A clinical study of fetal outcome following early and delayed cord clamping in births associated with anemia in pregnancy

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ABSTRACT

Background: As there is a risk for infant anaemia, early cord clamping which is usually performed at 10-15 seconds of delivery was changed to delayed cord clamping for at least for 30 seconds. Delayed cord clamping (DCC) increases the blood volume and haemoglobin levels in newborns and reduces risk of iron deficiency anaemia in both term and preterm infants. Early clamping allows cord blood collection in benefit for transplantation of stem cells. Research Objective: To compare levels of haemoglobin, hematocrit and serum ferritin at birth and 4 weeks of age in babies as well as neonatal outcome following early and delayed cord clamping in births associated with anaemia in pregnancy. Study Design: An observational study. Participants: Anaemic pregnant women with period of gestation 32-40 weeks admitted in labour room for delivery were enrolled. Intervention: Grouping of the patients was done according to the timing of the umbilical cord clamping. 1. Early cord clamping (< 60 seconds) 2. Delayed cord clamping (1 – 3 minutes) Of which 58 subjects were in ECC (early cord clamping) and 62 were in DCC (delayed cord clamping) group. Results: There was no significance of ECC or DCC in developing polycythemia, IVH or hyperbilirubinemia or increased need of blood transfusion. The levels of haemoglobin, hematocrit and ferritin levels were showing significant increased among DCC as compared to ECC. Conclusion: Delayed cord clamping significantly increases the levels of haemoglobin, serum ferritin and hematocrit at 4 weeks of age. It should be recommended in routine practice where it is not contraindicated especially in resource-poor settings.

Keywords: Early cord clamping, delayed cord clamping

Introduction

As there is a risk for infant anaemia, early cord clamping (ECC) that is usually performed at 10–15 s of delivery was changed to delayed cord clamping (DCC) for at least for 30 s. The prevalence of anaemia in pregnant women worldwide is 41.8% ⁵,⁶ DCC increases the blood volume and hemoglobin levels in newborns and reduces risk of iron deficiency anaemia in both term and preterm infants. In term infants, the positive effect on their iron status lasts up to 4–6 months after birth. In preterm infants, DCC is associated with fewer blood transfusions for anaemia, less intraventricular hemorrhage, and lower risk of necrotizing enterocolitis. Improved blood pressure, oxygen carrying capacity, urine output, and temperature were also observed. These potential benefits need to be balanced against possible harmful effects, for the mother (Post Partum Haemorrhage (PPH) and its consequences) and infant (delayed resuscitation,
hypothermia, polycythemia, hyperbilirubinemia, and risk of Intraventricular Haemorrhage (IVH)).

Recently, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion that supported DCC in preterm infants. Multiple systematic review and meta-analysis supported DCC benefits in term as well as preterm infants. ECC might decrease above mentioned maternal and infant risks but it also means loss of hematopoietic stem cells. The consequences of this is argued and the loss of stem cells could cause consequences later in life. This is presently not possible in conjunction with late cord clamping.

This study was conducted to assess the effect of delayed clamping on infants born to anemic mothers and whether this practice is worth adopting in delivery rooms.

### Material and Methods

The study was conducted in the Labor room of Department of Obstetrics and Gynaecology in Lady Hardinge Medical College and associated hospitals, New Delhi. The ethical and institutional permission taken same for the Anemic women with period of gestation 32–40 weeks admitted in labor room for delivery were enrolled in the study after taking informed consent. A total of 120 anemic pregnant women admitted in labor room were enrolled in the study. Grouping of the patients in the proposed observational study was done according to the timing of the umbilical cord clamping.

**ECC (<60 s)**

**DCC (1–3 min)**

### Results

Mean gestational age at delivery was 38.6 ± 1.437 and 38.4 ± 1.489 in ECC and DCC subjects without any significance (P < 0.621).

