ORIGINAL ARTICLE

# Delayed versus Immediate Cord Clamping in Preterm Infants

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## ABSTRACT

### BACKGROUND

The preferred timing of umbilical-cord clamping in preterm infants is unclear.

### METHODS

We randomly assigned fetuses from women who were expected to deliver before 30 weeks of gestation to either immediate clamping of the umbilical cord (≤10 seconds after delivery) or delayed clamping (≥60 seconds after delivery). The primary composite outcome was death or major morbidity (defined as severe brain injury on postnatal ultrasonography, severe retinopathy of prematurity, necrotizing enterocolitis, or late-onset sepsis) by 36 weeks of postmenstrual age. Analyses were performed on an intention-to-treat basis, accounting for multiple births.

### RESULTS

Of 1634 fetuses that underwent randomization, 1566 were born alive before 30 weeks of gestation; of these, 782 were assigned to immediate cord clamping and 784 to delayed cord clamping. The median time between delivery and cord clamping was 5 seconds and 60 seconds in the respective groups. Complete data on the primary outcome were available for 1497 infants (95.6%). There was no significant difference in the incidence of the primary outcome between infants assigned to delayed clamping (37.0%) and those assigned to immediate clamping (37.2%) (relative risk, 1.00; 95% confidence interval, 0.88 to 1.13; P=0.96). The mortality was 6.4% in the delayed-clamping group and 9.0% in the immediate-clamping group (P=0.03 in unadjusted analyses; P=0.39 after post hoc adjustment for multiple secondary outcomes). There were no significant differences between the two groups in the incidences of chronic lung disease or other major morbidities.

### CONCLUSIONS

Among preterm infants, delayed cord clamping did not result in a lower incidence of the combined outcome of death or major morbidity at 36 weeks of gestation than immediate cord clamping. (Funded by the Australian National Health and Medical Research Council [NHMRC] and the NHMRC Clinical Trials Centre; APTS Australian and New Zealand Clinical Trials Registry number, ACTRN12610000633088.)

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Delaying the time of umbilical-cord clamping costs nothing and may benefit preterm infants by increasing the amount of placental blood received[1] or the time for the physiological transition from fetal to newborn life.[2] In the past, immediate cord clamping was normal practice in preterm infants because of concerns about harm from delayed resuscitation, hypothermia, hyperbilirubinemia, or polycythemia.[3-6] However, increasing evidence suggested that immediate clamping may be harmful. Systematic reviews of randomized, controlled trials showed that in infants born before 37 weeks of gestation,[1,5] delayed clamping improved blood pressure[1,5] and reduced the incidences of blood transfusion,[1,5] intraventricular hemorrhage,[1,5] necrotizing enterocolitis,[1] and infection.[1] Furthermore, a systematic review of 12 randomized, controlled trials involving 531 very preterm infants (<32 weeks of gestation) concluded that enhanced placental transfusion — through delayed clamping, cord milking (milking the contents of the cord), or a combination of both — resulted in lower mortality and lower incidences of necrotizing enterocolitis and infection than immediate clamping.[7] Whether delayed clamping alone has benefits with respect to mortality or the incidence of neurodevelopmental disability remains unknown.[8,9] Various professional guidelines recommend delays of more than 30 seconds,[10] 30 to 60 seconds,[4,11] at least 60 seconds,[12,13] or 30 to 180 seconds,[14] all if resuscitation is unnecessary[4,10,11,14] Nevertheless, delayed clamping is not universally performed, owing to continuing anxiety about the risks of delayed resuscitation or hyperbilirubinemia.[15,16] We performed an unblinded, randomized, controlled trial comparing delayed versus immediate clamping with respect to a composite outcome of death or major morbidity in preterm infants.

## METHODS

### PATIENTS

A randomized pilot trial of the effects on hemoglobin concentration 6 hours after delivery of delayed clamping of the umbilical cord, milking the contents of the cord after delayed clamping, immediate cord clamping, or milking the contents of the cord after immediate clamping in infants born before 32 weeks of gestation was prospectively registered on May 12, 2009, and began on October 21, 2009 (Australian and New Zealand Clinical Trials Registry number, ACTRN12609000248268). In May 2010, among the 38 infants for whom hemoglobin data were available, there were no significant differences among the randomized groups. The trial management committee made the decision to compare only delayed versus immediate clamping in the main Australian Placental Transfusion Study (APTS), which was prospectively registered on August 2, 2010, and began on December 8, 2010.

