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Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants

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IMPORTANCE Umbilical cord milking as an alternative to delayed umbilical cord clamping may provide equivalent benefits to preterm infants, but without delaying resuscitation.

OBJECTIVE To determine whether the rates of death or severe intraventricular hemorrhage differ among preterm infants receiving placental transfusion with umbilical cord milking vs delayed umbilical cord clamping.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority randomized clinical trial of preterm infants (born at 23-31 weeks' gestation) from 9 university and private medical centers in 4 countries were recruited and enrolled between June 2017 and September 2018. Planned enrollment was 750 per group. However, a safety signal comprising an imbalance in the number of severe intraventricular hemorrhage events by study group was observed at the first interim analysis; enrollment was stopped based on recommendations from the data and safety monitoring board. The planned noninferiority analysis could not be conducted and a post hoc comparison was performed instead. Final date of follow-up was December 2018.

INTERVENTIONS Participants were randomized to umbilical cord milking (n = 236) or delayed umbilical cord clamping (n = 238).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of death or severe intraventricular hemorrhage to determine noninferiority of umbilical cord milking with a 1% noninferiority margin.

RESULTS Among 540 infants randomized, 474 (88%) were enrolled and completed the trial (mean gestational age of 28 weeks; 46% female). Twelve percent (29/236) of the umbilical cord milking group died or developed severe intraventricular hemorrhage compared with 8% (20/238) of the delayed umbilical cord clamping group (risk difference, 4% [95% CI, −2% to 9%]; $P = .16$). Although there was no statistically significant difference in death, severe intraventricular hemorrhage was statistically significantly higher in the umbilical cord milking group than in the delayed umbilical cord clamping group (8% [20/236] vs 3% [8/238], respectively; risk difference, 5% [95% CI, 1% to 9%]; $P = .02$). The test for interaction between gestational age strata and treatment group was significant for severe intraventricular hemorrhage only ($P = .003$); among infants born at 23 to 27 weeks' gestation, severe intraventricular hemorrhage was statistically significantly higher with umbilical cord milking than with delayed umbilical cord clamping (22% [20/93] vs 6% [5/89], respectively; risk difference, 16% [95% CI, 6% to 26%]; $P = .002$).

CONCLUSIONS AND RELEVANCE In this post hoc analysis of a prematurely terminated randomized clinical trial of umbilical cord milking vs delayed umbilical cord clamping among preterm infants born at less than 32 weeks' gestation, there was no statistically significant difference in the rate of a composite outcome of death or severe intraventricular hemorrhage, but there was a statistically significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group. The early study termination and resulting post hoc nature of the analyses preclude definitive conclusions.

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Placental transfusion has become the accepted standard in newborn care with benefits to the neonate including decreased mortality in preterm infants[1] and improved developmental outcomes in term infants.[2] Umbilical cord milking has been endorsed as an alternative to delayed umbilical cord clamping, which is the current standard of care. Umbilical cord milking provides a placental transfusion by pushing blood toward the newborn before the umbilical cord is clamped with a duration similar to immediate umbilical cord clamping, allowing the neonatal team to begin resuscitation promptly.

A phase 1 pilot trial compared umbilical cord milking vs delayed umbilical cord clamping in premature newborns delivered by cesarean delivery and demonstrated umbilical cord milking improved neonatal blood flow and organ perfusion (as measured by cardiac ultrasonography and improved urine output) and improved cognitive and language scores at 2 years of age.[3,4] A meta-analysis[5] demonstrated umbilical cord milking compared with immediate umbilical cord clamping was associated with higher levels of hemoglobin and hematocrit, a reduced risk of all-grade intraventricular hemorrhage, and a decreased risk of an oxygen requirement at 36 weeks' corrected gestational age in premature newborns. No trial to date has demonstrated harm with umbilical cord milking.

