

## Low Apgar, Need for Resuscitation and Neonatal Jaundice

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### Hypothesis

The increased need for phototherapy for non-haemolytic hyperbilirubinaemia is frequently given as a barrier to the introduction of routine delayed cord clamping. However, the evidence for this increased need is not consistent. At one end of the scale there is one subset of the McDonald (1996) study combined with the Oxford Midwives (1991) showing a relative risk (RR) of needing phototherapy to be 0.59 (0.32, 1.11) with early clamping compared with delayed clamping, and the other subset of the McDonald study showing a RR of 0.47 (0.22, 0.97) [1,2]. At the other end of the scale the Andersson (2011) and the Emhamed (2004) studies had very few babies getting phototherapy and the trend was in the opposite direction to that of McDonald and the Oxford midwives, with slightly more babies receiving phototherapy after early cord clamping [3,4]. There was no difference in the mean bilirubin level between the two groups. The two other studies by Nelson and van Rheenen also had very small numbers of babies receiving phototherapy [5,6]. The two studies which strongly influence the result that late cord clamping is associated with an increased need for phototherapy were both carried out before 2000. As Mercer and Erickson-Owens pointed out there was no consistent threshold of bilirubin for ordering phototherapy and the clinicians were not blinded, so some bias was possible [7]. In the three studies carried out before 2000, the use of phototherapy was 6% while in the three studies after 2000 it was only 0.9%. The use of phototherapy may have been refined since the 2000 and this explains the marked difference.

In neonates, jaundice tends to develop because of a combination of two factors - the breakdown of foetal haemoglobin while it is being replaced with adult haemoglobin and the relatively immature metabolic pathways of the liver, which are unable to conjugate and so excrete bilirubin as quickly as an adult. Foetal red blood cells have a shorter lifespan than adult cells, approximately 80 to 90 days in a full term infant, compared to 100 to 120 days in adults, thus there is higher bilirubin production due to more red cells being destroyed until all the foetal haemoglobin has been replaced. All these effects can cause an accumulation of bilirubin in the blood (hyper-bilirubinemia), leading to the symptoms of jaundice.

Physiological jaundice is the result of increased haemolysis of the red cells containing foetal haemoglobin and a limited capacity of the bilirubin to be conjugated and excreted. If haemolysis is increased (e.g. haemolytic disease of the new born) or the ability to conjugate the bilirubin is depressed (e.g. Gilbert's syndrome) then the jaundice becomes pathological.

Before birth, glucuronyl transferase is actively down-regulated, since bilirubin needs to remain unconjugated in order to cross the placenta and avoid accumulating in the foetus. After birth, it takes

some time for this enzyme to gain function. Only conjugated bilirubin can be excreted in the neonate. There is also a lower conversion of bilirubin to urobilinogen by the lack of intestinal flora in the neonate, which results in a relatively high absorption of bilirubin back into the circulation. Breast feeding is known to increase neonatal jaundice. It has been suggested that bilirubin uptake in the gut (enterohepatic circulation) is increased in breast fed babies, possibly as the result of increased levels of epidermal growth factor (EGF) in breast milk. Breast milk also contains glucuronidase which increases deconjugation and enterohepatic recirculation of bilirubin. There are several other mechanisms which are thought to reduce the excretion of bilirubin in breast fed babies.

### Hypothesis: Early Cord Clamping is Ictero-genic

If we make the hypothesis that early cord clamping and the consequent hypoxic ischemia disrupts the liver/bilirubin conjugation system, then these babies will have less capacity to excrete the bilirubin which will lead to a higher level of unconjugated bilirubin in the blood. Hypoxic ischemia is a consequence of early cord clamping. Clamping before respiration is established and a significant interval before respiration commences or ventilation can be established may be catastrophic [8]. Hypoxic ischemia is also recognised to be a consequence of the failure of an adequate placental transfusion, the result of early cord clamping when there has been cord compression [9]. These babies will not respond to ventilatory resuscitation until their blood volume is restored to normal by an emergency transfusion of uncross matched O negative blood or less satisfactory crystalloid volume. Inevitably there will be an interval of serious hypoxia and ischemia. Some of these babies will not survive.

