



# When to clamp the umbilical cord for full term babies?

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Dr. Elisabeth Semple



## **A review of the current literature comparing early and delayed clamping of the umbilical cord after term births.**

During the last 20 years evidence has been accumulating about the benefits to the newborn of delayed clamping of the cord after birth. These benefits include increased iron stores and a decreased risk of anemia up to 4-6 months of age.<sup>1,2</sup> Adequate availability of iron is important for the development of the brain during the first years of life<sup>3,4</sup> and transferring the cord blood at birth is an easy way to elevate the ferritin in the blood of newborn. As an increasing number of parents are considering storing or donating their cord blood, is there a way to both benefit the baby and collect cord blood?

### **What does “early” and “delayed” mean?**

One difficulty when assessing the data is the inconsistency of the definitions of “early” and “delayed” clamping. “Early” has been defined as any time between 10 sec to 1 min, and “delayed” as between 30 sec to 5 min.

A systematic review and meta-analysis of the available data was performed in 2006 by Hutton and Hassan<sup>1</sup> where they compared the outcomes in 15 clinical studies of term babies.<sup>5-19</sup> They defined “early” as within 10-15 sec of birth and “delayed” as 2 minutes or more after birth. A similar review, also on term babies, was e-published in 2013 from the Cochrane Collaboration, authored by McDonald et al.<sup>2</sup> Several of the studies used by Hutton were included but this analysis<sup>5-12</sup>, also included studies published between 1997 and 2012, a total of 15 studies.<sup>20-25</sup> The definition of “early” was less than 15 sec and of “delayed” was defined as more than 1 min after birth.

### **What do the SOGC and ACOG say?**

The SOGC (Society of Obstetricians and Gynaecologists of Canada) addressed the timing of cord clamping in their Clinical Practice Guideline, Active management of the third stage of labour: Prevention and treatment of postpartum hemorrhage, published Oct 2009.<sup>26</sup> They recommend the following: “Whenever possible, delaying the clamping of the cord by at least 60 seconds is preferred to clamping earlier in premature newborns (<37 weeks’ gestation)...” For term babies, they recommend caution about delaying clamping due to the possible risk of increased jaundice requiring phototherapy.

The ACOG (American Congress of Obstetricians and Gynecologists) released their updated recommendation in January 2017 and they conclude<sup>27</sup>: “Term and pre-term infants appear to derive benefit from delayed umbilical cord clamping; therefore delayed umbilical cord clamping for at least 30-60 seconds is recommended in term and pre-term infants except when immediate umbilical cord clamping is necessary because of neonatal or maternal indications.”

## What are the benefits of delayed clamping?

Both of the meta-analyses referred to above and most other published studies present data which show that delayed clamping gives newborns increased iron levels in their blood and a decreased risk for iron deficiency during the first months of life.<sup>1,2</sup> However, as the authors point out, there was a large variation among the studies in how they evaluated iron deficiency, including how iron deficiency was defined.

Moreover, in the two meta-analyses, the difference in iron levels between the groups with early versus delayed clamping varies. One factor in these differences could be the iron status of the mother. Several of the studies included in the analyses were conducted in low and medium income settings (e.g. Argentina<sup>5</sup>, Mexico<sup>6</sup>, Libya<sup>7</sup>, India<sup>8,11</sup>) where the level of maternal care may not be the same as in North America. One study that was included in both meta-analyses has evaluated the influence of maternal iron levels<sup>6</sup>. They found that delayed clamping had a greater impact on newborn iron levels when the mother had low iron levels (defined as  $<9\mu\text{g/L}$ ).

A group in Sweden has conducted the first modern-era long-term study of the impact of delayed cord clamping for term babies born in a country with rich resources.

Anderson et al.<sup>22</sup> published a study on 400 term babies born in Sweden in 2011. In this study, they defined “early clamping” as within 15 sec of birth and “delayed clamping” as after 3 min, during which time they held the baby 20 cm below the vulva. At the follow up four months after birth, they found that the group with delayed clamping had significantly higher iron levels (117  $\mu\text{g/L}$  versus 81  $\mu\text{g/L}$ ), and that iron deficiency was less prevalent in the delayed clamping group, but the prevalence of anemia was the same in both groups. The authors conclude that “delayed clamping, in this randomized controlled trial, resulted in improved ferritin levels and reduced the prevalence of iron deficiency at four months of age.”

