Published in final edited form as:
Pediatrics. 2006 April ; 117(4): 1235–1242.

Delayed Cord Clamping in Very Preterm Infants Reduces the Incidence of Intraventricular Hemorrhage and Late-Onset Sepsis: A Randomized, Controlled Trial

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Abstract

Objective—This study compared the effects of immediate (ICC) and delayed (DCC) cord clamping on very low birth weight (VLBW) infants on 2 primary variables: bronchopulmonary dysplasia (BPD) and suspected necrotizing enterocolitis (SNEC). Other outcome variables were late-onset sepsis (LOS) and intraventricular hemorrhage (IVH).

Study Design—This was a randomized, controlled unmasked trial in which women in labor with singleton fetuses <32 weeks' gestation were randomly assigned to ICC (cord clamped at 5–10 seconds) or DCC (30–45 seconds) groups. Women were excluded for the following reasons: their obstetrician refused to participate, major congenital anomalies, multiple gestations, intent to withhold care, severe maternal illnesses, placenta abruption or previa, or rapid delivery after admission.

Results—Seventy-two mother/infant pairs were randomized. Infants in the ICC and DCC groups weighed 1151 and 1175 g, and mean gestational ages were 28.2 and 28.3 weeks, respectively. Analyses revealed no difference in maternal and infant demographic, clinical, and safety variables. There were no differences in the incidence of our primary outcomes (BPD and suspected NEC). However, significant differences were found between the ICC and DCC groups in the rates of IVH and LOS. Two of the 23 male infants in the DCC group had IVH versus 8 of the 19 in the ICC group. No cases of sepsis occurred in the 23 boys in the DCC group, whereas 6 of the 19 boys in the ICC group had confirmed sepsis. There was a trend toward higher initial hematocrit in the infants in the DCC group.

Conclusions—Delayed cord clamping seems to protect VLBW infants from IVH and LOS, especially for male infants.

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The authors have indicated they have no financial relationships relevant to this article to disclose.

WHEN TRUST IN DOCTORS ERODES, OTHER TREATMENTS FILL THE VOID

"The most telling evidence of Americans' dissatisfaction with traditional health care is the more than $27 billion they spend annually on alternative and complementary medicine, according to government estimates. In ways large and small, millions of people are taking active steps to venture outside the mainstream, whether by taking the herbal remedy echinacea for a cold or by bettering their lives on an alternative cancer treatment, as did Coretta Scott King, who died this week at an alternative hospice clinic in Mexico. They do not appear to care that there is little, if any, evidence that many of the therapies work. Nor do they seem to mind that alternative therapy practitioners have a fraction of the training mainstream doctors do or that vitamin and herb makers are as profit-driven as drug makers. … Distrust in the medical industrial complex, as some patients call it, stems in part from suspicions that insurers warp medical decision making, and in part from the belief that drug companies are out to sell as many drugs as possible, regardless of patients' needs, interviews show."

Carey B. ***New York Times.*** **February 3, 2006**
Noted by JFL, MD

Keywords

delayed cord clamping; intraventricular hemorrhage; IVH; late-onset sepsis; VLBW infants; randomized; controlled trial

THE CURRENT OBSTETRIC practice in the United States is to clamp the umbilical cord of the very low birth weight (VLBW) infant immediately after delivery.[1] However, delaying cord clamping and lowering the infant below the perineum or incision site at cesarean section have been shown to significantly increase transfer of blood from the placenta to the infant.[2,3] A delay of 30 to 45 seconds in cord clamping of preterm infants results in an 8% to 24% increase in blood volume (2–16 mL/kg after cesarean birth and 10–28 mL/kg after vaginal birth).[4] Immediate cord clamping (ICC) may deprive the VLBW infant of essential blood volume and create a state of potential circulatory compromise[5] resulting in hypotension[6-8] and poor perfusion of tissues.[9,10]

Nine randomized, controlled trials over the last decade have documented the safety and efficacy of delayed cord clamping (DCC) in low birth weight or VLBW infants.[11] Benefits include higher blood pressure,[7,12] higher hematocrit levels,[13-15] more optimal oxygen transport and higher red blood cell flow,[10] fewer days on oxygen and ventilation,[16] fewer transfusions,[14,16] and lower rates of intraventricular hemorrhage (IVH).[17,18] Previous studies of cord-clamping interventions, however, have been limited by small sample size, inconsistent definition of variables, and lack of follow-up beyond 6 weeks.[11]

In a prior pilot study, we validated the feasibility and safety of the protocol for DCC as well as immediate and short-term physiological advantages of DCC.[8] Findings included higher initial blood pressure, less suspected necrotizing enterocolitis (SNEC), and fewer infants discharged on oxygen. Based on this pilot data, we hypothesized that the additional red blood cells obtained by delaying cord clamping may result in lower incidence of bronchopulmonary dysplasia (BPD).