A large multicenter trial (Australian Placental Transfusion Study) comparing 60 seconds of delayed umbilical cord clamping with immediate umbilical cord clamping, defined as 10 seconds or less after delivery, showed no significant difference in the composite primary outcome of death or major morbidity.[1] In that trial, 26% of the infants randomized to delayed umbilical cord clamping underwent umbilical cord clamping performed for less than 60 seconds due to concerns for maternal or neonatal conditions, thus limiting the efficacy analysis. That trial[1] and a recent meta-analysis[6] have demonstrated reduced in-hospital mortality with delayed umbilical cord clamping compared with immediate umbilical cord clamping.

The objective of the current randomized clinical trial was to determine whether umbilical cord milking was noninferior to delayed umbilical cord clamping among preterm infants.

Key Points

Question Is there a difference in the rates of death or severe intraventricular hemorrhage among preterm infants who receive placental transfusion with umbilical cord milking vs delayed umbilical cord clamping?

Findings In a randomized clinical trial that was terminated early, precluding the planned noninferiority analysis and requiring post hoc comparison, 474 of a planned 1500 infants born at less than 32 weeks' gestation were enrolled. There was no significant difference in the composite primary outcome of death or severe intraventricular hemorrhage for the umbilical cord milking group vs the delayed umbilical cord clamping group (12% vs 8%, respectively), but umbilical cord milking was significantly associated with a higher rate of severe intraventricular hemorrhage (8% vs 3%).

Meaning Among preterm infants born at less than 32 weeks' gestation, there was no significant difference in the rates of the composite primary outcome of death or severe intraventricular hemorrhage with umbilical cord milking vs delayed umbilical cord clamping, but a significantly higher rate of severe intraventricular hemorrhage (a signal of harm) in the umbilical cord milking group led to early termination of the study. The early study termination and post hoc nature of the analyses preclude definitive conclusions.

Methods

The research ethics committee or institutional review board at all 9 participating sites (6 in the United States and 1 site each in Ireland, Germany, and Canada) approved this randomized clinical trial. Three sites only had approval for prenatal consent. Six sites obtained institutional review board approval for a waiver or for deferred consent. When prenatal consent could not be obtained (ie, imminent delivery), the parents were approached after delivery for consent. Enrollment took place between June 2017 and September 2018. The final date of follow-up was December 2018. The trial protocol appears in Supplement 1 and the statistical analysis plan appears in Supplement 2.

