Neonatal Outcome Following Cord Clamping After Onset of Spontaneous Respiration

AUTHORS: Hege Langli Ersdal, PhD,a,b,c Jørgen Linde, MD,b,c Estomih Mduma, DLSHTM,b,c,d Bjørn Auestad, PhD,e and Jeffrey Perlman, MB, ChBf

aDepartment of Anesthesiology and Intensive Care, and bSAFER (Stavanger Acute medicine Foundation for Education and Research), Stavanger University Hospital, Norway; Departments of cHealth Studies, and dMathematics and Natural Sciences, University of Stavanger, Norway; eDepartment of Research, Haydom Lutheran Hospital, Haydom, Tanzania; and fDepartment of Pediatrics, Weill Cornell Medical College, New York, New York

KEY WORDS
— cord clamping, neonatal mortality and morbidity

ABBREVIATIONS
— BW birth weight
— CC cord clamping
— CI confidence interval
— DCC delayed cord clamping
— ECC early cord clamping
— FHR fetal heart rate
— GA gestational age
— OR odds ratio
— SR spontaneous respirations

WHAT’S KNOWN ON THIS SUBJECT: Delaying cord clamping beyond 30 to 60 seconds after birth seems beneficial for all infants due to blood transfusion from the placenta. Experimental data have demonstrated that ventilation implemented before cord clamping improved cardiovascular stability by increasing pulmonary blood flow.

WHAT THIS STUDY ADDS: Healthy self-breathing neonates in a low-resource setting are more likely to die if cord clamping occurs before or immediately after onset of spontaneous respirations. The risk of death/admission decreases by 20% for every 10-second delay in clamping after breathing.

abstract

BACKGROUND AND OBJECTIVE: Evolving data indicate that cord clamping (CC) beyond 30 to 60 seconds after birth is of benefit for all infants. Recent experimental data demonstrated that ventilation implemented before CC improved cardiovascular stability by increasing pulmonary blood flow. The objective was to describe the relationship between time to CC, onset of spontaneous respirations (SR), and 24-hour neonatal outcome.

METHODS: In a rural Tanzanian hospital, trained research assistants, working in shifts, have observed every delivery (November 2009–February 2013) and recorded data including time interval from birth to SR and CC, fetal heart rate, perinatal characteristics and outcome (normal, death, admission).

RESULTS: Of 15 563 infants born, 12 780 (84.3%) initiated SR at 10.8 ± 16.7 seconds, and CC occurred at 63 ± 45 seconds after birth. Outcomes included 12 730 (99.7%) normal, 31 deaths, and 19 admitted; 11 967 were of birth weight (BW) ≥2500 g and 813 <2500 g. By logistic modeling, the risk of death/admission was consistently higher if CC occurred before SR. Infants of BW <2500 g were more likely to die or be admitted. The risk of death/admission decreased by 20% for every 10-second delay in CC after SR; this risk declined at the same rate in both BW groups.

CONCLUSIONS: Healthy self-breathing neonates are more likely to die or be admitted if CC occurs before or immediately after onset of SR. These clinical observations support the experimental findings of a smoother cardiovascular transition when CC is performed after initiation of ventilation. Pediatrics 2014;134:265–272
Umbilical cord clamping (CC) and subsequent cutting are routine procedures performed at all facility-based deliveries, but the optimal time for clamping remains unclear. After decades with focus on immediate or early cord clamping (ECC), the past 15 years have seen a shift toward delayed cord clamping (DCC). This issue has provoked intense international debate and is further complicated from a lack of what defines both ECC and DCC. ECC has been described as CC performed from <10 seconds and up to 60 seconds postdelivery, whereas DCC is defined as CC performed after 30 to 60 seconds or extending up to 2 to 3 minutes of birth, and/or after cessation of pulsations in the cord. Accumulating evidence suggests that CC beyond 30 to 60 seconds after birth is of benefit for most infants.1–7