APTS aimed to enroll 1600 fetuses from women expected to deliver before 30 weeks of gestation. A total of 9 infants from the pilot trial who were delivered before 30 weeks of gestation and were randomly assigned to delayed or immediate clamping (without milking the cord) were included in APTS, with investigators unaware of clinical outcomes other than hemoglobin concentration until data analysis began after May 25, 2017.[17] Recruitment to APTS closed on January 6, 2017, with 25 centers in seven countries. Fetuses were eligible if obstetricians or maternal–fetal medicine specialists considered that they might be delivered before 30 weeks of gestation. Exclusion criteria included fetal hemolytic disease, hydrops fetalis, twin–twin transfusion, genetic syndromes, and potentially lethal malformations.

Participants were randomly assigned to immediate clamping, defined as clamping within 10 seconds after delivery, or delayed clamping, defined as clamping 60 seconds or more after delivery, with the infant held as low as possible below the introitus or placenta and without palpation of the cord. Variations in procedure were permitted in the interests of mother, infant, or both. If the infant was nonvigorous (heart rate <100 beats per minute, low muscle tone, or lack of breathing or crying), clinicians used discretion in conducting the intervention. No cord milking was intended in either group. A clock in the resuscitation room was used for timing. Infants of multiple births underwent randomization individually. Randomization was performed centrally when the operating theater was booked for cesarean section or when vaginal delivery was considered to be inevitable, with the use of an interactive voice-response system with minimization and with stratification according to gestational age (<27 weeks vs. ≥27 weeks), center, and multiple-birth status (singleton birth vs. multiple birth).

An ethics committee for each center approved the trial. A parent provided written informed consent. All the authors vouch for the accuracy and completeness of data from their centers, and the authors from the National Health and Medical Research Council Clinical Trials Centre vouch for the analysis and for the fidelity of the trial to the protocol. The protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

### OUTCOMES

The primary outcome was a composite of death or major morbidity, which was initially defined by the Australian and New Zealand Neonatal Network Data Dictionary[18] as severe brain injury on postnatal ultrasonography, severe retinopathy of prematurity, necrotizing enterocolitis, late-onset sepsis, or chronic lung disease, each diagnosed by 36 completed weeks of postmenstrual age. However, in March 2014, the trial management committee, which was monitoring pooled event rates with blinding to results according to treatment group, decided to remove chronic lung disease from the primary outcome. This followed recognition in November 2013 that the pooled primary outcome rate was 64%, much higher than the expected pooled rate of 26%, because more infants than expected met the trial definition of chronic lung disease[18,19] owing to a higher-than-expected rate of the use of continuous positive airway pressure by means of nasal cannula until 36 weeks of postmenstrual age, without supplemental oxygen.[20,21] This decision was communicated to the independent data and safety monitoring committee, which supported this recommendation. The protocol was amended in July 2016 to reflect the updated primary outcome of death, severe brain injury, severe retinopathy of prematurity, necrotizing enterocolitis, or late-onset sepsis.

Severe brain injury on postnatal ultrasonography was defined as intraventricular hemorrhage of grade 3 or 4 or late cerebral abnormality on ultrasonography. Late cerebral abnormality on ultrasonography was defined as echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, or ventriculomegaly between 14 days after birth and a postmenstrual age of 36 completed weeks. Severe retinopathy of prematurity was defined as stage 4 retinopathy of prematurity or treatment for retinopathy of prematurity by 36 completed weeks. Late-onset sepsis was defined as a positive culture in blood, cerebrospinal fluid, or urine between 48 hours from birth and 36 completed weeks in infants who died or who survived after at least a 5-day course of antibiotics. Chronic lung disease[18,22] was defined as the use of supplemental oxygen or assisted ventilation with or without supplemental oxygen at 36 weeks of postmenstrual age.[18,19] Detailed definitions are provided in the protocol. Infants who survived but had missing data for a component of major morbidity were excluded from the primary analysis. For practical reasons, no attempt was made to make staff who were diagnosing these morbidities unaware of the timing of cord clamping.