![Table 1](https://example.com/table1.png)

| Parameter                  | Mean±SD  | P     |
|----------------------------|----------|-------|
| Birth weight (kg)          | 2.835±0.3955 | 2.844±0.5069 | 0.917 |
| Apgar score at 5 min       | 9±0.0    | 9±0.0 | 1    |
| Duration of hospital stay (days) | 1.35±1.35 | 1.35±1.35 | 0.989 |
| Cord Hemoglobin (g/dL)     | 15.467±1.013 | 15.454±1.396 | 0.955 |
| Cord Hematocrit (%)        | 47.039±3.753 | 46.689±4.625 | 0.682 |
| Cord ferritin (µg/L)       | 192.18±88.31 | 199.04±102.87 | 0.724 |
| Gestational age (weeks)    | 38.6±1.437 | 38.4±1.489 | 0.621 |

In the present study, 100 anemic women were enrolled out of that 46 were in ECC and 54 in DCC group and none of them showed polycythemia (P-value <1); thus, it was statistically insignificant. Out of 46 subjects in ECC, 42 babies (44.7%) did not have hyperbilirubinemia and 4 (8.7%) babies developed hyperbilirubinemia. In DCC group, out of 54 subjects, 52 (55.3%) were normal and 2 (3.7%) developed hyperbilirubinemia (P-value <0.025). Thus, it shows that early or delayed clamping of cord does not affect the bilirubin levels in the babies [Table 2].

Out of 6 babies who developed hyperbilirubinemia, only 2 babies required phototherapy, one in each group (P < 0.909), none required exchange transfusion (P < 1), none required blood transfusion (P < 1), thus showing that there was statistically no significant adverse effect of cord clamping on babies [Table 2].

Out of 100 babies, not even a single baby had intraventricular hemorrhage (P < 1), showing no statistical significance of ECC or DCC [Table 2].

Out of 6 babies developing hyperbilirubinemia, total duration of hospital stay (days) in ECC was 6.33 ± 1.155 and 7.33 ± 3.055 in DCC and it is showing the insignificant effect of ECC and DCC (P < 0.624).

Thus, above table shows no significance of ECC or DCC in developing polycythemia, IVH or hyperbilirubinemia or increased need of blood transfusion. The mean cord hemoglobin in ECC and DCC of Group A, Group B, and total was comparable (P < 0.760, P < 0.730, and P < 0.961, respectively).

The mean hemoglobin at 4 weeks was slightly higher in all the groups and total in the DCC study group (P-value <0.00), thus, showing increased levels of hemoglobin at 4 weeks in DCC group as compared to ECC group and the difference is statistically significant.

Cord hematocrit and cord ferritin levels are comparable in both the groups at birth, showing no statistical difference. Hematocrit and cord ferritin at 4 weeks in both groups are 28.12 ± 1.63 and 29.5 ± 2.30 in ECC and 30.99 ± 2.49 and 31.578 ± 3.7579 in DCC showing statistically significant values (P < 0.0, P < 0.03, respectively). Thus, there is an increase in hematocrit levels and cord ferritin in both the groups A and B in DCC as compared to ECC group showing a significant effect of delayed clamping.

### Discussion

The type of study done was an observational study.
In the present study, the mean birth weight was 2.835 ± 0.3955 in ECC and 2.844 ± 0.506 (P < 0.917) and was comparable to the study done in India by Gupta and Ramji with mean birth weight of 2.707 ± 0.4172 in ECC and 2.743 ± 0.4078 in DCC group (P < 0.05). In other similar studies conducted in western countries, the mean birth weight was higher but there was no statistically significant difference in both the groups. Thus, the babies born to anemic mothers tend to have lower birth weight and also differences in ethnicity may be an additive factor to decreased birth weight.

In our study, we considered Apgar score at 5 min (P-value < 1), which was also reported by Rabe et al., 2008 with RR 1.17 (0.62–2.20) P = 0.64 in both groups. The study included Apgar score at 1 min, P value not significant. Thus, Apgar score is not related to umbilical cord clamping observed in many studies.