The objective of this study was to compare the incidence of BPD in infants <32 weeks' gestation randomly assigned to early (<10 seconds) and late (30–45 seconds) cord clamping. The study was also designed to evaluate the effects of DCC on other neonatal morbidities, including late-onset sepsis (LOS), IVH, and retinopathy of prematurity (ROP).

MATERIALS AND METHODS

This randomized, controlled trial was conducted between August 2003 and December 2004 at Women and Infants' Hospital of Rhode Island. The study was approved by the institutional review boards at Women and Infants' Hospital and the University of Rhode Island. An independent data safety and monitoring committee consisting of a maternal-fetal medicine obstetrician, a neonatologist, a nurse physiologist, and a nurse statistician reviewed the data after 14 and again after 50 patients were randomly assigned.

The primary outcome variable was BPD and the secondary outcome variables were SNEC, IVH, LOS, and ROP. Other outcome variables included: Apgar scores, temperature on arrival in the NICU, the highest serum bilirubin level, initial and hourly blood pressures for 4 hours, initial hematocrit, and need for blood transfusion during the infant's hospital stay.

All women admitted between 24 and 31.6 weeks' gestation with preterm labor were candidates for inclusion in the study. The gestational age assessment using last menstrual period and/or early pregnancy ultrasound was used to establish eligibility for the study. Exclusion criteria

included: obstetrician's refusal to participate, major congenital anomalies or multiple gestations, intent to withhold care, severe maternal illnesses, or placenta abruption or previa. Women had to be admitted to the hospital at least 2 hours before delivery to allow time for enrollment. Once a potential subject was identified, approval of the attending obstetrician was obtained, the mother was approached, and written informed consent was obtained.

A statistician who was not involved in the trial developed a computer-generated random number system. Block-stratified randomization was used to assign the intervention to the subjects above and below 28 weeks with a prespecified equal probability to avoid unequal numbers of participants in each gestational age group. Two sets of cards labeled for randomization were enclosed in sequenced, opaque envelopes containing group assignment and kept in the labor unit. Research assistants who were registered nurses and the principal investigator (J.S.M.) shared an on-call schedule to screen potentially eligible women, enroll them, and attend the births. When called for a subject's impending birth, the principal investigator or RN opened the next randomization card, informed the staff of the group assignment, reviewed the protocol with the attending obstetrician, attended the birth, and timed the cord clamping.

Women were assigned to receive either ICC or DCC. For the ICC group, the obstetrician clamped the umbilical cord immediately (<10 seconds) after birth. For the DCC group, the obstetrician clamped the cord at 30 to 45 seconds and held the infant in a sterile towel or blanket approximately 10 to 15 inches below the mother's introitus at vaginal delivery or below the level of the incision at cesarean section. Care was taken that no tension or traction was placed on the cord. A stopwatch was used to mark the time when the infant's buttocks were delivered from the vagina or the uterus (or head if breech), and then the time elapsed was counted out in 10-second intervals for the obstetrician. At 30 to 45 seconds, the obstetrician clamped and cut the umbilical cord, and the infant was moved to the radiant warmer for care. Infants in both groups were supplied with an additional warming mattress (Transwarmer Infant Mattress; Cooper Surgical, Trumbull, CT) to assist in maintaining temperature. The obstetricians could alter the protocol based on their clinical judgment, although this event did not occur throughout the course of the study. In the event that the timing of the cord clamping was <30 seconds and the infant was randomly assigned to the DCC group, a protocol violation report was completed and the infant remained in the late clamped group (intention to treat).