For those that do survive there will be a spectrum of effect and, in some babies, the degree of hypoxia and ischemia following early cord clamping may be sufficient for them to have a depressed Apgar and/or a need for resuscitation. This hypoxic ischemia may result in brain injury and be sufficient to depress the activity or production of glucuronyl transferase.

### Evidence

Is there any evidence to support the idea that term babies with a low Apgar and/or needing resuscitation have higher levels of bilirubin or are more likely to require phototherapy? Birth asphyxia has been shown to be a risk factor for neonatal jaundice [10]. If we compare the babies with a good Apgar at birth with those with a very poor Apgar, the odds ratio for jaundice is 27.4 (14.5, 51.7).

The degree of hypoxia at birth and severity of hyper-bilirubinemia modulate both bilirubin and hypoxia related neurologic damage [11]. This paper links the long term neurological injury of hypoxia with the

degree of hyper-bilirubinaemia and would fit with the hypothesis that hypoxia and hyper-bilirubinaemia are linked in some way.

### Analysis

The McDonald RCT showed the greatest number of babies receiving phototherapy and this had the greatest influence on the conclusion of the Cochrane review. Although there was no statistically significant difference between the babies with early or late cord clamping for clinical jaundice, there was for receiving phototherapy. This suggests there may have been some bias in ordering phototherapy or at least no consistency based on a bilirubin threshold. The Hutton and Hasson systematic review which did not include the unpublished McDonald data did not show any increased use of phototherapy in babies after delayed cord clamping [12].

Intention-to-treat analysis (ITT) is used in the Cochrane systematic reviews. This is particularly important and helps to remove the effect of protocol violations and loss of follow-up, especially when patient compliance is required. However patient compliance does not apply to cord clamping. For optimal design the protocol should ensure maximal adherence. A large number of protocol violations invalidate the results of intention to treat analysis. The perceived need for neonatal resuscitation was a reason why babies allocated to delay cord clamping had early cord clamping. The McDonald trial did not specifically exclude babies requiring resuscitation. Resuscitation was always carried out after early cord clamping. McDonald stated "In particular, difficulty was experienced in the trial arms where late cord clamping was intended but only occurred in 50% of cases within the allocated time frame. The reasons listed mainly related to umbilical cord being tightly wound around the baby's neck, presence of meconium liquor or requirement for some form of active resuscitation that necessitated premature cord clamping." Thus there was a 50% non-compliance with 34% in the late cord clamping babies who needed active resuscitation. 38 babies in the late cord clamping arms had early clamping versus only one in the early cord clamping arm with late clamping. In the Andersson study there were only 12.5% protocol violations equally distributed between early and late cord clamping. Andersson re-analysed for the main and secondary outcomes, including cases of protocol breach at inclusion together with as per protocol (n=334), and this did not alter the conclusions. The authors noted that there have been "inconsistent results on the possible association between delayed cord clamping and neonatal jaundice, and the Cochrane review that reported a significant increase in infants needing phototherapy for jaundice relied heavily on unpublished data" [3].

In the McDonald study there were 38 (24 +14) babies who were allocated delayed cord clamping but received early cord clamping [1]. Within these two groups the allocation was for early oxytocic and late cord clamping or late oxytocic and late cord clamping. It is possible that the non-compliance was in the timing of the oxytocic but this seems unlikely since early rather than delayed cord clamping is generally agreed as an indication for resuscitation. Although a tight nuchal cord is mentioned as a cause for non-compliance with delayed cord clamping, the numbers were not provided. A tight nuchal cord managed by clamping and cutting is a significant risk for hypoxia and ischemia [13].