Total duration of hospital stay was comparable in both the groups 1.35 ± 1.35 (P < 0.989), which was nonsignificant and showed it was not affected by the timing of cord clamping. Thus, admission in NICU was not affected in the babies who underwent DCC.

The mean hemoglobin of the babies included in the study was slightly higher as compared to the study done in India by Gupta and Ramji, which had mean cord ferritin levels of 148.4 in ECC and 124.9 in DCC group (P-value NS) [Table 3-5].

Thus, higher cord ferritin levels were possibly due to higher ferritin levels in mothers as compared to the study done by Gupta and Ramji. Both the studies were carried out in India but possible cause of difference in ferritin levels may be the socio-economic status and dietary habits of mother.

| Table 2: Comparison of neonatal outcomes in the study groups |
|-------------------------------------------------------------|
| ECC (n=46) | DCC (n=54) | P  |
| No. of babies developing polycythemia | 0 | 0 | 1 |
| No. of babies with hyperbilirubinemia (clinically visible) | 4 | 2 | 0.295 |
| No. of babies requiring phototherapy | 1 | 1 | 0.909 |
| Exchange transfusion | 0 | 0 | 1 |
| Intraventricular hemorrhage | 0 | 0 | 1 |
| Blood transfusion | 0 | 0 | 1 |
| Mean total duration of hospital stay (days) | 1.35±1.35 | 1.35±1.35 | 0.989 |
| Mean total duration of hospital stay with hyperbilirubinemia (days) | 6.33±1.155 | 7.33±3.055 | 0.624 |
| Apgar score at 5 min | 9±0.0 | 9±0.0 | 1 |

| Table 3: Comparison of levels of cord hemoglobin in ECC and DCC and hemoglobin at 4 weeks of age in ECC and DCC |
|---------------------------------------------------------------|
| Mean Maternal Hb 7-9.9 GROUP A | Maternal Hb 10-10.9 GROUP B | Total |
|---------------------------------------------------------------|
| Cord hemoglobin | 15.292±1.0657 | 15.387±1.2904 | 0.760 |
| Hemoglobin at 4 weeks | 9.448±0.5440 | 10.474±0.8029 | 0.000 |
| t-tests |
| Cord ferritin | 189.047±97.7754 | 200.154±115.9226 | 0.704 |
| Serum ferritin at 4 weeks | 151.837±81.1275 | 245.316±76.8427 | 0.000 |

| Table 4: Comparison of cord hematocrit and hematocrit at 4 weeks in both the study groups |
|---------------------------------------------------------------|
| Mean Maternal Hb 7-9.9 GROUP A | Maternal Hb 10-10.9 GROUP B | Total |
|---------------------------------------------------------------|
| Cord hematocrit | 46.376±3.6737 | 46.129±4.0225 | 0.813 |
| Hematocrit at 4 weeks | 28.120±1.6304 | 30.994±2.2946 | 0.000 |
| t-tests |

| Table 5: Comparison of ferritin levels in cord blood and effect of cord clamping after 4 weeks of age |
|---------------------------------------------------------------|
| Mean Maternal Hb 7-9.9 GROUP A | Maternal Hb 10-10.9 GROUP B | Total |
|---------------------------------------------------------------|
| Cord ferritin | 189.047±97.7754 | 200.154±115.9226 | 0.704 |
| Serum ferritin at 4 weeks | 151.837±81.1275 | 245.316±76.8427 | 0.000 |
| t-tests |

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Another similar study conducted in Sweden by Andersson et al.\textsuperscript{[11]} did not do cord ferritin instead they did ferritin levels on day 2 showing no significant changes with mean ferritin of 300 in ECC and 312 in DCC \((P < 0.45)\).