Secondary outcomes included death by 36 completed weeks of postmenstrual age, death or severe brain injury on postnatal ultrasonography, severe brain injury, late cerebral abnormality on ultrasonography, intraventricular hemorrhage (all grades, grade 3 or 4, and grade 4 only), severe retinopathy of prematurity, necrotizing enterocolitis, late-onset sepsis, treated patent ductus arteriosus, and chronic lung disease,[18,22] defined as above.[18,19] Additional secondary outcomes of death, disability, and death or disability by 3 years are not reported here.

Tertiary outcomes (analyses of which were considered to be hypothesis generating) included birth weight, the number of red-cell transfusions by 36 weeks, the temperature of the infant on admission, the peak bilirubin level in the first week, the peak hematocrit in the first week; the duration of hospital stay if the infant was discharged alive, maternal blood transfusion for postpartum hemorrhage, the use of uterotonic drugs, and exchange transfusions by 36 weeks of gestation. Because rates of endotracheal intubation at delivery can vary considerably among centers[23] and may not correlate with the rate of morbidity,[20,23] they were not recorded. A 5-minute Apgar score of less than 4 was considered to be a better index of initial risk than endotracheal intubation.[24,25] The Apgar score at 1 minute and 5 minutes and an Apgar score of less than 4 at 5 minutes were prespecified as tertiary outcomes in the statistical analysis plan.

### STATISTICAL ANALYSIS

The original sample was 1600 infants, yielding 90% power (two-sided $P=0.05$) to detect an absolute difference in the incidence of the primary

outcome of 8 percentage points between the two groups (30% in the immediate-clamping group vs. 22% in the delayed-clamping group; relative difference, 27%), with the assumption of 10% nonadherence. If the rate of nonadherence to the intervention and loss to follow-up reached 20%, there was more than 80% power to detect this difference. After the change in the primary outcome to exclude chronic lung disease, the pooled rate of the new primary outcome (36.7%) allowed the detection of an absolute difference of 9.9 percentage points (41.6% in the immediate-clamping group vs. 31.7% in the delayed-clamping group; relative difference, 24%) in 1500 infants with 80% power and 30% nonadherence.

An independent data and safety monitoring committee conducted three interim analyses with the use of the Haybittle–Peto method.[26,27] The committee charter[28] (provided in the Supplementary Appendix, available at NEJM.org) expressed the view that a difference of at least 3 SD (i.e., $P<0.003$) in a major outcome suggesting net clinical benefit may be needed to advise that the trial management committee consider stopping the trial prematurely. This allowed the use of an unadjusted significance test to compare the final results.[26,27]

Data on infants born alive before 30 weeks of gestation were analyzed according to the intention-to-treat principle. Analyses were prespecified in the trial protocol or the statistical analysis plan before investigators were made aware of the results according to treatment group. Primary and secondary outcomes were assessed by means of generalized estimating equations with a log-link function and compound symmetric correlation structure accounting for multiple births.[29] Our analysis plan specified no adjustment for multiple outcomes. We performed post hoc adjustment (Benjamini–Hochberg procedure)[30] for 13 prespecified secondary outcomes (3 of which were to be assessed at follow-up). Treatment effects were summarized with the use of relative risks and 95% confidence intervals. The denominator for events was the number of infants for whom each outcome was known. Short-term secondary outcomes were analyzed with the use of chi-square tests, two-sample t-tests, or Wilcoxon tests as appropriate. Tests for interaction were used to detect heterogeneity for the primary outcome in three prespecified subgroups: gestational age (<27 weeks vs. ≥27 weeks), sex, and method of delivery (cesarean section vs. vaginal delivery). An exploratory analysis was undertaken with randomization ignored and clamping time included as a continuous predictor. Another exploratory analysis, in relation to clusters of sites ordered according to adherence to treatment, is outlined in the statistical analysis plan; results are not reported here. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

## RESULTS

### TRIAL INFANTS

Of 1634 fetuses that underwent randomization, 54 were born after 30 weeks, 10 were stillborn, and 4 had consent withdrawn (Fig. 1). A total of 1566 infants were born alive before 30 weeks of gestation and were eligible for evaluation. Of these, 782 were assigned to immediate cord clamping and 784 to delayed cord clamping. Of all infants, 65.7% were born by cesarean delivery, 24.9% were of multiple births, and 56.4% were male (Table 1). The 54 infants who were born after 30 weeks were treated off-protocol according to the usual practice of the trial site, and outcomes are unknown. Data on infants who were screened for eligibility were not recorded and are not shown in Figure 1.