The subsequent clinical management of the infants was at the discretion of the attending neonatologists. Because of the obvious nature of the intervention, the study could not be blinded. Our institutional policy requires the presence of a pediatric staff member because of low gestation. However, staff that attended each birth adhered to the principal investigator's request not to reveal the infant's grouping in the infant's medical charts.

Prenatal and delivery data were collected from the mothers' charts. Time of cord clamping, placement of the infant, Apgar scores, and time and date of birth were collected in the labor unit. Infant data were collected after 12 hours of age and after discharge. BPD was defined as requiring oxygen therapy up to 36 weeks' postmenstrual age or death. SNEC was defined as clinical impression when the neonatology staff ordered a radiograph to rule out NEC and the infant was made NPO (nothing by mouth) for at least 24 hours. Cranial ultrasound (CUS) readings used the grading system of Papile: grade 1 is a germinal matrix hemorrhage; grade 2 is extension into the lateral ventricle with blood filling <50% of the ventricular area; grade 3 is IVH with distension or dilatation of the lateral ventricles with blood; and grade 4 is IVH with parenchymal involvement. CUS were read by a single pediatric radiologist (M.W.) who was blinded to the infant's grouping. Late-onset sepsis was defined as blood culture-positive in infants >72 hours of age. NEC was diagnosed based on Bell's criteria[19] and ROP was

identified by an ophthalmologist per our routine eye examinations during the infants stay in the nursery.

Power analysis was based on the event rate of BPD (56%) in the control group of our pilot study[8] with a 30% relative reduction that would result in a 39% event rate. An α level of .05, and a β level of .20 with a medium effect size ($r = 0.30$), was used to determine that 26 infants were needed in each cord-clamping interval group. An oversampling of 20% brought each group to 36 infants for a total of 72 subjects. All data were analyzed on an intention-to-treat basis. Despite directional primary hypotheses, we used 2-tailed tests to be as conservative as possible. Continuous variables were examined with Student *t* test and categorical variables were tested by using χ^2 and Fisher's exact test if cells contained counts <5. Logistic regression was used to control for gestational age and obtain odds ratios for significant findings.

RESULTS

Figure 1 shows the distribution of the 296 women who were admitted with preterm labor and who were screened for eligibility for this study. All additional analyses were performed on the 72 randomly assigned subjects.

There were 7 protocol violations. Six occurred in the DCC group with cord-clamping time ranging between 2 and 18 seconds instead of 30 seconds. These were mainly as a result of miscommunication at births. There was 1 protocol violation in the ICC group when a physician delayed clamping for 25 seconds as a result of a misunderstanding of the protocol. All infants remained in their assigned groups for analyses.

Table 1 shows no significance difference in maternal demographics, clinical characteristics, and medical management.

Table 2 shows no significant difference in the demographic and clinical characteristics of the study infants. Cord-clamping time was significantly different per protocol; infants in the DCC group had significantly longer cord-clamping times (32 ± 13 vs 7 seconds ± 4; $P < .001$). All other neonatal variables, including those used for safety (1- and 5-minute Apgar scores, temperature on admission, serum bilirubin levels), were not significantly different between the groups.

Table 3 shows that there were no significant differences in the incidence of death or BPD, NEC, amount of blood loss and transfusion, and ROP between the 2 groups. There were also no differences between the infants in surfactant use (27 vs 24), days of ventilation (39 vs 35), and oxygen use at 28 days (11 vs 13) for the ICC and DCC groups, respectively.

Table 4 shows that infants in the DCC group had less IVH (five [14%] vs 13 [36%]; $P = .03$) during the first 28 days in the NICU. The incidence of IVH was equally divided between the stratified groups (<28 weeks = 10; 28 ± weeks = 8), although the majority occurred in infants <30 weeks gestation (data not shown). In the infants <28 weeks, 7 (47%) of the 15 infants in the ICC group had IVH vs 3 (21%) of the 14 infants in the DCC group (not significant), whereas in those born after 28 weeks, 6 (29%) of 21 in the ICC group and 2 (10%) of 22 in the DCC group had IVH.

Similar number of infants in each group received low-dose indomethacin for IVH prophylaxis within the first 24 hours. All of the infants between 24 and 27 weeks had indomethacin, whereas 59% and 62% received indomethacin in the DCC and ICC groups, respectively. The grade 4 IVH was not seen until day of life 12. One infant in the DCC group with IVH was a protocol violation and had ICC.