The mean hematocrit in the present study in ECC and DCC is 47.039 ± 3.75 and 46.689 ± 4.625 \((P < 0.682)\). This parameter has been measured in many similar studies but in those studies, there was a significant difference in the levels of hematocrit in early and DCC.\textsuperscript{[10]}

The possible reason for the difference could have been the timing of measurement, which varied from 2–6 h. In the present study, it was measured at the time of birth \([\text{Table 7}]\).

### Neonatal outcomes

If the effect of DCC is attributed to increased risk of polycythemia in babies, then in the present study, there is no statistical effect on babies with DCC (\(P\)-value <1).

None of the babies developed polycythemia in the present study.

It is thought that risk of polycythemia after birth is more in neonates allocated to DCC rather than ECC and it was showed by 2 studies at 7 h of birth\textsuperscript{[11,12]} (RR, 3.44; 95% CI, 1.25 to 9.52) and some studies at 24 to 48 h\textsuperscript{[11,13-15]} (RR, 3.82; 95% CI, 1.11 to 13.21) but statistical significance was not reached \([\text{Table 8}]\). DCC was associated with moderate increase in rates of polycythemia, but there was no evidence of any significant harm like need for phototherapy to treat jaundice or by admission to the NICU in the above mentioned studies. The study of Ceriani Cernadas et al.\textsuperscript{[13]} and Emhamed et al.\textsuperscript{[13]} showed same results and none of the polycythemic infants were symptomatic \(i.e., \) had symptoms of Central Nervous System (CNS), Cardio Vascular System (CVS), pulmonary, gastrointestinal tract, or renal impairment.

In the present study, there were 4 babies out of 46 in ECC group who developed hyperbilirubinemia and 2 babies out of 54 developed hyperbilirubinemia in DCC group with \(P < 0.295\) explaining no statistical significance. The study of Ceriani Cernadas et al.\textsuperscript{[13]} and Emhamed et al.\textsuperscript{[13]} supports our observation results.

### Neonatal hemoglobin and hematocrit (at 4 weeks of age)

In the present study, the study subjects were anemic pregnant women and babies were followed up at 4 weeks. The normal range of hemoglobin levels in babies at birth and 1 month of age is 18 ± 4.0 and 14 ± 2.5, respectively. In the present study, the observed values in babies at 4 weeks of age born to anemic mothers are lower than the normal values for that age, which could be due to anemic mothers having low iron stores and so transfer of iron to baby from mother.

We divided the groups into Group A (maternal hemoglobin levels between 7%–9.9 g%, \(i.e., \) moderate anemia) and Group B (maternal hemoglobin levels between 10–10.9, \(i.e., \) mild anemia) to see any difference associated with severity of anemia.

The study group, \(i.e., \) ECC and DCC, was divided into Group A and B. None of the study groups followed babies after 4 weeks. Other studies had follow-up after 3–4 months.

The mean hemoglobin level at 4 weeks in ECC and DCC was 9.65 ± 0.6214 and 10.65 ± 0.1018 showing increased level of hemoglobin in DCC group. The mean hematocrit level at 4 weeks in ECC and DCC was 28.750 ± 1.9320 and 31.243 ± 2.9879,

