Royal College of Obstetricians & Gynaecologists

Clamping of the Umbilical Cord and Placental Transfusion

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1. Background

After birth, blood flow in the umbilical arteries and veins usually continues for a few minutes. The additional blood volume transferred to the baby during this time is known as placental transfusion. Immediate clamping of the umbilical cord has traditionally been recommended as part of active management of the third stage of labour, together with a prophylactic uterotonic drug and controlled cord traction, to reduce postpartum haemorrhage.[1] Use of a prophylactic uterotonic drug clearly does reduce the risk of major haemorrhage.[2] The timing of cord clamping does not appear to have a major impact on blood loss at the time of birth.[3]

A difficulty in reviewing this subject is that different terminology and definitions have been used in different studies. We suggest that the term 'immediate cord clamping' be used to mean that this is done within 30 seconds of the birth of the baby. The definition 'deferred cord clamping' means not clamping until at least 2 minutes after delivery. We prefer the term 'deferred' (because it suggests a planned policy) to the previously used 'delayed', which might be felt to imply later than ideal. Those definitions leave clamping of the cord between 30 seconds and 2 minutes unclassified, which might be called intermediate timing of cord clamping. However, when possible in this paper we will clarify the definitions used in each study. In any case, during clinical maternity care, the ideal is to simply document the time that the umbilical cord is clamped rather than an artificial classification.

The role of 'immediate', rather than 'deferred', cord clamping has not been universally accepted as part of the active management of the third stage of labour and the optimal timing for cord clamping is unclear. For example, a survey of policy at 1175 units in 14 European countries found that two-thirds clamped the cord immediately after birth, although 90% routinely administered prophylactic uterotonics.[4] The International Federation of Gynecology and Obstetrics[5] and the World Health Organization (WHO)[6] no longer recommend immediate cord clamping as a component of active management. Current guidance from the RCOG is that 'The cord should not be clamped earlier than is necessary, based on clinical assessment of the situation.'[7] The WHO states 'Late cord clamping (performed after 1 to 3 minutes after birth) is recommended for all births while initiating simultaneous essential newborn care … Early cord clamping (<1 minute after birth) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation.'[6] For healthy women with term births, the National Institute for Health and Care Excellence (NICE) recommends that the cord is not clamped in the first 60 seconds, except where there are concerns about the cord's integrity or the baby's heart rate.[8] They recommend that the cord should be clamped before 5 minutes, although women should be supported if they wish this to be delayed further.

This opinion paper summarises the physiology of placental transfusion and reviews the evidence related to the timing of umbilical cord clamping.

2. Physiology of placental transfusion

For a term baby, postnatal placental transfusion provides an additional 80–100 ml of blood.[9–11] For the fetus, blood volume/kilogram of body weight is similar to that for an adult (around 65–75 ml/kg). At birth, this increases to around 90 ml/kg but the rise is reduced by 20–35% if the cord is clamped immediately.[5,9] Within a few hours, the additional plasma from the placental transfusion is lost to the circulation, leaving a high red cell mass. This is quickly broken down and the iron stored. Immediate cord clamping reduces placental transfusion and potentially deprives the term baby of 20–30 mg/kg of iron, sufficient for the needs of a newborn baby for around 3 months. Although there are few data, the relative reduction in blood volume and red cell mass following immediate clamping may be even greater for preterm babies than for those born at term, as a higher proportion of the intrauterine blood volume is sequestered within the

placenta. The physiology of placental transfusion for preterm babies and for sick term babies, particularly those with intrapartum asphyxia, is less well understood.

At birth, the umbilical circulation slows and pulmonary vascular resistance falls, rapidly increasing pulmonary blood flow. This is the beginning of the transition from the fetal to the neonatal circulation. Continued flow in the umbilical vein and arteries at birth may be part of the physiological mechanisms assisting the baby as it makes this transition.[12] Immediate cord clamping may restrict the baby's ability to deal with the transition from the fetal to the neonatal circulation. While most healthy babies at term adapt without major consequences, for those born preterm or with their cardiorespiratory circulation already impaired, there may be an impact on clinical outcome. A brief delay in cord clamping will increase the baby's blood volume. With a longer delay there may be other advantages, such as better cardiorespiratory transition and more stable blood pressure, and these might occur even with no further change in net blood volume.[12]

Studies of preterm lambs support the hypothesis that deferring cord clamping until the neonatal circulation is established may benefit cardiovascular function.[13] Starting ventilation at birth and waiting until respiration was established before clamping the cord improved cardiovascular function compared with immediate clamping followed by ventilating the lambs.[13] Ventilation with deferred cord clamping was associated with improved pulmonary blood flow and less variability in carotid artery pressure, carotid artery blood flow and heart rate in the lambs. This suggests that the mechanisms for improvement in cardiorespiratory function may be a more stable haemodynamic transition rather than increased neonatal blood volumes.

