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The early effects of delayed cord clamping in term infants born to Libyan mothers

Musbah Omar Emhamed¹, Patrick van Rheenen², Bernard J Brabin¹²

1 Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool, UK
2 Emma Kinderziekenhuis, Academic Medical Centre Amsterdam, Netherlands

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SUMMARY

This study was conducted to evaluate the haematological effects of the timing of umbilical cord clamping in term infants 24 h after birth in Libya. Mother-infant pairs were randomly assigned to early cord clamping (within 10 s after delivery) or delayed clamping (after the cord stopped pulsating). Maternal haematological status was assessed on admission in the delivery room. Infant haematological status was evaluated in cord blood and 24 h after birth. Bilirubin concentration was assessed at 24 h. 104 mother-infant pairs were randomized to delayed (n=58) or early cord clamping (n=46). At baseline the groups had similar demographic and biomedical characteristics, except for a difference in maternal haemoglobin, which was significantly higher in the early clamping group (11.7 g/dL (SD 1.3) versus 10.9 g/dL, (SD 1.6); P=0.0035). Twenty-four hours after delivery the mean infant haemoglobin level was significantly higher in the delayed clamping group (18.5 g/dL versus 17.1g/dL; P=0.0005). No significant differences were found in clinical jaundice or plethora. Surprisingly, blood analysis showed that two babies in the early clamping group had total serum bilirubin levels (>15mg/dL) that necessitated phototherapy. There were no babies in the late clamping group who required phototherapy. Three infants in the delayed clamping group had polycythemia without symptoms, for which no partial exchange transfusion was necessary. Delaying cord clamping until the pulsations stop increases the red cell mass in term infants. It is a safe, simple and low cost delivery procedure that should be incorporated in integrated programmes aimed at reducing iron deficiency anaemia in infants in developing countries.
INTRODUCTION
Iron deficiency anaemia (IDA) is the most common nutritional disorder worldwide. Its prevalence is highest among children aged under five years in developing countries, where approximately 50% are affected. Severe anaemia in infancy is a life threatening condition and a major contributor to infant mortality in developing countries. IDA has been associated with impaired cognitive development in children under five. These children fail to catch up with iron therapy.

Strategies to reduce IDA in infants include iron supplementation and iron-fortification. Although these measures have been shown to be clinically effective, they are either cost-ineffective or difficult to implement, especially in developing countries.

A first step towards reducing anaemia in infancy can be taken during birth. Delayed cord clamping or placental transfusion could be a cost-effective intervention to improve the iron status of infants by enhancing their red cell mass.

The main objective of this study was to examine the effect of the time of umbilical cord clamping in term infants on haematological status 24 hours after birth. A second objective was to assess possible adverse effects, especially hyperviscosity and hyperbilirubinaemia. There have been controlled trials evaluating the short-term haematological effects of delayed cord clamping in term infants, but as far as we know this is the first randomised controlled trial.

SUBJECTS AND METHODS
Term infants delivered at Tripoli Medical Centre (TMC) in Libya between April and June 2003 were enrolled. Their mothers were contacted while in their first stage of labour to obtain informed consent. After giving consent, and prior to vaginal delivery, the infants were randomly assigned by means of sealed opaque envelopes to either delayed cord clamping (DCC) or immediate cord clamping (ICC). In the DCC group the umbilical cord was clamped after it stopped pulsating. The exact time was recorded by use of a stopwatch, with complete expulsion of the infant as the starting point. In the ICC group clamping was done within 10 seconds after delivery, which was the standard delivery practice at that time in TMC. Following vaginal birth the infant was placed on the mother’s abdomen and dried and wrapped in a warm towel. Oxytocin was given to the mother intramuscularly after cord clamping. Common practice is to give oxytocics with the delivery of the anterior shoulder. This delivery practice was adapted for the trial period to minimise confounders, as the administration of oxytocin in the third stage might speed up placental transfusion. The nurse midwives attending the deliveries were closely monitored by one of the authors (MOE).