\begin{table}[h]
\centering
\caption{Mean hemoglobin of the babies included in the study}
\begin{tabular}{|c|c|c|c|c|}
\hline
Study & ECC & DCC & MD g/dL (95% CI) & \(P\) \\
\hline
Present study & 15.467 ± 1.013 & 15.4 ± 1.396 & 0.0137 (−0.478–0.505) & 0.955 \\
Gupta and Ramji\textsuperscript{[12]} & 13.9 ± 1.5 & 14.1 ± 1.4 & NS & \\
Andersson et al.\textsuperscript{[11]} & 16.3 ± 1.6 & 15.9 ± 1.8 & 0.47 (<−0.84–0.11), & 0.01 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Mean hematocrit in the present study in ECC and DCC}
\begin{tabular}{|c|c|c|c|c|}
\hline
Study & ECC & DCC & MD (95%CI) & \(P\) \\
\hline
Present study & 47.039 ± 3.753 & 46.689 ± 4.625 & 0.3502 (−1.34–2.041) & 0.682 \\
Andersson et al.\textsuperscript{[11]} & 49 ± 4 & 47 ± 5 & 0.013 (<−0.024–0.003) & 0.01 \\
Andersson et al.\textsuperscript{[11]} (after 48 h of delivery) & 50 ± 5 & 53 ± 5 & 3.5 (2.4–4.6) & <0.001 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Effect of delayed cord clamping attribution to risk of polycythemia}
\begin{tabular}{|c|c|c|c|}
\hline
Study & No. of Polycythemia & ECC & DCC & RR (95%CI) \\
\hline
Present study & 0/46 & 0/54 & 1 & \\
Ceriani Cernadas et al.\textsuperscript{[13]} (at 7 h) & 4/90 & 13/90 & 3.25 (1.10–9.59) \\
Chaparro et al.\textsuperscript{[11]} (at 7 h) & 0/22 & 2/22 & 5.00 (0.25–99.67) \\
Emhamed et al.\textsuperscript{[13]} (at 24–48 h) & 0/45 & 3/57 & 5.55 (0.29–104.79) \\
Geethanath et al.\textsuperscript{[14]} (at 24–48 h) & 0/1 & 0/1 & NS & Not Estimable \\
Grajeda et al.\textsuperscript{[13]} (at 24–48 h) & 0/12 & 2/18 & 3.42 (0.18–65.58) \\
Ceriani Cernadas et al.\textsuperscript{[13]} (at 24–48 h) & 2/89 & 7/90 & 3.46 (0.74–16.21) \\
\hline
\end{tabular}
\end{table}
Neonatal serum ferritin levels

In the present study, Iron status was assessed in terms of mean ferritin level. In our study, the mean serum ferritin level at 4 weeks in ECC and DCC was 161.58 ± 81.384 and 246.78 ± 89.508 showing an increased level of serum ferritin in DCC group (P < 0.000) with MD = 85.2 (95% CI of −119.39 to −51.00).

The mean serum ferritin level at 4 weeks in Group A and Group B in ECC/DCC was 151.837 ± 81.1275/245.316 ± 76.8427 MD = 93.4797 (95% CI −135.93 to −51.025) P < 0.00 and 173.181 ± 82.1270/248.755 ± 106.0276 MD = 75.57 (95% CI −133.68 to −17.4676) P < 0.002.

The present study shows statistically significant ferritin levels at 4 weeks in DCC group. In Group A irrespective of ECC/DCC, the serum ferritin levels were clinically and statistically lower (161.58 P value <0.00) than Group B (246.78) showing that maternal anemia does affect iron stores in newborns. The studies Qian et al\[13\] and Geethanath et al\[14\] conducted follow-up at the age of 2 to 3 months and observed higher ferritin levels in DCC. Chaparro et al\[15\] conducted follow-up in the study at age of 6 months, found that ferritin levels were higher in DCC (MD=11.80 µg/L; 95% CI, 4.07 to 19.53).

Thus, the present study and other studies\[13\] have shown that serum ferritin levels increase in DCC group.

Limitations

This study excluded the high-risk pregnancies and additional variables such as socioeconomic status, motivation, lifestyle, and how babies are brought up.

However, this study adds a finding: Delayed cord clamping leads to improvement in iron stores, which is important considering the prevalence of anemia in pregnant women worldwide is 41.8%. Anemic pregnant women have low iron stores suggesting higher chances of having low hemoglobin and iron stores in fetuses as well. In order to tackle anemia in infants which is more likely in babies born to anemic mothers, delayed cord clamping should be practiced. It is an additional cost-effective intervention in low-resource settings and developing countries for anemia management in infancy. Studies have shown 7 times higher chances of developing anemia and 10 times higher chances of reduced iron stores at 3 months of age in the ECC group compared DCC.

Ethical clearance

Ethical committee clearance was obtained (17 May 2014).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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