### TREATMENT ADHERENCE

The median time between delivery and cord clamping was 5 seconds (range, 0 to 360) for immediate clamping and 60 seconds (range, 0 to 94) for delayed clamping. The rate of adherence to randomized treatment was 94.9% in the immediate-clamping group and 73.2% in the delayed-clamping group (Table 2). In the immediate-clamping group, nonadherence mostly reflected implementation issues (in 14 of 34 infants [41%]) or a slightly longer than specified time between delivery and cord clamping (in 13 of 34 infants [38%]); in the delayed-clamping group, the primary reason was clinical concerns about infant well-being (in 146 of 209 infants [69.9%]).

### PRIMARY AND SECONDARY OUTCOMES

There was no significant difference in the incidence of the primary outcome at 36 weeks between

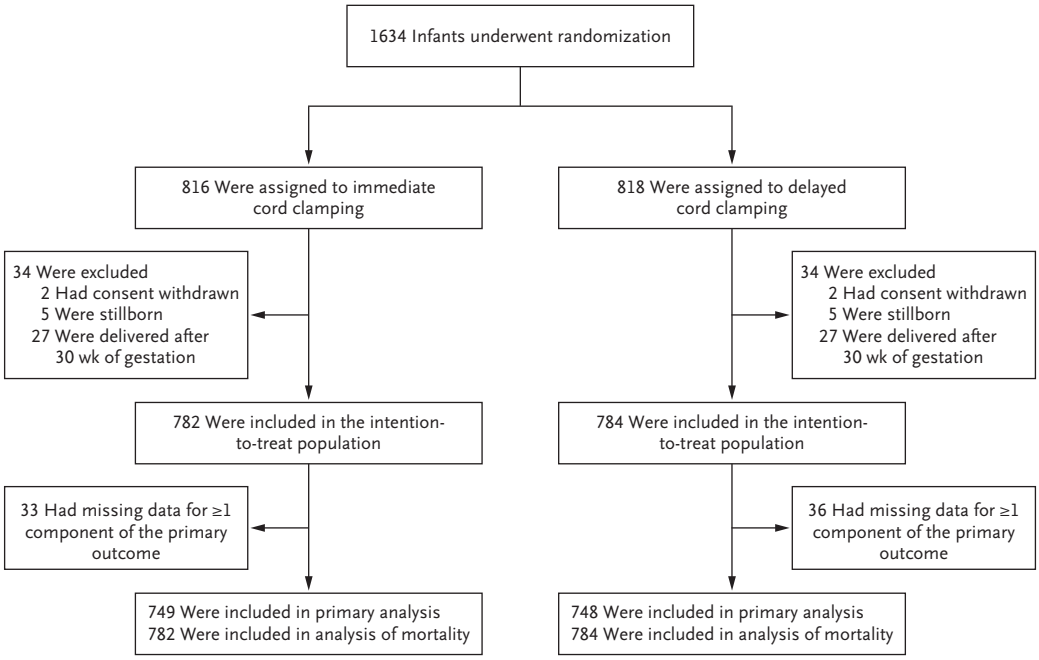


**Figure 1. Randomization and Follow-up.**

Immediate cord clamping was defined as clamping within 10 seconds after delivery, and delayed cord clamping was defined as clamping 60 seconds or more after delivery. The primary outcome was a composite of death or major morbidity (defined as severe brain injury on postnatal ultrasonography, severe retinopathy of prematurity, necrotizing enterocolitis, or late-onset sepsis) by 36 weeks of postmenstrual age. A total of nine infants (four in the immediate-clamping group and five in the delayed-clamping group) from a pilot trial were included in this trial.[17]