Analysis by intention to treat becomes meaningless when there is a 50% protocol violation. So analysis by actual allocation can be considered as Andersson et al did in their study [3]. Those 38 babies allocated to DCC but we know had ICC because of a need for

resuscitation could have contributed to the babies needing phototherapy for hyper-bilirubinaemia. If all 37 babies who developed jaundice sufficient to need phototherapy in the DCC arm had been within the 38 babies actually given early cord clamping, then there would be no babies within the DCC arm who required phototherapy. Even if the proportion was only 50% then 19 (50% of 37) of the babies receiving DCC would require phototherapy, and 18 babies who received early cord clamping require phototherapy.

This results in an almost identical use of phototherapy in both arms. (Table 1)

	ICC	DCC
Phototherapy	19	18
No phototherapy	499	427
OR = 0.9 [0.4, 1.7]		

**Table 1:** Identical use of phototherapy in both arms.

Clearly as one postulates a higher percentage of babies with early cord clamping and resuscitation requiring phototherapy, the risk ratio climbs steeply. At the very least this demonstrates the fragility of the McDonald results in terms of jaundice and the need for phototherapy, but also strengthens the hypothesis that neonatal jaundice may be partly the result of reduced liver function from peripartum hypoxia and ischemia.

### Discussion and Conclusion

The prime hypothesis of the McDonald study was focused on the prevention of PPH rather than the health of the neonate. Removal of the high use of phototherapy in the DCC arm of the McDonald study completely changes the conclusion of the Cochrane review with respect to jaundice and the use of phototherapy. If the hypoxia and ischemia induced by early cord clamping can result in a reduction in the conjugation of bilirubin in a term baby, then it is reasonable to conclude that the Cochrane systematic review actually shows no increase in bilirubin with delayed cord.

The risk of hyper-bilirubinaemia leading to kernicterus is often raised as a concern. However it is quite possible that early cord clamping may also have a role in the development of kernicterus. Kernicterus has been reported at all levels of bilirubin [14]. Ranck and Windle undertook experiments on asphyxia at birth to produce a primate model of cerebral palsy [15]. Their plan then was to seek treatments that would prevent the development of cerebral palsy. Monkeys were asphyxiated at birth by clamping the cord and preventing onset of breathing. Death occurred if resuscitation was delayed longer than 8 to 10 minutes. However, in monkeys subjected to 6 to 8 minutes of asphyxia, although developmental delay was reported, no brain damage was found. Then Seymour Kety, Chief of Experimental Research at the National Institute of Mental Health, suggested looking for damage in the auditory pathway. A second look for damage following asphyxia revealed severe damage in centres of the midbrain auditory pathway. Kety had discovered that nuclei in the auditory pathway have higher blood flow than any other area of the brain [16]. Ranck and Windle looked at other subcortical sites in the brains of asphyxiated monkeys.

## Conclusion

The human neuropathologic entity most closely resembling the effects of asphyxia neonatorum in the monkey is kernicterus. There are similarities in the distribution and type of nerve cell changes in both conditions. Major differences between the findings in the monkey and those in human infants with kernicterus are absence in the former of the usual history of erythroblastosis fetalis, lack of clinical jaundice, lack of pigment in the lesions, frequent presence of neuroglia cell damage, and presence of marked astrocytic and phagocytic reactions [15].

In follow-up research on kernicterus, Lucey et al. were unable to cause this pattern of damage even with very large injections of bilirubin, except in monkeys that had been subjected to asphyxia, and they concluded that bilirubin only entered brain sites in which the blood-brain barrier was damaged by asphyxia [17]. This has since been demonstrated by other researchers [18-21]. Thus there is strong link between asphyxia and kernicterus and a strong link between asphyxia and hyper-bilirubinaemia.

Evidence that delayed cord clamping increases the risk of jaundice and the need for phototherapy is very weak. We present evidence that in fact the reverse could be the case and propose that early cord clamping increases the risk of hyper-bilirubinaemia and kernicterus.

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