We compared all infants with IVH (n = 18) with all infants without IVH (n = 54). Infants with IVH had shorter time between birth and cord clamping (13 vs 22 seconds; P = .04) and were less likely to have had a cesarean delivery (three [17%] vs 15 [48%]; P = .03). There was no relationship between IVH and sepsis.

Table 4 shows that infants in the DCC group were less likely to have blood culture-proven sepsis during the NICU stay (3% vs 22%; P = .03). Six cases of confirmed sepsis occurred in the 24- to 27-week-old infants, whereas 3 were in infants 28 to 31 weeks. Of the 9 infants who had LOS, 7 (78%) occurred between 11 and 18 days of age. Infants with sepsis had lower initial hematocrit levels at birth (48 ± 6 vs 42 ± 5; P = .03) even when controlling for gestational age.

Analyses by gender revealed that male infants had an advantage with DCC for IVH, sepsis, and NEC. Gender effects are shown in Table 5.

There were no adverse events or deaths in the DCC group. Three infants died in the ICC group. The causes of death included fulminating NEC (two) and terminal respiratory failure with probable sepsis syndrome.

Additional multivariate analyses were performed to evaluate the association of cord clamping with IVH and LOS. The impact of cord-clamping group on IVH was evaluated adjusting for gestational age and cesarean section. The final model indicated that the IVH rate was >3 times higher in the ICC group (odds ratio [OR]: 3.5, 95% confidence interval [CI] 1.1–11.1). A similar model for LOS adjusted for gestational age showed that infants in the DCC group were less likely to have sepsis (OR: 0.10, 95% CI: 0.01–0.84).

The eligible women not enrolled during the study period did not differ from the 72 randomly assigned participants on any of the demographic variables. They differed from randomly assigned women only in antenatal steroid use (87% vs 100%; P = .01), premature rupture of membranes in hours (20 ± 36 vs 40 ± 45; P = .01), and cesarean section rate (64% vs 40%; P = .01). Infants of eligible women not enrolled differed from study infants only on admission temperature (96.3 ± 1.4 vs 97 ± 1.4; P = .01). There was no significant difference in the overall incidence of IVH (25% vs 18%; P = .35) or sepsis (3% vs 8%; P = .42) between the subjects and the infants of eligible women not enrolled.

DISCUSSION

Our primary null hypothesis was that infants in the DCC group would have the same rate of BPD based on the results from the pilot study. The null hypothesis proved to be true. The reason for the failure to reject the null hypothesis is that the study event rate of BPD in the ICC group (25%) turned out to be much lower than the event rate used for sample size calculation (56%) resulting in an underpowered estimate. The finding that DCC resulted in less IVH and less sepsis was unanticipated.

Our data indicates that a brief delay in cord-clamping time accompanied by lowering the infant to hasten the placental transfusion offers protection from IVH and LOS. The fact that the groups had almost identical demographic and baseline characteristics shows that the randomization process was successful. Like in our previous pilot study, this study provided evidence that the protocol does not put even the smallest infants at risk of harm.[8]

The theoretical foundation for the study was that the additional blood volume received as a result of DCC would help to reduce neonatal morbidity by providing more blood volume and improving cardiovascular stability. The preterm infant has less fetal-placental blood volume in his body at any point in time than the term infant making him more likely to have a deficit

if immediate clamping occurs.[20] The high pressure in the placental circulation continues briefly after birth and fosters transfer of blood to the infant.[21]

The increase in cardiac output to the lung from 8% during fetal life to the 45% immediately after birth necessitates transfer of an adequate blood volume.[20] When the cord is clamped before an adequate placental transfusion to the infant has occurred, blood volume may be taken from other capillary beds resulting in relative hypoperfusion.[22] A potential circulatory effect of relative hypoperfusion may be disruption of the autoregulation essential to stabilize cerebral blood flow and prevent a pressure-passive circulation.[23] If the infant is not hemodynamically stable, there may be ischemic injury to the brain,[24] the gastrointestinal tract, and the lung.