delayed clamping (37.0%) and immediate clamping (37.2%) (relative risk, 1.00; 95% confidence interval [CI], 0.88 to 1.13; P=0.96) (Table 3). Death by 36 weeks occurred in 6.4% of the infants in the delayed-clamping group versus 9.0% of those in the immediate-clamping group (relative risk, 0.69; 95% CI, 0.49 to 0.97; P=0.03 unadjusted and 0.39 after post hoc adjustment for multiple secondary comparisons). There was no significant difference between the two groups in other secondary outcomes. In a post hoc sensitivity analysis, 520 of 756 infants in the delayed-clamping group (68.8%) and 498 of 748 infants in the immediate-clamping group (66.6%) met the original definition of the primary composite outcome, which included chronic lung disease (relative risk, 1.03; 95% CI, 0.96 to 1.10; P=0.45). In post hoc sensitivity analyses with imputation of missing values as either an event of death or major morbidity or no event, the results were materially unchanged from those of the primary analysis (Table S2A in the Supplementary Appendix).

### ANALYSES OF PRESPECIFIED SUBGROUPS

The effects of delayed clamping versus immediate clamping on the primary outcome did not differ significantly according to sex, gestational age (<27 weeks vs. ≥27 weeks), or method of delivery (cesarean section vs. vaginal delivery) (P≥0.10 for all interactions) (Fig. 2).

### TERTIARY OUTCOMES

There were no significant differences between the two groups in median Apgar scores at 1 minute and 5 minutes or in the percentage of infants with an Apgar score of less than 4 at 5 minutes (Table S5 in the Supplementary Appendix). The mean temperature on admission was lower by 0.1°C in the delayed-clamping group than in the immediate-clamping group (P<0.001). The average peak hematocrit was higher by 2.7 percentage points (95% CI, 1.9 to 3.5) in the delayed-clamping group than in the immediate-clamping group (P<0.001). There were no significant differences between the two groups in the peak bili-

**Table 1. Characteristics of Infants, According to Randomized Treatment Group.***

| Characteristic | Immediate Cord Clamping (N=782) | Delayed Cord Clamping (N=784) |
|---|---|---|
| Male sex — no. (%) | 451 (57.7) | 432 (55.1) |
| Gestational age — wk† | 28±2 | 28±2 |
| Birth before 27 wk of gestation — no. (%)† | 257 (32.9) | 267 (34.1) |
| Presentation at birth — no. (%) | | |
| Cephalic | 487 (62.3) | 477 (60.8) |
| Breech | 257 (32.9) | 274 (34.9) |
| Other, including transverse | 34 (4.3) | 26 (3.3) |
| Unknown | 4 (0.5) | 7 (0.9) |
| Method of delivery — no. (%) | | |
| Vaginal with instruments | 40 (5.1) | 44 (5.6) |
| Vaginal without instruments | 233 (29.8) | 220 (28.1) |
| Cesarean in labor | 165 (21.1) | 160 (20.4) |
| Cesarean not in labor | 344 (44.0) | 360 (45.9) |
| Multiple-birth status — no. (%)‡ | | |
| Singleton | 588 (75.2) | 588 (75.0) |
| Twin | 168 (21.5) | 176 (22.4) |
| Triplet | 23 (2.9) | 19 (2.4) |
| Quadruplet | 3 (0.4) | 1 (0.1) |
| White race, mother — no. (%)§ | 575 (73.5) | 568 (72.4) |
| Birth weight — g | 1000±269 | 1018±281 |
| Birth weight <10th percentile for gestational age — no. (%) | 83 (10.6) | 94 (12.0) |

* Plus–minus values are means ±SD. There were no significant differences between the groups. Percentages may not total 100 because of rounding. Data on the use of uterotonic drugs are provided in Table S1 in the Supplementary Appendix, and data on Apgar scores are provided in Table S5 in the Supplementary Appendix.

† Gestational age is the estimated gestational age at randomization before birth.

‡ Numbers of infants in the intention-to-treat population are shown. Infants of multiple births underwent randomization individually.