Our understanding of placental transfusion in humans comes largely from observational studies conducted half a century ago, which estimated placental transfusion as 60–200 ml. Few of these studies included caesarean section or preterm birth and they belong to an era before the widespread use of oxytocin. Key determinants of placental transfusion seem to be how hard the placenta is squeezed by the uterus after birth of the baby, how far the baby is held below or above the placenta during this time and how long before the cord is clamped.

2.1 Influence of prophylactic uterotonic drugs

Using a prophylactic uterotonic drug during the third stage substantially reduces the risk of postpartum haemorrhage.[2] Although these drugs do not appear to influence the final volume of placental transfusion, they do change the speed and duration of flow. For example, if intravenous ergometrine is given 10 seconds after birth of the baby, the rapid uterine contraction increases the initial flow to the baby and leads to placental transfusion being complete by 1 minute while the final volume of transfusion is not significantly altered.[10] However, intravenous ergometrine is no longer used as a prophylactic uterotonic owing to the high incidence of adverse effects, largely being replaced by intramuscular alternatives.[2] Intramuscular oxytocin leads to uterine contraction after 2.5 minutes and intramuscular ergometrine acts after 7 minutes.[14] It is unlikely that intramuscular oxytocin or Syntometrine® (Alliance, Chippenham, Wiltshire, UK) given intramuscularly with delivery of the anterior shoulder, as in the UK, will have a substantive effect on placental transfusion, which is largely completed by 2 minutes after term birth. The effect of intravenous oxytocin, as commonly used during caesarean section, is not known.

Administration of intramuscular uterotonic drugs before cord clamping is unlikely to have a major effect on placental transfusion. However, further research is merited to confirm whether there could be a clinically relevant effect on either duration or net volume.

2.2 Influence of gravity

Oxygenated blood flow to the baby via the umbilical vein is more influenced by gravity than flow in the umbilical artery. Raising the baby above the level of the placenta while the cord is intact is expected to reduce venous flow to the baby, while the umbilical artery continues to carry blood back into the

placenta. Hence lifting the baby may lead to flow from the baby to the placenta. Conversely, lowering the baby below the level of the placenta speeds flow to the baby, but without apparently influencing the net volume of placental transfusion.[10,13] These reports do not state whether a uterotonic drug was used. Without the influence of a uterotonic, gravity has a substantial effect on placental transfusion if the baby is held 20 cm or more either above or below the introitus.[15] There are few data on how giving a uterotonic drug might interact with gravity on placental transfusion, but in women given oxytocin within a minute of birth, placing the baby on the mother's abdomen or chest at term vaginal birth had no impact on the volume of placental transfusion.[16] There are no data for caesarean section or for preterm births.[17]

2.3 Other factors

Placental transfusion at caesarean section appears to be less than for vaginal birth.[18] This may be due to gravity, if the baby is lifted up before clamping the cord, and lower uterine tone.

Cord 'stripping' or 'milking' either before or after the cord is clamped has been compared with immediate cord clamping in a number of recent trials of preterm births[19] and of term or near term births.[20,21] However, the greatest interest in this procedure is for preterm births. Although the studies were small, there is some evidence of improved early neonatal cardiovascular stability and reduced need for oxygen at 36 weeks of postmenstrual age,[22,23] and reduced blood transfusion.[22,24] With milking, the cord blood is pushed rapidly into the fetal circulation (typically, a 20 cm length of cord is stripped three times, each done for about 2 seconds, before clamping). Clearly cord milking impairs flow in the umbilical arteries, and may have other effects through stimulation of the endothelium. This needs further randomised trials to evaluate the possible benefits and adverse effects.[25]

3. Evidence from systematic reviews

3.1 Timing of cord clamping for term birth

The Cochrane review comparing immediate with deferred cord clamping for term births includes 15 randomised trials with 3911 woman and baby pairs, and both vaginal and caesarean births.[3] The trials were judged to have a moderate risk of bias. Four trials had fewer than 100 participants, nine had between 100 and 500, and two more than 500. Most studies defined immediate or 'early' clamping as within the first 15 seconds or 'immediately'. Definitions of deferred or 'delayed' clamping were more varied, including 2–5 minutes, cessation of pulsation or presence of the placenta in the vagina. Use and timing of uterotonics was not specified in nine trials. Many outcomes were only reported by a few studies, so there is concern about potential reporting bias.