Reduced blood volume does not necessarily result in immediately reduced blood pressure or lower hematocrit because the infant's cardiovascular system increases vascular resistance to stabilize blood pressure.[25] Increased capillary permeability in the preterm newborn allows rapid fluid shifts.[5] These factors and lack of available accurate measurement techniques for blood volume, make hypovolemia difficult to verify in the newborn, although its effect may be profound. DCC allows time for placental transfusion to supply essential blood volume to the infant and lowering the infant speeds the transfer of blood volume.[26]

The finding that IVH was higher in the immediately clamped group is consistent with the recent meta-analysis of randomized, controlled trials on DCC in preterm infants.[11] Other authors have reported reduced cerebral blood volume preceding development of IVH.[27,28] Any reduction in IVH is important because of its association with later morbidity, mortality, and/or developmental delay.[29] Even grades 1 and 2 are not without sequelae.[30]

Our nursery practiced prophylactic indomethacin to prevent IVH based on the study of Ment et al.[31] However, the number of infants receiving this intervention was similar between the 2 study groups.

All the infants with confirmed LOS had immediate cord clamping. The one listed for the DCC group was a protocol violation and her cord was clamped at 3 seconds. This finding is important as LOS continues to be an important cause of morbidity and mortality in the NICU and neurodevelopmental delay.[32] We speculate that sepsis may be a result of immunocompromise as a result of loss of protective primitive hematopoietic progenitor cells along with blood volume at birth. The cord blood of preterm infants (24–31 weeks) contains the highest concentration of primitive hematopoietic progenitor cells and long-term culture-initiating cells when compared with the cord blood of infants closer to term.[33]

The apparent protective effect of delayed cord clamping for the male infants suggests the hypothesis that the additional blood volume the infant obtains may have gender-specific neuroprotective and immunoprotective effects. This finding is of interest because there is increasing evidence of gender-specific differences in neonates. For example, indomethacin has been shown to exhibit gender-specific effects on cerebrovascular reactivity, which were associated with a significantly decreased rate of IVH in boys.[34]

Limitations of this study are that the primary null hypothesis was accepted because the study was underpowered as a result of the use of a high event rate from our pilot study and the rejection of secondary null hypothesis that is unanticipated. Nonetheless, the fact that our findings are consistent with the result of the recent meta-analysis[11] strengthens the idea that these findings are generalizable to the population of VLBW preterm infants. This study adds to the growing body of knowledge on the benefits of delayed cord clamping in preterm infants.[11] It may be that the small amounts of addition blood preterm infants obtain by delaying cord clamping helps to stabilize cerebral blood flow, autoregulation, increase oxygen delivery to vulnerable

tissues, prevent ischemia and cytokine release, and provide additional stem cells to establish adequate immunocompetence.

We have demonstrated that a brief delay in cord-clamping time, accompanied by lowering the infant to hasten the placental transfusion, offers protection from IVH and LOS. The innovation of this study is the simplicity of the intervention of delaying cord clamping 30 to 45 seconds and lowering the infant. The additional blood volume received seems to contribute to the improved outcomes of tiny preterm infants.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health, National Institute for Nursing Research grant K23 NR00078.

Statistical consultation was provided by Jenifer Allsworth, PhD (Division of Research, Department of Obstetrics and Gynecology, Women and Infants' Hospital, Providence, RI), and Yeong Kwak, RN, PhD (University of Connecticut School of Nursing, Storrs, CT).

We wish to thank the parents and infants who participated in this study and the nurses and doctors at Women and Infants' Hospital. Without their trust and cooperation, this study would not have been possible.

Abbreviations

BPD, bronchopulmonary dysplasia
CUS, cranial ultrasound
DCC, delayed cord clamping
ICC, immediate cord clamping
IVH, intraventricular hemorrhage
LOS, late-onset sepsis
NEC, necrotizing enterocolitis
ROP, retinopathy of prematurity
SNEC, suspected necrotizing enterocolitis
VLBW, very low birth weight
CI, confidence interval