§ The mother's race was reported by the mother.

rubin level, the need for exchange or partial exchange transfusions, the number of blood transfusions received by 36 weeks, the length of hospital stay, the number of maternal blood transfusions, or the use of uterotonic agents (Tables S1 and S5 in the Supplementary Appendix).

### SENSITIVITY AND ADDITIONAL EXPLORATORY ANALYSES

In a prespecified sensitivity analysis, the relative risk of death or major morbidity was not significantly lower in the delayed-clamping group than in the immediate-clamping group after adjustment for gestational age, sex, and method of delivery (Table S2A in the Supplementary Appendix). In an exploratory analysis, the relative risk of death or major morbidity was not significantly reduced with each 10-second delay in clamping (Table S2B in the Supplementary Appendix). There were no significant differences between the two groups in rates of intraventricular hemorrhage or late cerebral abnormality on ultrasonography (Table S4 in the Supplementary Appendix). More infants in the delayed-clamping group than in the immediate-clamping group had polycythemia (defined as a peak hematocrit of either ≥65% or ≥70%), and fewer infants in the delayed-clamping group received red-cell transfusions (52.1%, vs. 60.5% in the immediate-clamping group; P=0.001) (Table S5 in the Supplementary Appendix). Among infants who were assigned to delayed clamping, those who had a delay of less than 60 seconds before clamping were of a younger mean gestational age, had a lower mean birth weight, and had lower Apgar scores at 1 minute and 5 minutes than those who had a delay of 60 seconds or more (Table S6 in the Supplementary Appendix).

## DISCUSSION

In this large, multicenter, randomized trial, we found no significant difference in the primary composite outcome of death or major morbidity at 36 completed weeks of postmenstrual age between infants assigned to delayed cord clamping and those assigned to immediate cord clamping. There was also no significant difference in the primary outcome according to sex, gestational age, or method of delivery (Fig. 2) or in the originally defined primary composite outcome of death or major morbidity, which included chronic lung disease.

Fewer infants in the delayed-clamping group than in the immediate-clamping group died by 36 weeks (unadjusted P=0.03).[31] However, this may be a chance finding, because death by 36 weeks was 1 of 13 prespecified secondary outcomes that we analyzed, 10 of which are included in the present report; in post hoc analyses with adjustment for multiple comparisons, the difference was not significant (P=0.39). A previous systematic review of randomized, controlled trials showed lower

**Table 2. Summary of Treatment Adherence.***

| Variable | Immediate Cord Clamping (N=782) | Delayed Cord Clamping (N=784) |
|---|---|---|
| Cord milked — no. (%) | 4 (0.5) | 17 (2.2) |
| Time between delivery and cord clamping — no. (%) | | |
| ≤10 sec | 745 (95.3) | 97 (12.4) |
| 11–30 sec | 25 (3.2) | 66 (8.4) |
| 31–59 sec | 3 (0.4) | 40 (5.1) |
| ≥60 sec | 3 (0.4) | 580 (74.0) |
| Not available† | 6 (0.8) | 1 (0.1) |
| Overall treatment adherence — no. (%) | | |
| Information on time between delivery and clamping or on cord-milking status not available† | 6 (0.8) | 1 (0.1) |
| Intervention not as per protocol‡ | 34 (4.3) | 209 (26.7) |
| Intervention as per protocol§ | 742 (94.9) | 574 (73.2) |
| Reason for nonadherence — no./total no. (%) | | |
| Implementation issues¶ | 14/34 (41) | 35/209 (16.7) |
| Clinician concern about infant | 2/34 (6) | 146/209 (69.9) |
| Clinician concern about mother | 0/34 | 10/209 (4.8) |
| Time between delivery and clamping as per protocol and cord milked | 4/34 (12) | 8/209 (3.8) |
| Parental concern | 1/34 (3) | 2/209 (1.0) |
| Time between delivery and clamping was just outside of cutoff point‖ | 13/34 (38) | 8/209 (3.8) |

