate cord clamping at that institution). Patients (n. 39) born between 24 and 32 weeks of gestation were followed

at 2- and 3.5-year corrected age, that is the longest follow-up of infants involved in a placental transfusion trial. No significant differences in Bayley scores were identified between the two groups, but cord milking compared to DCC was associated with better language scores at 2-year follow-up (with borderline significance). Of note, infants studied by Rabe, *et al.* [10] had higher (about 10 points) motor scores compared with those studied by Mercer, *et al.* Neither of these studies provided details about resuscitation in the delivery room.

Das, *et al.* [9] studied 461 infants born at 30 - 33 weeks of gestation, who were randomized to early cord clamping (within 10 seconds) or placental transfusion (DCC after 60 seconds or cord milking). Infants were evaluated at multiple time intervals until 24 - 30 months' chronological age by means of an Indian adaptation of Bayley Scale of Infant Development III. The authors found that the survival free of neurodevelopmental impairment at 24 - 30 months of chronological age was similar in the placental transfusion and early cord clamping groups (47% vs. 50%, $p = 0.9$). They also found no difference between groups in the incidence rates of neurodevelopmental impairment at 24 - 30 months (37% vs. 39%, $p = 0.8$), anthropometric parameters, incidence rates of intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis stage 2 and 3 and need for phototherapy and exchange transfusion.

Conclusions

The findings of these studies suggest that placental transfusion compared to early cord clamping might be associated with better neurodevelopment among preterm infants, at least at earlier (< 30 weeks) gestational ages and possibly in some settings. However, available studies were underpowered to detect significant differences between groups. DCC appears safe and was associated with similar subsequent neurodevelopmental outcomes when compared to immediate cord clamping in preterm infants; cord milking is similar to delayed cord clamping and can be considered an alternative treatment. One can speculate that cord milking could be preferred when a preterm infant is likely to require resuscitation, while DCC could be performed in the remaining cases, provided other protective factors are assured (i.e. stable maternal conditions and good temperature of the newborn). However, further studies are needed to confirm these findings and to assess the optimal timing of cord clamping.

Bibliography

1. American College of Obstetricians and Gynecologists. "Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth". *Obstetrics and Gynecology* 129.1 (2017): e5-e10.
2. Perlman JM, *et al.* "Part 7: neonatal resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations". *Circulation* 132.16 (2015): S204-S241.
3. World Health Organization. Guidelines on basic newborn resuscitation 2012. Geneva, Switzerland: World Health Organization (2012).
4. Royal College of Obstetricians and Gynaecologists. "Clamping of the Umbilical Cord and Placental Transfusion". Scientific Impact Paper No. 14 (2015).
5. National Institute for Health and Care Excellence. Guideline version 2.0: Preterm labour and birth methods, evidence and recommendations (2015).
6. Italian Association of Obstetrics and Gynaecologists. Linee guida sulla gestione del parto pretermine (2016).
7. Rabe H, *et al.* "Neurodevelopmental Outcomes at 2 and 3.5 Years for Very Preterm Babies Enrolled in a Randomized Trial of Milking the Umbilical Cord versus Delayed Cord Clamping". *Neonatology* 109.2 (2016): 113-119.
8. Mercer JS, *et al.* "Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial". *Journal of Pediatrics* 168 (2016): 50-55.e1.

9. Das B., *et al.* "Placental transfusion in preterm neonates of 30-33 weeks' gestation: a randomized controlled trial". *Journal of Perinatology* 38.5 (2018): 496-504.
10. Rabe H., *et al.* "Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes (Review)". *Cochrane Database of Systematic Reviews* 8 (2012): CD003248.

Volume 8 Issue 7 July 2019

© All rights reserved by Stefano Nobile and Michela Anna Tenace.