All subjects meeting the following selection criteria were included: expected birth weight ≥ 2500 g, gestational age between 37 and 42 weeks (estimated by early ultrasound) and singleton birth. Mother-infant pairs were excluded when the baby had low birth weight (< 2500 g) or when the gestational age (as assessed by Ballard-external method) was less than 37 weeks. Other exclusion criteria were maternal gestational diabetes or (pre) eclampsia, instrumental
delivery, serious haemorrhage during pregnancy or delivery, major congenital abnormalities (neural tube defects, respiratory distress syndrome) and the need for early cord clamping (medical history of post-partum haemorrhage; tight nuchal cord; resuscitation).

One venous blood sample was taken from the mother upon arrival in the labour ward for estimation of maternal haemoglobin (Hb) and hematocrit (Ht). Women with Hb < 10 g/dL were considered to be anaemic. Before delivery a small structured survey questionnaire was used to gather socio-economic and demographic details from the mothers, as well as information on reproductive health. A sample of cord blood was collected from the placental side after clamping and ligating the fetal side for Hb and Ht estimation. Babies with cord Hb < 12.5 g/dL were considered to have fetal anaemia. Before discharge home (16-24 hours after birth) the babies were assessed for clinical signs of polycythaemia, hyperviscosity or hyperbilirubinaemia, and, if necessary, an estimation of the gestational age was done by using the Ballard-external method. Finally, an infant venous blood sample was taken for Ht and bilirubin analysis. Polycythaemia was defined as venous Ht > 65%. Phototherapy was considered to be necessary when bilirubin levels exceeded 15 mg/dL on day 1.

Based on the results of a recent systematic review, we expected a difference in mean haemoglobin between the ICC and DCC group at 24 hours of 1.5 g/dL with a standard deviation of 2.0 g/dL. On this assumption with a power of 90% and a confidence level of 95%, a sample size of 40 babies was required in each group.

As the aim of this study was to evaluate the effects of late cord clamping under ideal circumstances, data were analysed according to the per-protocol principle. Epi Info 2002 (Centers for Disease Control and Prevention, CDC, USA) was used for data analysis. The t-test for independent samples was used to compare group means for normally distributed data. When variances were not homogeneous the Mann-Whitney rank-sum test was used. A P-value < 0.05 was considered significant.

Ethical approval for the study was given by the Ethics Committee of the Liverpool School of Tropical Medicine and by local authorities of the departments of Obstetrics & Gynaecology and Paediatrics in TMC.

RESULTS
There were 112 mother-infant pairs eligible for inclusion (figure 1); 62 were randomised to DCC and 50 to ICC. Eight mother-infant pairs, equally distributed over both randomisation groups, were excluded from the final analysis. The infants needed resuscitation for intrapartum asphyxia. As a consequence, 58 mother-infant pairs remained in the DCC group (mean clamping time: 215 seconds (SD 51), and 46 in the immediate clamping group (mean 13 seconds (SD 6)). The mothers in the ICC and DCC groups were comparable in terms of age, parity, gestational age, ultrasound confirmation, level of education and antenatal iron supplementation. The mean maternal (Hb) level on admission to the labour ward was higher in the ICC group (11.7 g/dL (SD 1.3)) than in the
DCC group (10.9 g/dL (SD 1.6), and this difference was significant (p = 0.0035). The proportion of women with anaemia at delivery was also higher in the DCC group: 29% versus 9% (p=0.0096). Other maternal baseline characteristics were not significantly different (Table1).

Figure 1 Recruitment into the study. DCC=delayed cord clamping; ICC=immediate cord clamping
Table 1. Maternal baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early clamping (n=46)</th>
<th>Delayed clamping (n=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age in yrs (mean ± SD)</td>
<td>28.9 (4.8)</td>
<td>28.4 (4.7)</td>
<td>0.64</td>
</tr>
<tr>
<td>Parity</td>
<td>2.2 (2.4)</td>
<td>1.7 (1.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Primigravida (%)</td>
<td>26</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Multigravida (%)</td>
<td>74</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Iron supplementation in pregnancy (%)</td>
<td>78</td>
<td>81</td>
<td>0.73</td>
</tr>
<tr>
<td>Number of antenatal visits to clinic</td>
<td>6.8 (3.2)</td>
<td>6.2 (3.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Maternal schooling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>6.5</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Primary (%)</td>
<td>8.7</td>
<td>12.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Secondary (%)</td>
<td>71.7</td>
<td>60.3</td>
<td></td>
</tr>
<tr>
<td>Tertiary (%)</td>
<td>13.0</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>Ultrasound in first trimester (%)</td>
<td>91</td>
<td>93</td>
<td>0.74</td>
</tr>
<tr>
<td>Oxytocics prior to clamping (%)</td>
<td>39</td>
<td>45</td>
<td>0.56</td>
</tr>
<tr>
<td>Hb on admission to labour ward (g/dL)</td>
<td>11.7 (1.3)</td>
<td>10.9 (1.6)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Proportion maternal anaemia (%)</td>
<td>9</td>
<td>29</td>
<td>0.0096</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless stated otherwise