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Shown are infants whose parents withdrew consent, who were transferred before delivery, or for whom information has not been recorded.
‡ Shown are infants in the immediate-clamping group who had a time between delivery and cord clamping of more than 10 seconds, infants in the delayed-clamping group who had a time between delivery and cord clamping of less than 60 seconds, and infants in either group whose cord was milked.
§ The protocol specified a time between delivery and cord clamping of no more than 10 seconds in the immediate-clamping group and of at least 60 seconds in the delayed-clamping group as well as no cord milking in either group.
¶ Implementation issues included miscommunication and logistic issues.
‖ Shown are infants for whom the time between delivery and cord clamping was 11 to 14 seconds in the immediate-clamping group and 53 to 59 seconds in the delayed-clamping group.

mortality with placental transfusion than without it, although that report included trials of delayed clamping or milking of the umbilical cord.[7] Whether delayed clamping reduces mortality requires clarification in an updated systematic review.[32] No trials of delayed versus immediate cord clamping, including the present one, have been powered for mortality. To yield 90% power to detect a 20% difference in the risk of death (8.0% in the immediate-clamping group vs. 6.4% in the delayed-clamping group), a trial would need more than 11,000 patients, probably requiring international collaboration and a greater integration of clinical research with routine care.[33]

We found no significant difference in the rates of major morbidity between the randomized groups (Table 3). This finding contrasts with those of earlier systematic reviews involving smaller populations,[1,5] which concluded that delayed clamping reduced intraventricular hemorrhage,[1,5] necrotizing enterocolitis,[1] and late-onset sepsis[1] — evidence that underpins current recommendations for delayed clamping.[4,10-14] Discrepancies between past and current evidence might be explained if the infants in APTS were less severely ill than earlier cohorts. Although we did not have detailed clinical data on infants in the trial overall, all 266 infants in the APTS echocardiographic substudy (see the protocol) received antenatal glucocorticoids, and their average systemic

**Table 3. Outcomes with Respect to Death and Major Morbidity by 36 Weeks of Postmenstrual Age.**

| Outcome | Ascertainment of Outcome* | Immediate Cord Clamping | Delayed Cord Clamping | Relative Risk with Delayed Cord Clamping (95% CI) | P Value |
|---|---|---|---|---|---|
| | % | *no./total no. (%)* | | | |
| Primary outcome | | | | | |
| Death or major morbidity† | 95.6 | 279/749 (37.2) | 277/748 (37.0) | 1.00 (0.88–1.13) | 0.96 |
| Death or major morbidity, including chronic lung disease† | 96.0 | 4958/748 (66.6) | 520/756 (68.8) | 1.03 (0.96–1.10) | 0.45 |
| Secondary outcomes | | | | | |
| Death | 100 | 70/782 (9.0) | 50/784 (6.4) | 0.69 (0.49–0.97) | 0.03‡ |
| Death or severe brain injury | 95.5 | 115/754 (15.3) | 101/741 (13.6) | 0.85 (0.67–1.08) | 0.18 |
| Severe brain injury§ | 95.1 | 45/684 (6.6) | 51/691 (7.4) | 1.07 (0.74–1.56) | 0.71 |
| Late cerebral abnormality on ultrasonography§ | 95.1 | 38/684 (5.6) | 37/691 (5.4) | 0.93 (0.61–1.42) | 0.74 |
| Intraventricular hemorrhage of grade 3 or 4§ | 100 | 17/712 (2.4) | 24/734 (3.3) | 1.35 (0.73–2.48) | 0.34 |
| Late-onset sepsis§ | 100 | 132/712 (18.5) | 151/734 (20.6) | 1.11 (0.90–1.36) | 0.33 |
| Necrotizing enterocolitis§ | 100 | 44/712 (6.2) | 41/734 (5.6) | 0.91 (0.60–1.37) | 0.64 |
| Severe retinopathy of prematurity§ | 98.3 | 48/700 (6.9) | 38/721 (5.3) | 0.75 (0.50–1.11) | 0.16 |
| Chronic lung disease§ | 99.5 | 365/708 (51.6) | 398/731 (54.4) | 1.04 (0.95–1.14) | 0.38 |
| Patent ductus arteriosus requiring treatment | 99.1 | 259/773 (33.5) | 249/779 (32.0) | 0.92 (0.81–1.06) | 0.24 |

* Shown is the percentage of all 1566 infants, except as noted.
† Major morbidity was defined as severe brain injury (intraventricular hemorrhage of grade 3 or 4 or late cerebral abnormality on ultrasonography), late-onset sepsis, necrotizing enterocolitis, or severe retinopathy of prematurity. The original protocol included chronic lung disease in the definition of major morbidity. Detailed definitions are provided in the trial protocol.
‡ P=0.39 after post hoc adjustment for multiple comparisons of 13 secondary outcomes.
§ The analysis was restricted to the 1466 infants who survived to 36 weeks of postmenstrual age.