There were no statistically significant differences between immediate and deferred cord clamping groups in terms of postpartum haemorrhage, severe postpartum haemorrhage or manual removal of placenta. At age 24–48 hours, babies in the immediate cord clamping group had lower haemoglobin levels than those in the deferred clamping group (mean difference [MD] –1.49 g/dl, 95% CI –1.78 to –1.21, four trials, 884 babies). By age 3–6 months, however, there was no significant difference between the groups (MD –0.15 g/dl, 95% CI –0.48 to 0.19). Iron deficiency at 3–6 months was reported by five trials (1152 babies), which all used different definitions of iron deficiency. Immediate clamping was associated with a higher risk ratio of iron deficiency, although there was heterogeneity between studies (average risk ratio [RR] 2.65, 95% CI 1.04–6.73, I^2 82%).

Reflecting reduced haemolysis associated with immediate clamping, these babies had a lower relative risk of being given phototherapy for jaundice (RR 0.62, 95% CI 0.41–0.96, seven trials, 2324 babies). This equates to two additional babies (95% CI 0–4) in every 100 with deferred rather than immediate clamping receiving phototherapy. There are insufficient data for reliable conclusions about the comparative effects on other substantive short-term outcomes, such as symptomatic polycythaemia, respiratory problems, hypothermia, infection and need for admission to special care.

The conclusion of this review was that the evidence justifies 'A more liberal approach to delaying clamping of the umbilical cord in healthy term infants … as long as access to treatment for jaundice requiring phototherapy is easily accessible.'

3.2 Timing of cord clamping for preterm birth

Timing of cord clamping for births before 37 weeks of gestation has been evaluated in 15 randomised trials involving 738 babies.[26] Recruitment was between 24 weeks and 36 weeks of gestation, although most were before 33 weeks.[26] Risk of bias was unclear in many of the trials. Primary outcomes for the babies were death, death or neurosensory disability at 2 years of age, grade 3 or 4 intraventricular haemorrhage, and periventricular leucomalacia. Timing of immediate cord clamping ranged from 5 seconds to 20 seconds, and deferred clamping ranged from 30 to 180 seconds, although some studies did not state the timing definitions. Most studies stated that babies in the deferred clamping arm were also held below the level of the vagina. The only study to use 180 seconds recruited moderately preterm infants (34–36 weeks of gestation). One small study compared immediate clamping with cord milking. A sensitivity analysis excluding this study showed no clear difference in neonatal outcomes. The trials do not report data for all the important outcomes and data on long-term follow-up of the children are sparse. No studies in the review[26] reported outcome for the women.

Neonatal death before discharge from hospital was reported in 13 trials and there was no clear difference between the groups (10/319 more placental transfusion versus 17/349 less placental transfusion). No studies have reported death or neurodisability at 2 years of age. There was no clear difference between the groups in either severe intraventricular haemorrhage or periventricular leucomalacia (Table 1). There was no clear difference between the groups in the three trials reporting temperature on admission to the special care baby unit. Deferred cord clamping was associated with fewer transfusions for anaemia, but there was no clear difference in transfusion for hypotension. Deferred clamping was also associated with higher mean arterial blood pressures at birth and at 4 hours of age, and less requirement for inotropes than immediate cord clamping. It was also associated with a reduction in the risk of necrotising enterocolitis. Preterm babies allocated to deferred cord clamping had higher serum bilirubin levels, but there was no clear difference in jaundice requiring phototherapy in the three trials reporting this outcome and no clear difference between the groups in oxygen requirement at 36 weeks of postmenstrual age.