The same group published follow ups on the same babies at 12 months and 4 years of age.<sup>28,31</sup> To our knowledge, this is the first study since 1941<sup>29</sup> to look at the effects of delayed clamping beyond 6 months. After 12 months, they found that there was no longer a difference between the groups in any of the iron status indicators, nor was there a difference in the level of anemia<sup>28</sup>.

Because adequate iron levels are important for pediatric brain development, the researchers evaluated the neurodevelopment of children in the study by asking parents to answer the Ages and Stages Questionnaire (ASQ) to assess their child’s development. This tool did not find any difference between the two groups at age 12 months and there was no correlation between neurodevelopment and iron status at birth or at 4 months<sup>28</sup>.

The neurodevelopment of the same children was again followed up at 4 years of age.<sup>31</sup> The researchers found that, for girls, the time of clamping did not make any difference in any of the tests performed. However, boys that had early cord clamping showed slightly late development in fine motor skills and social skills. Unfortunately, this study only reported on neurodevelopment, not on iron levels or nutrition (the natural way to get iron). As neurodevelopment can be influenced by many factors, not just the level of iron at birth, further research is needed on larger groups of children to ensure that this result can be confirmed.

## Are there any risks with delayed clamping?

It has often been suggested that delayed cord clamping in full term infants could result in more instances of jaundice requiring light therapy, but this has not been proven with published data.<sup>2</sup> In addition to clamping delay, there are other factors that influence the transfer of blood from the placenta to the baby. It has been suggested that focusing only on clamping delay and ignoring other factors such as when the baby starts breathing could be counter-productive for the infant and could even result in infant-to-placenta transfer of blood.<sup>33</sup>

## Are there any risks with early clamping?

It is known that it is important to prevent iron deficiency in order to achieve optimal brain development.<sup>4</sup> While all the available data show that delayed clamping will increase the iron levels, are there any data showing that early clamping results in iron levels that are too low? This analysis is complicated by the fact that the studies are using different definitions for identifying iron deficiency and low ferritin.

Table 1 below shows iron levels of early versus delayed clamping groups in the Cochrane review.<sup>2</sup> Using blood ferritin levels as an indicator for iron deficiency, we can see that although there are significant differences between the early versus late clamping groups, none of the groups has a mean ferritin level close to the limit of low ferritin. In the study by Andersson<sup>22</sup>, 7% of the infants that had early clamping had a ferritin level  $<20 \mu\text{g/L}$ , compared with none in the delayed group. However at the 12 months follow up 1% and 2% of the infants had low ferritin levels (early and delayed clamping, respectively).<sup>28</sup>

**There is no reliable data so far showing that there is any impact of the timing of cord clamping on the long-term iron levels and neurodevelopment of the infants in any of the studies.**

| <b>Table 1:<br/>Study</b>                       | <b>Definition:<br/>Iron deficiency</b>   | <b>Definition:<br/>Low Ferritin</b>                    | <b>Ferritin:<br/>Study result at 3-6 months<br/>mean<math>\pm</math>sd; median (range)</b>   |
|---|--|--|--|
| Al-Tawil 2012<br>Saudi-Arabia <sup>21</sup>     | MVC $<73\text{fL}$<br>Transferrin saturation $<10\%$   | $<20\mu\text{g/L}$                                     | Early: $228\pm 147 \mu\text{g/L}$<br>Delayed: $430\pm 132 \mu\text{g/L}$   |
| Andersson 2011, 2014<br>Sweden <sup>22,28</sup> | $>2$ indicators outside ref. values<br>(ferritin $<20 \mu\text{g/L}$ , MCV $<73\text{fL}$ ,<br>transferrin saturation $<10\%$ ,<br>transferrin receptors $>7\text{mg/L}$ ) | $<20 \mu\text{g/L}$ (4 m)<br>$<12 \mu\text{g/L}$ (12m) | <b>At 4 months:</b><br>Early: $81 \mu\text{g/L}$ (6-670)<br>Delayed: $117 \mu\text{g/L}$ (20-880)<br><br><b>After 12 months:</b><br>Early: $34\pm 0.24 \mu\text{g/L}$<br>Delayed: $35\pm 0.22 \mu\text{g/L}$ |
| Cernadas, 2010<br>Argentina <sup>5</sup>        | Hemoglobin $<105 \text{g/L}$<br>and ferritin $<9 \mu\text{g/L}$  | $<9 \mu\text{g/L}$                                     | Early: $20\pm 26 \mu\text{g/L}$<br>Delayed: $33\pm 37 \mu\text{g/L}$   |
| Chaparro 2006<br>Mexico <sup>6</sup>            | Ferritin $<9 \mu\text{g/L}$  | $<9 \mu\text{g/L}$                                     | Early: $35\pm 32 \mu\text{g/L}$<br>Delayed: $47\pm 38 \mu\text{g/L}$   |
| Gupta 2002<br>India <sup>8</sup>                | Not reported   | Not defined  | Early: $80 \mu\text{g/L}$ (15-180)<br>Delayed: $105 \mu\text{g/L}$ (30-500)  |
| Geethanath 1997<br>India <sup>11</sup>          | Not reported   | Not defined  | Early: $56\pm 4 \mu\text{g/L}$<br>Delayed: $74\pm 3 \mu\text{g/L}$   |