Infant baseline characteristics did not differ significantly (Table 2). Low birth weight was not observed in any infant. Cord Hb and Ht levels were comparable in both groups. The prevalence of fetal anaemia was higher in the DCC group, although this difference was not significant. Polycythaemia was not observed at birth. There was no correlation between maternal and cord haemoglobin in either the ICC or DCC group.

Table 2 Infant baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early clamping (n=46)</th>
<th>Delayed clamping (n=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clamping time (sec)</td>
<td>12.8 (5.5)</td>
<td>214.6 (50.6)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>40.0 (1.4)</td>
<td>39.8 (1.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td>3428 (424)</td>
<td>3390 (421)</td>
<td>0.65</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>46</td>
<td>55</td>
<td>0.33</td>
</tr>
<tr>
<td>Cord haemoglobin (g/dL)</td>
<td>15.4 (1.4)</td>
<td>14.9 (1.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Proportion Fetal Anaemia (%) (Hb &lt; 12.5 g/dL)</td>
<td>4.3</td>
<td>6.9</td>
<td>0.58</td>
</tr>
<tr>
<td>Cord haematocrit</td>
<td>45.0 (4.6)</td>
<td>44.1 (5.8)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless stated otherwise
A single child was lost to follow-up in each group, as their parents had taken them home before they could be reviewed. Evaluation after 24 hours revealed no significant differences in clinical jaundice or the proportion of infants with clinical plethora. There were no significant differences in serum total bilirubin levels at 24 hours, although surprisingly 4.6% of the infants in the ICC group had bilirubin levels (>15 mg/dL) that necessitated phototherapy.

The Ht level was significantly higher in the DCC group (p = 0.0037), but only 5% of infants in this group had polycythaemia. Hb levels after 24 hours showed higher values in the DCC group (18.5 g/dL (SD 2.1) versus 17.1 g/dL (SD 1.9)) and these differences were significant (p = 0.0005). The infants’ haematological outcomes are summarised in Table 3.

Table 3. Infant haematological outcome after 24 hours

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early clamping (n=45)</th>
<th>Delayed clamping (n=57)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical jaundice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (%)</td>
<td>68.9</td>
<td>73.7</td>
<td></td>
</tr>
<tr>
<td>Mild-moderate (%)</td>
<td>28.9</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>Severe (%)</td>
<td>2.2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>6.1 (3.0)</td>
<td>5.8 (1.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Proportion (%) above phototherapy threshold (bilirubin &gt; 15 mg/dL)</td>
<td>4.6</td>
<td>0</td>
<td>0.11</td>
</tr>
<tr>
<td>Clinical plethora (%)</td>
<td>24.4</td>
<td>40.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>17.1 (1.9)</td>
<td>18.5 (2.1)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Difference in cord haemoglobin and at 24 hrs (g/dL)</td>
<td>1.7 (1.7)</td>
<td>3.5 (1.9)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>49.3 (5.7)</td>
<td>52.9 (6.3)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Difference in cord haematocrit and at 24 hrs (%)</td>
<td>4.4 (5.6)</td>
<td>8.7 (5.7)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Proportion polycythaemia (%) (Hct &gt; 65%)</td>
<td>0</td>
<td>5.3</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless stated otherwise
DISCUSSION

The aim of this study was to evaluate whether DCC could enhance red cell mass in term infants in Libya. We found a difference in the mean Hb and Hct levels of infants at 24 hours after delivery in favour of the DCC group. This difference is statistically significant and is possibly of clinical importance. This result is in accordance with earlier published studies on the short-term effects of placental transfusion.\textsuperscript{16} It should be noted that the incidence of moderate maternal anaemia (Hb < 10 g/dL) was significantly higher in the group randomised for DCC, while both groups were comparable for all other variables. No women had severe anaemia (Hb<7g/dL). The fact that a considerable number of babies (6 out of 104) were found to have fetal anaemia, can possibly be explained by the existence of \( \alpha \)-thalassaemia in the study population, which is known to reduce cord Hb levels.