Table 1. Immediate versus deferred cord clamping for preterm births: effects for babies

Outcome	Number of trials	Number of participants	Risk ratio	95% confidence interval
death	13	668	0.63	0.31–1.28
intraventricular haemorrhage				
any (grade 1 to 4)	10	539	0.59	0.41–0.85
severe (grade 3 or 4)	6	305	0.68	0.23–1.96
periventricular leucomalacia	2	71	1.02	0.19–5.56
temperature on SCBU admission (°C)	3	143	0.14†	−0.03 to 0.31†
transfusion				
for anaemia	7	392	0.61	0.46–0.81
for hypotension	4	130	0.52	0.24–1.11
number of transfusions (mean)	5	210	−1.3†	−1.9 to −0.6†
mean arterial pressure				
at birth	2	97	3.52†	0.60–6.45†
at 4 hours	2	111	2.49†	0.26–4.72†
inotropes for low blood pressure	4	158	0.42	0.23–0.77
necrotising enterocolitis	5	241	0.62	0.43–0.90
serum bilirubin peak (mmol/l, mean)	7	320	15.01†	5.62–24.40†
jaundice requiring phototherapy	3	180	1.21	0.94–1.55
oxygen supplementation at 36 weeks	5	209	0.69	0.42–1.13

†mean difference SCBU = special care baby unit

Follow-up at 7 months of age (corrected for gestation at birth) was reported for one study of 72 babies (but five died before 7 months and nine were lost to follow-up). There was no overall difference between the groups in Bayley Scales of Infant Development-II. The review concludes that deferring cord clamping may be beneficial but that further evidence is needed, including long-term follow-up for the children and outcome for the women. This is supported by two additional reviews, one of which underlines the need for further study on long-term outcomes[27] and the other highlights the lack of evidence to guide practice for babies requiring immediate resuscitation.[28] The latter review concluded that deferred umbilical cord clamping or umbilical cord milking at birth provides better neonatal outcomes than does immediate cord clamping.[28] However, this meta-analysis included small studies and combined data from studies evaluating deferred umbilical cord clamping and those evaluating cord milking.

Multicentre trials of preterm births are ongoing.[29] The Australian trial is recruiting babies below 30 weeks of gestation and comparing clamping at 60 seconds and lowering the baby with clamping within 10 seconds. The UK trial is recruiting women giving birth before 32 weeks of gestation and comparing a policy of cord clamping after at least 2 minutes with clamping within 20 seconds. For clamping after at least 2 minutes, initial neonatal care is with the cord intact, at the woman's bedside and with the baby level with the vagina.[30] For previous trials in the Cochrane review, if babies required stabilisation at birth, clinicians generally had to balance the timing of cord clamping with the need to transfer the baby to resuscitation facilities. Techniques for care and early stabilisation of the baby with the cord intact mean that cord clamping can be deferred without deferring neonatal care.[31,32]

Umbilical cord 'milking' or 'stripping' is seen as an alternative to deferring cord clamping but, as discussed above, requires further evaluation.

4. Discussion

For decades, immediate cord clamping has been included in the package of care known as 'active management'. Prophylactic uterotonic drugs reduce the risk of postpartum haemorrhage, but the optimal timing of cord clamping needs to be reconsidered.[1,25] Current guidance on the collection of umbilical cord blood for stem cell banks does not state when the cord should be clamped. It would be reasonable to advise parents of the advantages and disadvantages of placental transfusion when they are considering cord blood banking.

The concern that immediate clamping with preterm babies may increase the risk of intraventricular haemorrhage merits rigorous and prompt evaluation in randomised trials. Possible mechanisms for this increase are hypovolaemia or increased fluctuations in blood pressure during the transition from fetal to neonatal circulation. If there is no need to rush a newborn baby to the resuscitaire, simple measures such as drying and keeping warm may be instituted before separating the infant from the placenta. It is possible that enhancing placental transfusion by deferring cord clamping helps to reduce the need for resuscitation at birth. Stabilisation with the cord intact and the baby close to the level of the uterus is feasible[31,32] and appears to be acceptable to clinicians and valued by parents.[32] An advantage of this strategy is that it allows evaluation of deferring cord clamping until placental transfusion is likely to be complete.[30] Arterial and venous cord blood gas results are influenced by timing of cord clamping[33] and so a consequence of deferred clamping is difficulty interpreting those results. However, the differences are small and unlikely to be of clinical importance, but reinforce the need to record the timing of cord clamping to facilitate correct interpretation of cord blood gases using appropriate reference ranges. A recent study has shown progressive acidaemia if the cord is left unclamped in neonates between 36 and 42 weeks of gestation. In this study, cord samples were obtained successfully immediately at delivery and then 45 seconds later without the cord being clamped.[34] In a randomised trial, obtaining cord blood from the unclamped pulsating cord has been shown to be possible and as successful in deferred cord clamping as it was in early cord clamping.[35]