## Is it possible to delay clamping and still collect cord blood?

It is evident that there will be less cord blood to collect if the clamping of the cord has been extensively delayed. Physiological studies in term infants have shown that approximately 70-80% of the blood in the cord and placenta is transferred in the first minute after birth<sup>16,30,38</sup>. The study by Andersson et al<sup>22</sup> measured the remaining volume in placentas after both early and delayed clamping and found that the volume decreased by 40% when clamping was delayed for 3 minutes and the baby was held 20 cm below the vulva.

Two studies looked specifically at collected cord blood volume as a function of clamping delay. Allan et al 2016<sup>36</sup> found that a delay of 20-60 sec decreased the collection volume approximately 15%, thereby decreasing the fraction of cord blood units with a high enough cell count for public storage (defined as >1.25 billion cells) from 50% to 25% compared with units collected with no delay (<20 sec). In their study, delaying clamping even further to >120 sec, decreased the number of units with high cell counts to 14%. At the International Cord Blood Symposium in June 2016 and in the Dec. 2016 newsletter of Parent's Guide to Cord Blood, Ciubotariu<sup>37</sup> presented data that supported these findings. In this study, early clamping was defined as <60 sec and delayed clamping >60 sec, and they found that units with high cell content (here defined as >1.6 billion cells) decreased from approximately 18% with early clamping to approximately 2% if the clamping was delayed more than 60 sec.

Would delayed clamping still benefit the baby if the delay is only 30 sec to 1 minute? Table 2 below shows iron levels as a function of clamping delay time for two studies that provide this data. In both studies, Cernadas et al<sup>5</sup> in Argentina and Andersson, et al<sup>32</sup> in Sweden, there was no significant difference in blood iron levels between the early versus late clamping groups months after birth, despite variable clamping times, variable months to measurement, and delivery via C-section versus vaginal birth.

| <b>Table 2:<br/>Study</b>                | <b>Incidence of Iron deficiency and anemia</b>   | <b>Ferritin levels; # of infants with &lt;9 µ g/L</b>   |
|--|--|---|
| Cernadas, 2010<br>Argentina <sup>5</sup> | At 6 months:<br>15 sec: 6 out of 86 infants<br>1 min: 3 out of 84 infants<br>3 min: 2 out of 84 infants  | <b>At 6 months:</b><br>15 sec: 20 ± 26 µ g/L, 13/86<br>1 min: 26 ± 26 µ g/L, 10/83<br>3 min: 33 ± 37 µ g/L, 6/83  |
| Andersson, 2016<br>Sweden <sup>32</sup>  | At 4 months:<br>30 sec C-section: 0 out of 52 infants<br>180 sec, vaginal delivery: 0/148 infants<br><br>At 12 months:<br>30 sec C-section: 1 out of 46 infants<br>180 sec, vaginal delivery: 0 out of 128 infants | <b>At 4 months:</b><br>30 sec C-section: 103 µg/L, 1/55<br>180 sec, vaginal delivery: 117 µg/L, 0/149<br><br><b>At 12 months:</b><br>30 sec C-section: 35 µg/L, 2/46<br>180 sec, vaginal delivery: 35 µg/L, 2/129 |

**Conclusions: Following the recommendations of SOGC<sup>26</sup> and ACOG<sup>27</sup>, providing the mother is not iron deficient and that the pregnancy is at least 37 weeks gestation, cord clamping at 30 - 60 seconds after birth will ensure a safe outcome for the baby and yet allow for an adequate umbilical cord blood collection if the parents wish to do so.**

Elisabeth Semple PhD is the Director of the Victoria Angel Registry of Hope public cord blood bank and the Scientific Director of the family cord blood bank Cells for Life in Toronto, Canada. She has over 35 years experience in the field of cell collection, processing and banking. After receiving her PhD in Sweden, Dr. Semple has worked with cells in the hospital setting, in academia, and in business, both in Europe and in North America.

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