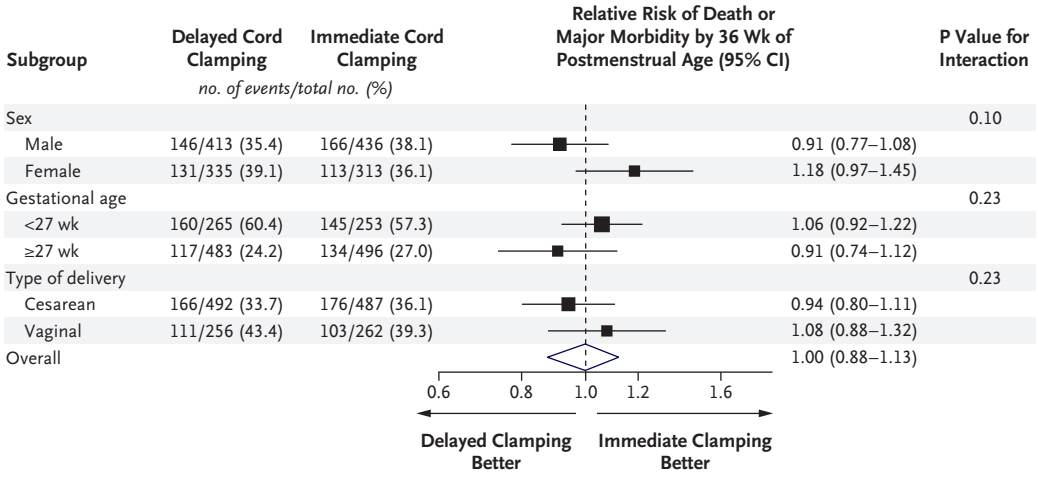


**Figure 2. Subgroup Analyses of the Primary Outcome.**
The size of the squares indicates the relative weight of that group.

blood flow was higher than in infants enrolled in previous studies.[34] The difference of 2.7 percentage points in peak hematocrit in the first week between the delayed-clamping group and the immediate-clamping group (P<0.001) is consistent with placental transfusion (Table S5 in the Supplementary Appendix). Although the number of transfusions overall did not differ significantly between the two groups, an additional analysis that was prespecified in the statistical analysis plan showed that a smaller percentage of infants in the delayed-clamping group than in the immediate-clamping group received any red-cell transfusions. However, these analyses were considered hypothesis-generating and should be interpreted cautiously.

The high rate of nonadherence to delayed clamping reflects widespread concern about the possible hazards of delayed resuscitation in preterm infants.[15,16] We found no significant difference between the two groups in the risk of a low Apgar score at 5 minutes, and previous trials comparing delayed clamping versus immediate clamping showed no significant differences in rates of intubation at delivery.[7] However, among infants who were assigned to delayed clamping, those who underwent earlier clamping (<60 seconds) were more premature and had lower Apgar scores than those who underwent clamping after 60 seconds or more; some may have needed, and benefited from, rapid resuscitation. The preferred care of infants who are judged to need immediate resuscitation remains unknown.

This pragmatic trial minimized data collection to maximize enrollment.[17,35,36] We did not collect data for this trial on antenatal glucocorticoids, heart rate, oxygen saturation, the fraction of inspired oxygen, time to onset of breathing, and intubation rates. We include only short-term outcomes in the present report; follow-up in childhood is planned.[8,9]

In conclusion, among infants in our trial population, delayed clamping of the umbilical cord did not result in a lower incidence of the primary outcome of death or major morbidity by 36 weeks of postmenstrual age than immediate clamping.

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## APPENDIX

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