Term babies who have immediate cord clamping have lower iron stores for up to 3–6 months after birth.[3] The potential implications of the reduced iron status in early childhood have not been adequately investigated. Iron deficiency in the first few months of life is associated with neurodevelopmental delay, which may be irreversible.[36] Whether increasing placental transfusion by deferring cord clamping will improve neurodevelopment in early childhood is not known but this hypothesis should be studied. Even a modest effect would have important public health implications, not only for low-income countries but also for countries such as the UK where anaemia and iron deficiency in early childhood remain common.[37]

Immediate cord clamping became routine practice without rigorous evaluation. There is now a body of evidence suggesting that deferred rather than immediate clamping may have benefits at both term and preterm births. As this has implications for every birth, even a modest difference in beneficial or harmful effects would be important. Trials to date have been less than ideal: a) they have not reported data for all the important outcomes; b) they have been underpowered to compare serious adverse effects between the two strategies; c) they have not studied the time of oxytocic administration; and d) they have not had adequate long-term follow-up of the women or children. In order to understand the advantages and disadvantages of these alternative strategies, large randomised trials with assessment of substantive outcomes and long-term follow-up for both mother and baby would be needed.

5. Opinion

- In healthy term babies, the evidence supports deferring clamping of the umbilical cord, as this appears to improve iron stores in infancy. Jaundice may be more common after deferred cord clamping but this management is likely to be beneficial as long as phototherapy for jaundice is available. This assessment of the evidence is concordant with the Cochrane review and the recommendations by NICE.
- For term births, while the cord is intact the baby can be placed on the mother's abdomen or chest following a vaginal birth without influencing the volume of placental transfusion. Owing to the influence of gravity on placental transfusion, sensible advice is that while the cord is intact the baby should not be lifted higher than this. The timing of cord clamping should be routinely recorded in medical notes.
- The administration of intramuscular uterotonic drugs before cord clamping is unlikely to have a substantive effect on placental transfusion.
- For preterm births the evidence is less clear than for term births, although data from the trials suggest potential benefit by deferred rather than immediate cord clamping. Strategies and equipment for providing initial neonatal care and resuscitation at the woman's bedside with the cord intact should be developed further and evaluated.
- Cord milking is an alternative to deferred cord clamping for preterm births, but requires further evaluation of its benefits and risks before entering routine practice.

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This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Professor LMM Duley FRCOG, Nottingham; Professor JO Drife FRCOG, Leeds; Dr A Soe FRCPCH, Medway; and Professor AD Weeks FRCOG, Liverpool**

and peer reviewed by:
Professor CM Begley, Trinity College Dublin; British Maternal and Fetal Medicine Society; Mrs A Diyaf MRCOG, Barnstaple; Mr DJR Hutchon FRCOG, Darlington; Dr M March, University Hospitals Case Medical Center, Cleveland, Ohio, USA; Dr H Rabe, Brighton & Sussex Medical School, Brighton & Sussex University Hospitals, Brighton; RCOG Women's Network; Dr N Wiberg, Lund University Hospital, Sweden; Women's Health Patient Safety Expert Group.

The Scientific Advisory Committee lead reviewers were: Dr S Ghaem-Maghami MRCOG, London; Miss PA Law MRCOG, London; and Professor PW Soothill FRCOG, Bristol.

Conflicts of interest:
Professor Duley is Chief Investigator for the Cord Pilot Trial, which is comparing alternative policies for timing of cord clamping at very preterm birth.

Professor Duley and Professor Weeks are two of eight designers of the BASICS trolley: a neonatal resuscitation trolley designed to allow resuscitation alongside deferred cord clamping. They work as unpaid advisors to Inditherm Ltd who make the commercial version (LifeStart), but receive no money from them. Inditherm Ltd pay £75 into a charity for each trolley sold in lieu of royalty payments.

Professor Weeks receives £150 annually for being a British National Formulary (BNF) obstetric advisor. He has a patent on a device for assessing head descent in labour (iPush) and one in development for a device to treat postpartum haemorrhage (PPH Butterfly).

Professor Drife is President of Baby Lifeline.

Dr Soe: none declared.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The review process will commence in 2018, unless otherwise indicated.