Participants

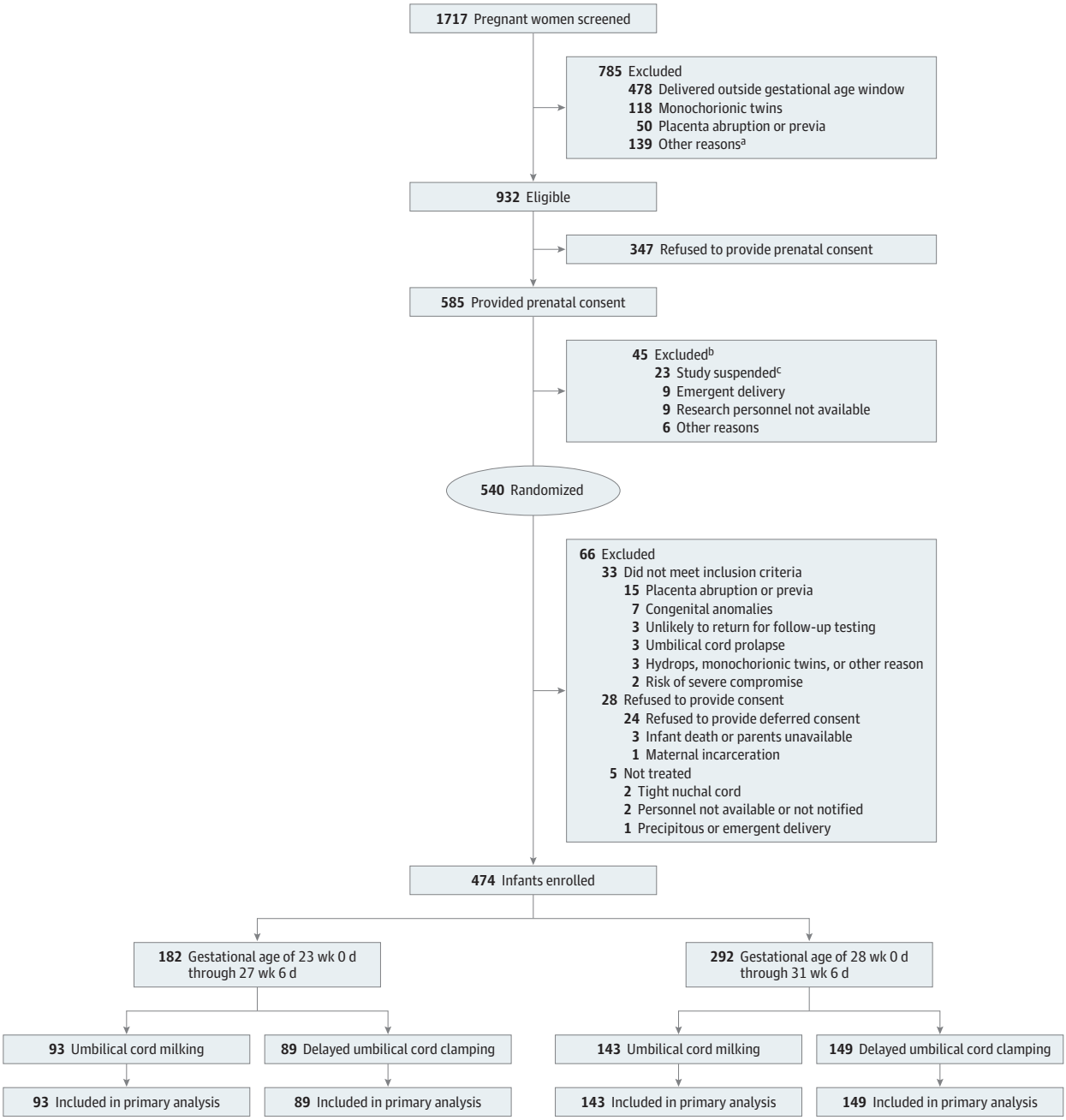
Pregnant women less than 32 weeks' gestation by clinical and ultrasonographic criteria were identified and recruited from the labor and delivery floor or perinatal special care unit at each site. Exclusion criteria were major congenital anomalies, severe placental abruption, transplacental incision, umbilical cord prolapse, hydrops, bleeding accreta, monochorionic multiple births, fetal or maternal risk for severe compromise at delivery, and family unlikely to return for 24-month neurodevelopmental testing. Standard classifications of race from the National Institutes of Health were used for demographic purposes. The data on race/ethnicity were obtained either directly from the parent or guardian or from the medical record. Race/ethnicity data were collected for demographic purposes to ensure there were no racial/ethnic biases between groups.

Randomization and Study Procedures

Immediately prior to delivery, the research staff or neonatal delivery team opened a sequentially numbered opaque randomization envelope from the appropriate gestational age strata (23 weeks 0 days through 27 weeks 6 days or 28 weeks 0 days through 31 weeks 6 days). Randomization was computer generated at the central data coordinating center (University of Alabama at Birmingham) using permuted block sizes of 2 and 4 and was stratified by site. The infants were considered to be randomized at the time the envelope was opened (**Figure**). The parents were not told the randomization group; however, the study could not be completely blinded (additional information appears later).

Participants were stratified by gestational age to ensure enrollment of an approximately equal number of infants born at less than 28 weeks' gestational age in each group.

Figure. Patient Recruitment, Randomization, and Follow-up in the Trial



[a] Includes fetal or maternal risk for severe compromise at delivery (n = 30), congenital anomalies of newborn (n = 27), family unlikely to return for neurodevelopmental testing at 24 months (n = 22), cardiac defects (n = 11), and other unspecified reasons.

[b] There were 2 women who had more than 1 reason indicated.

[c] Refers to women who had provided consent, but had not yet delivered when the trial was stopped.