Observational studies in the 1960s and 1970s suggested an association between DCC and overtransfusion of the infant, causing polycythemia, hyperbilirubinaemia, and respiratory symptoms.8–10 Other studies indicated that ECC prevented placental transfusion and resulted in more respiratory distress syndrome among preterm infants.11–13 Importantly, in settings with a high prevalence of HIV infection, immediate CC has been thought to reduce the risk of mother-to-child transmission. Furthermore, active management of third-stage labor, including use of oxytocin, together with ECC within 30 to 60 seconds and controlled cord traction, is considered important in the prevention of postpartum bleeding. However, a recent systematic review found no difference in maternal blood loss with varying time of CC, but a decreased need for neonatal blood transfusions was noted with DCC.4

Indeed the renewed interest in the timing of CC is in part directed at preventing the need for donated blood transfusions by increasing the placental transfusion of red blood cells to the newborn and thereby reducing the risk of anemia and iron deficiency for all newborns.1–7 This is particularly important in developing countries where anemia during infancy and childhood is highly prevalent. Additionally, for preterm infants, DCC has been shown to increase systemic blood pressure. However, Rabe et al have reported higher rates of phototherapy and clinical jaundice with DCC.15 Interestingly, a recent experimental study demonstrated that positive pressure ventilation before CC in preterm lambs improved cardiovascular function and stability by increasing pulmonary blood flow, supporting the concept of DCC.16

We have previously described the mean time to initiation of spontaneous respirations (SR) after birth as early, that is, within 10 ± 15 seconds, with a median time of 5 seconds.17 indicating that many neonates likely have expanded their lungs, creating a large low-resistance vascular bed into which blood can readily flow before the cord is clamped. However, no studies have evaluated the optimal timing of CC in relation to initiation of SR, expansion of the lungs, and dilatation of the low-resistant pulmonary vascular bed.

The aim of this study is to determine the optimal time for CC in a population of self-breathing neonates in relation to the initiation of SR and to 24-hour neonatal outcome including death and continued medical problems in a low-resource setting.

METHODS
This is an ongoing descriptive observational study initiated in November 2009 at Haydom Lutheran Hospital; a rural referral hospital in northern Tanzania. Haydom provides comprehensive emergency obstetric care and basic emergency newborn care to a population of ~500 000 people.18 Midwives largely conduct deliveries with doctors on call 24 hours. The current hospital guideline for CC is to wait 1 to 3 minutes if the infant is breathing, consistent with the most recent World Health Organization recommendation.19

Research assistants/observers are continuously present in the labor ward, working in shifts. Three observers cover each shift; 2 are always located in the delivery room or in the theater; 1 covers an adjacent neonatal area.17 Time intervals from birth to initiation of SR and CC are timed using stopwatches. The findings are recorded on a data collection form and include labor information and fetal heart rate (FHR) measurements, neonatal characteristics and interventions in the delivery room, and perinatal outcome within 24 hours (normal, admitted to neonatal unit, death, or stillbirth; Appendix 1). The research assistants also review the partograms that are filled out by the birth attendants.

For this report, the data collection was from November 2009 through January 2013. After birth, infants who required more than routine care (eg, prolonged resuscitation, difficulties with breathing or feeding, prematurity) were triaged to the neonatal area with the capability of providing intravenous fluids and antibiotics and were intermittently cared for by family members and the labor staff.

Gestational age (GA) was based on self-report of the last menstrual period and distance from symphysis pubis to fundus on admission. Normal term GA at Haydom Lutheran Hospital is routinely defined as ≥36 weeks. Normal outcome was defined as survival >24 hours without detected difficulties. Intrapartum death/fresh stillbirth was defined as an Apgar score of 0 at both 1 and 5 minutes with intact skin and suspected death during labor/delivery. The study was approved by The National Institute for Medical Research in Tanzania and The Regional Committee for Medical and Health Research Ethics in Norway.