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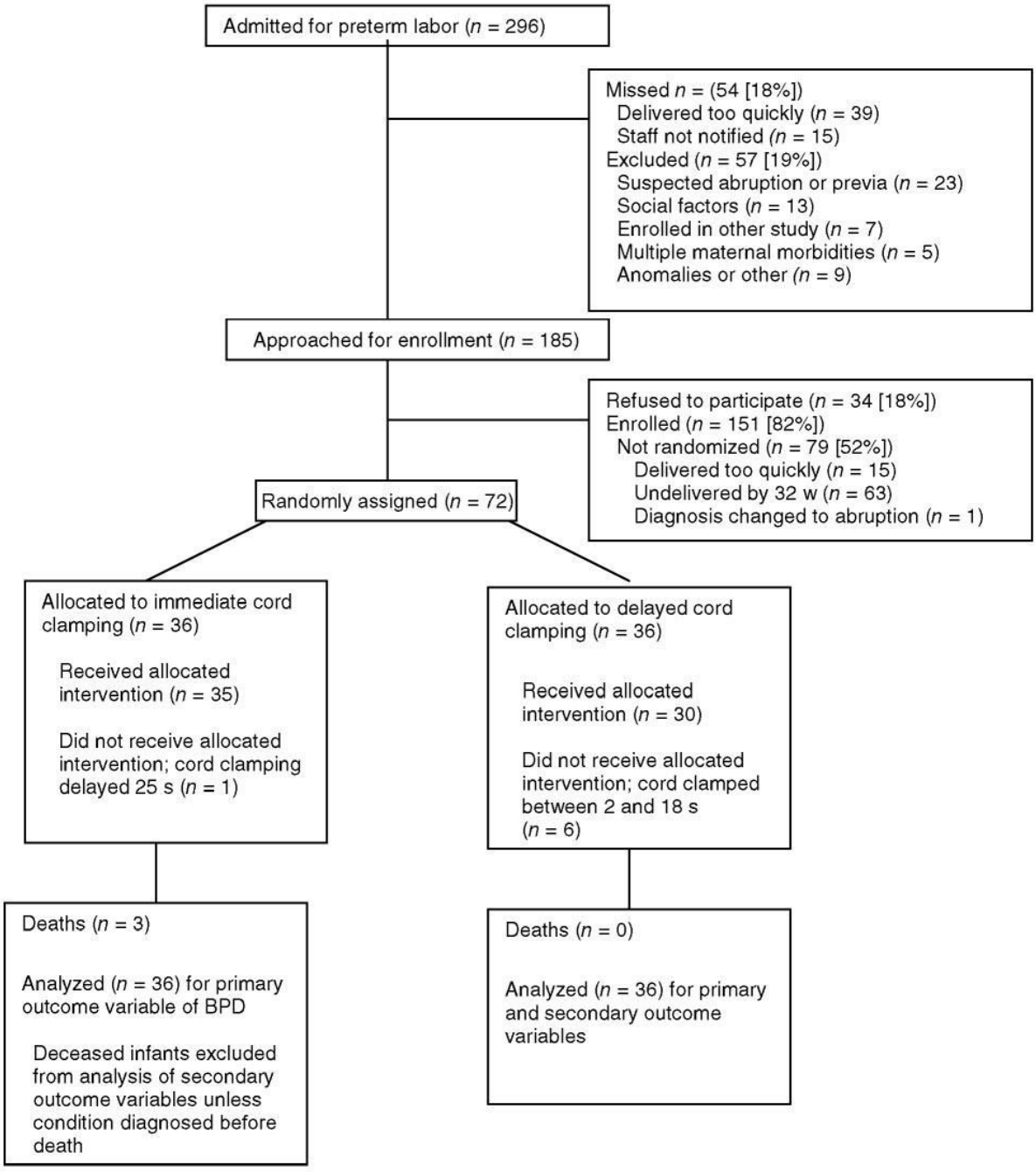

FIGURE 1.
Flow of women admitted for preterm labor between August 2003 and November 2004, including participants in the cord-clamping study.

TABLE 1

Maternal Demographics, Clinical Characteristics, and Prenatal Medical Management

Characteristics	ICC (*n* = 36)	DCC (*n* = 36)
Mother's age, mean ± SD, y	26.8 ± 6.5	27.1 ± 6.7
Primiparas, *n* (%)	25 (69)	23 (64)
Race, *n* (%)		
Black	4 (11)	5 (14)
White	20 (56)	18 (50)
Hispanic	11 (30)	11 (31)
Other	1 (3)	2 (6)
Public insurance, *n* (%)	17 (47)	15 (42)
Received antenatal steroids, *n* (%)	36 (100)	36 (100)
Received antenatal $MgSO_4$ in 24 h before birth, *n* (%)	21 (58)	14 (39)
Premature rupture of membranes, mean ± SD, h	40 ± 44	41 ± 47
Cesarean section, *n* (%)	14 (39)	15 (43)
Reasons for preterm birth, *n* (%)[a]		
Premature rupture of membranes	19 (53)	18 (50)
Preterm labor	19 (53)	16 (44)
Presumed chorioamnionitis	10 (28)	11 (31)
Incompetent cervix	5 (14)	7 (19)
Pregnancy-induced hypertension	5 (14)	5 (14)

None of the differences are statistically significant.