Maternal iron deficiency has also been related to fetal anaemia in a study from Malawi.\textsuperscript{17} Four randomised controlled trials have been published that examined longer-term effects of DCC in developing countries have been published. Two found a significant difference in Hb levels at 2-3 months in favour of the DCC group.\textsuperscript{18;19} The other two studies showed no difference in indicators for infant iron status.\textsuperscript{20,21} Three controlled trials from Germany (published in four papers) showed a significant increase in Ht levels in favour of DCC.\textsuperscript{10-13} This difference was seen by 2-4 hours after delivery, and remained significant during the following five days.

Hyperbilirubinaemia, polycythaemia and hyperviscosity syndrome are frequently mentioned adverse effects of placental transfusion. In our study in term infants no significant difference was found between the DCC and ICC groups in total serum bilirubin levels at 24 hours, the number of infants requiring phototherapy, or the prevalence of plethoric skin and polycythaemia. None of the children showed signs of hyperviscosity syndrome (cyanosis, feeding difficulties, tachypnea or neurological depression). Blood glucose levels were not checked routinely, but none of the children showed signs of hypoglycaemia. Placental transfusion in term infants was not associated with perinatal complications in this study.

No previously published trials reported any clinical manifestations of polycythaemia.\textsuperscript{10-13,18-21} The German trials reported that some newborns with DCC had bilirubin levels > 15 mg/dL. It was not stated how many days after delivery these neonates were assessed. Neither did they report whether phototherapy or exchange transfusions were needed. A trial from Canada examined both pre-term and term infants.\textsuperscript{14} When analysing the data for term infants separately no cases of hyperbilirubinaemia were found.

The major objective of this trial was to evaluate whether DCC could improve the haematological status of infants. The difference we found in the mean Hb and Ht levels of infants at 24 hours after delivery in favour of the DCC group is possibly of clinical importance. It is estimated that in full-term infants placental transfusion can increase red cell mass by 25-33\%\textsuperscript{22,23} Iron stores in the term newborn are normally adequate to maintain iron sufficiency for approximately four months of postnatal growth.\textsuperscript{24} Improved iron status from these additional red cells might increase the stores sufficiently to cover the first 5-6 months.
A recent systematic review showed that DCC in premature babies should be done with more caution. Delaying cord clamping in premature babies for more than 1 minute increases the risk of complications such as polycythaemia and hyperbilirubinaemia. It seems advisable to delay clamping of the umbilical cord in this group of neonates for not more than 45-60 seconds.25

The policy of delayed cord clamping is in contrast with active management of the third stage of labour to reduce post-partum haemorrhage. Active management involves ICC, prophylactic use of oxytocic drugs before delivery of the placenta and controlled cord traction.26 In our opinion delaying cord clamping can be done safely in selected groups. Women who have a history of post-partum haemorrhage should be exempted from this delivery procedure. Although the administration of oxytocin was postponed until after cord clamping in this study, this is not necessary in practice. Early intramuscular injection of oxytocin can even speed up placental transfusion.15

Delaying cord clamping until the pulsations stop is a physiological way of treating the cord and is not associated with adverse effects, at least in term vaginal deliveries. Many children living in less developed countries belong to anaemia risk groups (low birthweight; severe maternal anaemia, chronic infection, iron deficient diets after 5-6 months) and should therefore be given the opportunity to boost their iron stores at birth. DCC, which is a safe, simple and low-cost delivery procedure, should be incorporated in the routine labour management. It could serve as an additional cost-effective intervention within integrated programmes aimed at reducing IDA in infants in developing countries.

ACKNOWLEDGEMENTS
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