Statistical Analyses
Analysis has been performed by using Statistical Package for Social Sciences 22 and R.20 Descriptive statistics were used to present data as mean ± SD unless as otherwise stated. $\chi^2$ calculations and
independent-sample t tests were used to compare subpopulations. To describe the association between CC relative to SR (time interval between initiation of SR and CC) and neonatal outcome, multiple logistic regression modeling was used. The significant associated explanatory variables were identified after stepwise forward and backward variable selection, including pregnancy complications (no versus yes), labor complications (no versus yes), FHR (normal versus abnormal), time-interval to initiation of SR (in seconds), and time interval between initiation of SR and CC (in seconds). The final models showed satisfactory fit according to the Hosmer-Lemeshow statistic. Odds ratios (OR), 95% confidence intervals (CI), and P values are reported.

RESULTS

The cohort comprised 15,563 infants of BW 3110 ± 485 g and GA 36.4 ± 1.4 weeks. Of these, 12,780 initiated SR and received only routine care, 12,730 (99.7%) were classified as normal 24 hours after birth, 31 (0.2%) died, and 19 (0.1%) remained in the neonatal area (Fig 1). Mean time to initiation of SR was 10.8 ± 16.7 seconds with a median time of 5 seconds. The mean time to CC was 63 ± 45 seconds, with a median time of 54 seconds. This included 60% clamped within 1 minute, 90% within 2 minutes, 98% within 3 minutes, and 2% beyond 3 minutes after birth.

The population descriptors in relation to outcome are shown in Table 1. In all instances, complications (ie, pregnancy and labor, including cesarean delivery) and abnormal FHR were more frequently recorded in infants who died or remained admitted versus normal infants. The BW and GA of infants who died/remained admitted were significantly less than those of normal infants. Time to initiation of SR was delayed among infants who died/ remained admitted versus normal, and CC occurred earlier among dead/ remained admitted versus normal infants.

The neonatal outcome at 24 hours in relation to time to CC relative to the onset of SR is shown in Table 2. For the total cohort, infants who had the CC before onset of SR were more likely to die/remain admitted versus infants who started SR before CC, that is, 9 of 639 versus 38 of 12,088, respectively (OR = 4.53, 95% CI: 1.92–9.58, P = .0005); 53 cases were not valid because of missing time to start SR or to CC.

Within the cohort, 11,967 (93.6%) were of BW ≥2500 g. Outcome included 11,949 (99.8%) normal, 7 (0.1%) dead, and 11 (0.1%) admitted (Fig 1). The mean time to CC and SR was 64 ± 45 and 10.7 ± 16.1 seconds, respectively. Table 3 presents population descriptors in relationship to outcomes among infants of BW ≥2500 g, which parallel the findings for the entire cohort.

Within the cohort, 813 (6.3%) infants were of BW <2500 g of whom 881 (97%) were healthy, 24 (3.0%) died, and eight (1.0%)...
to adjust for confounding effects. In further logistic regression analyses, the length of the time interval between CC and SR showed no significance when CC occurred before the onset of SR ($P = .76$) for both BW groups ($\geq 2500$ and $<2500$ g). This indicates a constantly higher risk of “death/admitted” when CC occurred before SR, an effect largely attributable to the relationship of CC preceding the onset of SR (Fig 2).

Infants of BW $<2500$ versus $\geq 2500$ g were more likely to die or remain admitted when CC occurred before initiation of SR (OR = 5.6; 95% CI: 2.3–13.7, $P= .0001$; Table 2).

A significant time dependency was noted when CC was performed after onset of SR (OR = 0.977, 95% CI: 0.965–0.991, $P= .0007$), that is, the risk of “death/admission” decreased the longer the time difference from SR to CC up to 2 minutes (Table 2, Fig 2). The risk declined at the same rate in both BW groups (Fig 2). The latter results were derived from fitting a model with constant time interval effect before zero and effect dependent on length of time interval after zero (ie, CC in seconds after onset of SR). In summary, the logistic regression analysis adjusting for BW, GA, FHR, and pregnancy complications indicated that the OR for “death/admitted” decreased by 20% (95% CI: 9%–30%) for every 10 seconds delay in CC after initiation of SR up to 2 minutes (Fig 2).