[a] Some mothers had >1 condition.

TABLE 2

Neonatal Demographic, Clinical, and Safety Variables

	ICC (*n* = 36)	DCC (*n* = 36)	P
Birth weight, mean ± SD (range), g	1151 ± 379	1175 ± 346	NS
Gestational age, wk	28.2 ± 2.4	28.3 ± 2.1	NS
24 wk 0 d to 27 wk 6 d, *n*	15	14	
28 wk 0 d to 31 wk 6 d, *n*	21	22	
Male/female ratio	19/17	23/13	NS
Apgar score, median			
1 min	7 (1–9)	7 (1–9)	NS
5 min	8 (1–9)	8 (2–9)	
Temperature on admission to NICU, °F (range)	96.8 ± 1.5 (92.8–99.3)	97.1 ± 1.2 (94–99.4)	NS
°C (range)	36 ± 0.8 (33.8–37.4)	36.2 ± 6 (34.4–37.4)	
Maximum serum bilirubin, mg/dL (range)	9.5 ± 2.10 (5.5–13.8)	10.1 ± 2.4 (6.6–15.1)	NS
Initial hematocrit, %	46 ± 6 (34–60)	49 ± 6 (37–62)	.06
Mean of first 4-h mean blood pressure	31.9 ± 6	33.8 ± 4.5	NS
SNAP scores	13.3 ± 12	12.3 ± 11	NS
Cord clamp time, sec (range, median)	6.9 ± 4.3 (1–25, 5)	32.1 ± 12.6 (2–49, 33)	< .001

NS indicates nonsignificant; SNAP, Score for Neonatal Acute Physiology.

TABLE 3

Neonatal Morbidities, Blood Loss, and Transfusions

	ICC (*n* = 36), *n* (%)	DCC (*n* = 36), *n* (%)
Death or BPD (O_2 therapy at 36 wk)	9 (25)	8 (22)
Discharge on O_2[a]	4 (12)	5 (14)
SNEC	20 (56)	14 (39)
NEC, Bell's[19] stage		
No sign	25 (69)	27 (75)
1a	7	6
1b	0	2
2a	1	1
3b	2	0
Perforation	1	0
Blood loss: week 1, mL	11.4 ± 5.8	11.3 ± 5.7
Infants transfused	22 (61)	18 (50)
Transfusions	2.47 ± 3.7	1.94 ± 3.1
Total amount transfused, mL	33 ± 45	27 ± 42
ROP (all)[a]	13 (40)	10 (28)
Deaths	3 (8)	0

None of the differences are statistically significant.

[a] Number of 33 for the ICC group because 3 infants in the ICC group died before 1 month of age.

TABLE 4

IVH and LOS in Study Infants

	ICC (*n* = 36), *n* (%)	DCC (*n* = 36), *n* (%)	P	Odds Ratio	95% CI
IVH					
All IVH	13 (36)	5 (14)	.03	3.5	1.1–11
Grade 1	4 (11)	3 (8)			
Grade 2	8 (22)	2 (6)			
Grade 4	1 (3)	0 (0)			
Sepsis	8 (22)	1 (3)	.03	.01	0.01–0.84

TABLE 5

Gender Differences in IVH, LOS, and NEC Among Infants With ICC and DCC

	ICC		DCC	
	Boys (*n* = 19), *n* (%)	**Girls (*n* = 17), *n* (%)**	**Boys (*n* = 23), *n* (%)**	**Girls (*n* = 13), *n* (%)**
IVH	8 (42)[a]	5 (29)	2 (9)	3 (23)
Sepsis	6 (32)[a]	2 (12)	0 (0)	1 (8)
NEC	3 (16)[a]	1 (6)	0 (0)	2 (15)

[a] Differences for boys between groups; $P < .05$, Fisher's exact test.