**DISCUSSION**

The data in this report describe for the first time the time relationship of CC to the onset of SR and early neonatal outcome. Infants who had their cord clamped before the initiation of SR were more likely to die or exhibit early medical issues after delivery. Conversely the risk of death and/or admission decreased to a minimum if CC was delayed for $\geq 2$ minutes after initiation of breathing, an effect independent of BW, GA, FHR, and pregnancy complications.

During fetal to neonatal transition, several important physiologic cardiopulmonary...
changes occur, which appear to be modulated by the timing of CC (Fig 3). At birth, the fetal circulation is characterized by right-to-left shunts because of (1) the low vascular resistance in the placenta receiving 30% to 50% of fetal cardiac output, causing a low systemic pressure in the receiving 30% to 50% of fetal cardiac output, probably arterial pressures were detected, probably because the placenta with its low vascular resistance was removed from the neonatal circulation.\textsuperscript{16,22} Importantly, interrupting the venous return from the placenta before ventilation, with minimal pulmonary blood flow, reduces blood flow to the left atrium and, combined with the increased afterload, eventually decreases the cardiac output.\textsuperscript{23} However, if CC was performed after lung aeration in newborn lambs, a marked increase in pulmonary blood flow occurred, and the immediate hemodynamic changes were mitigated.\textsuperscript{16,23} This supports the long-standing clinical observations by Redmond et al who suggested that the first breath triggers dilatation of the pulmonary vascular bed into which blood can flow from the placental circulation if the umbilical cord is left open.\textsuperscript{24} An increase in pulmonary blood flow will accordingly increase venous return from the lungs to the left atrium and maintain left ventricular pressure and cardiac output and thereby systemic blood pressure. Consequently, right-to-left shunting across the ductus arteriosus and foramen ovale will decrease and reverse, resulting in increased blood flow through the pulmonary arteries. Any delay in CC beyond the onset of SR is therefore likely to be of great importance in modulating immediate cardiopulmonary transition and preventing hemodynamic instability at birth, as suggested by the experimental studies.\textsuperscript{16}

The findings in this report are consistent with these observations. Thus, half of the deaths and/or medical issues in the spontaneously-breathing newborns ensued if CC was performed before or few seconds after onset of SR. Furthermore, this risk decreased rapidly if CC was performed 10 seconds after initiation of SR. An interesting observation is that the risk of adverse outcome did not show any time relationship when CC preceded SR, that is, the risk was consistently higher (OR = 4.48). This strongly points to the importance of lung expansion and dilatation of the pulmonary vascular bed in facilitating blood transfusion from the placenta.
It is important to note that the time interval to SR was delayed among infants who died or who were admitted. However, based on the statistical modeling that included several covariates (BW, GA, FHR, labor complication, pregnancy complication, time to start SR, and time interval between CC and SR), the time to initiation of SR after birth was not related to either death or medical issues, suggesting that these infants were born with sufficient oxygen reserve and/or a well-functional placenta and umbilical cord venous flow, providing them with oxygenated blood. It is conceivable that some infants could have had shallow breathing patterns not detected by the observers.

An important observation is that death and medical admission was significantly more likely to occur in infants of low BW and GA, with 60% of the deaths and medical admissions noted in this group. Definition and calculation of GA in this rural area is inaccurate, thus selecting infants of BW $\geq$2500 g was considered to be more reliable for analysis. Apparently strong and healthy infants of BW $<$2500 g had a 5.6-fold higher OR for adverse outcome if CC was performed before onset of SR compared with infants of BW $\geq$2500 g. However, the risk declined at a comparable rate when CC was performed after SR in the 2 groups.

These cumulative observations support the theory of a smoother cardiovascular transition and hemodynamic stability when CC is delayed, allowing lung aeration, increasing blood flow through the lungs and thus venous return to the left atrium. This likely sustains left cardiac output and stabilizes systemic pressure and flow when the placental circulation is removed. In addition, avoidance of large hemodynamic swings may reduce the risk of intraventricular hemorrhage, especially among premature infants. In 2010, the International Liaison Committee on Resuscitation recommended a delay in umbilical CC for at least 1 minute after birth in neonates not requiring resuscitation, and the World Health Organization states that in term or preterm infants who do not require positive pressure ventilation, the cord should not be clamped earlier than one minute after birth. These recommendations are based on the described benefits of blood transfusion from placenta; however, we speculate that there is a combined effect of smoother cardiovascular transition, hemodynamic stability, and blood transfusion when CC occurs after onset of breathing.

A limitation of this study is the lack of specific information about causes of admission to the neonatal area and/or death. Admitted neonates were cared for by midwives and family members, occasionally a doctor, with oxygen saturation as the only parameter monitored and a limited capacity for analysis of blood samples. Therefore, specific diagnoses were difficult to obtain. It is also unclear if ECC was performed in neonates who seemed depressed or “sick” to the provider, in anticipation of moving the newborn to the resuscitation area if clinically indicated. However, only a few neonates were assigned an Apgar score <7 at 1 (0.3%) and 5 (0.03%) minutes, and none received any kind of assistance beyond routine care at birth (ie, drying, clean cord cutting, and maintaining warmth). They were all allowed to initiate SR without being stimulated or suctioned, indicating that the midwives considered these infants as “strong and healthy.” Additionally, labor complications, FHR abnormalities, and time to initiate SR did not influence outcome when subjected to logistic modeling, indicating a negligible problem of birth asphyxia in the cohort. Furthermore, in this rural setting, the midwives have practiced immediate or ECC for decades because of concern of mother-to-child transmission of HIV, so it is likely that ECC is a well-established habit of older midwives.

**CONCLUSIONS**

Apparently healthy spontaneously breathing neonates are more likely to die or be admitted if CC is performed before or immediately after onset of SR. This increased risk is not related to...
duration of time between CC and SR but rather to the intervention CC that preceded SR. Conversely the risk decreased by 20% for every 10 seconds up to 2-minute delay in CC after onset of SR. These cumulative observations support the experimental findings of a smoother cardiovascular transition when CC is performed after initiation of ventilation.

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REFERENCES
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## APPENDIX 1 Information Recorded on the Data Collection Form

<table>
<thead>
<tr>
<th>Information Type</th>
<th>Details</th>
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| Antenatal information         | Antenatal care: Yes or no  
Antenatal complications: Yes or no  
Maternal infections: None, uterine, malaria, HIV, sepsis, or other  
Fetal presentation: Cephalic, breech, shoulder dystocia, transverse, or other  
FHR: Normal: 120 to 160 beats/min  
Abnormal: <120 or >160 beats/min  
None detected or not measured  
Mode of delivery: Spontaneous vaginal delivery, caesarean delivery, assisted breech delivery, and vacuum extraction  
Labor complication: Prolonged labor, obstructed labor, preeclampsia, eclampsia, uterine rupture, hemorrhage, and cord prolapse  
| Labor information             | FHR: Normal: 120 to 160 beats/min  
Abnormal: <120 or >160 beats/min  
None detected or not measured  
Mode of delivery: Spontaneous vaginal delivery, caesarean delivery, assisted breech delivery, and vacuum extraction  
Labor complication: Prolonged labor, obstructed labor, preeclampsia, eclampsia, uterine rupture, hemorrhage, and cord prolapse  
| Neonatal information          | Transitional newborn adaptation: Time intervals (s) from birth to initiation of spontaneous respirations and cord clamping  
Gender: Male or female  
BW: Grams  
GA: Weeks  
Apgar scores: 1 and 5 minutes  
Interventions in the delivering room: Stimulation, suction ± BMV with a self-inflating bag, and time interval (s) to initiation of BMV  
Specific observations: Newborn heart rate present or not, time interval (s) from initiation of BMV to the onset of spontaneous breathing or death  
| Perinatal outcome at 24 h postpartum | Normal: Survival >24 h without any detected difficulties  
Admitted: Designated neonatal area  
| Stillbirth: Macerated = antepartum or fresh = intrapartum  
BMV = bag mask ventilation. |
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