Multiple births were given the same treatment assignment for ease of consent and family considerations. There was no crossover allowed between the umbilical cord milking group and the delayed umbilical cord clamping group. If the physician abandoned the assigned procedure due to safety concerns, the infant received immediate umbilical cord clamping (ie, physicians were not to milk the umbilical cord if the infant was randomized to the delayed umbilical cord clamping group).

Delayed umbilical cord clamping was performed at cesarean delivery by having the delivering obstetrician hold the infant below the level of the incision for at least 60 seconds in warm, sterile towels. Infants were dried and given gentle tactile stimulation to promote respiratory effort. For

vaginal delivery, the obstetrician held the infant below the level of the introitus for at least 60 seconds in warm sterile towels and gentle stimulation was done.

Umbilical cord milking was performed by having the obstetrician hold the infant below the level of the cesarean incision (or below the level of the introitus for vaginal delivery) and 20 cm of the umbilical cord was milked during approximately 2 seconds allowing refill, and then repeating 3 more times. In an effort to ensure consistency, participating sites video recorded each technique and reviewed it with the lead principal investigator prior to enrollment of the first participant. Newborns were resuscitated according to the local unit's protocol.

Several potential biases were addressed in a number of ways. All potentially eligible pregnancies between 23^0 to 31^6 weeks' gestational age were screened and logged to detect selection biases. Randomization was concealed in opaque envelopes prior to delivery. However, the parents or caregivers could access the randomization group assignment by watching what their infant was receiving, but were not explicitly told by the neonatal or obstetrical clinicians. In addition, documentation of the intervention was charted in the medical record as placental transfusion rather than as delayed umbilical cord clamping or umbilical cord milking.

All outcome assessments were performed by blinded team members. Ascertainment of intraventricular hemorrhage was performed by a board-certified pediatric radiologist at each site who was blinded to treatment group. All grade 2 or higher intraventricular hemorrhage events (defined as presence of blood in the ventricles) were adjudicated by 2 independent pediatric radiologists or neuroradiologists who were not affiliated with any of the study sites and were blinded to randomization assignment.[7]

Primary and Secondary Outcomes

The primary outcome of the trial was incidence of death or severe intraventricular hemorrhage at 6 months' corrected gestational age. Severe intraventricular hemorrhage was categorized as grade 3 or grade 4.

Death and severe intraventricular hemorrhage also were investigated individually as secondary outcomes. Other secondary outcome measures that appear in this report include any grade intraventricular hemorrhage (grades 1-4) and levels of hemoglobin and hematocrit collected at 4 hours (or within 2-6 hours) of life. Data on the secondary outcome of death or neurodevelopmental impairment at 22 to 26 months are still being collected.

Prespecified expected and serious adverse events, in addition to the components of the primary outcome, were grade 1 or 2 intraventricular hemorrhage, polycythemia (not requiring treatment or requiring exchange transfusion), periventricular leukomalacia, sepsis (early or late onset), chronic lung disease, necrotizing enterocolitis (stage ≥2), spontaneous intestinal perforation, patent ductus arteriosus requiring treatment, retinopathy of prematurity, maternal death, delivery room intervention (compressions or epinephrine), and hyperbilirubinemia requiring exchange transfusion.

Sample Size Calculation

The initial pilot study included cesarean deliveries of 154 newborns and revealed a 6% difference in the combined outcome of death or severe intraventricular hemorrhage between newborns treated with umbilical cord milking and delayed umbilical cord clamping (4.1% vs 10.1%, respectively).[3] The sample size for noninferiority testing of infants born by cesarean delivery in each group was set at 502 per group based on the pilot study. This estimate assumed a 2-group large sample normal approximation test of proportions with a 1-sided significance level of .05 and 90% power.

The null hypothesis stated that umbilical cord milking was inferior to delayed umbilical cord clamping by at least a 1% noninferiority margin (the difference [$P_{\text{umbilical cord milking}} - P_{\text{delayed umbilical cord clamping}}$] in composite outcome rates was ≥1%) and the alternative hypothesis stated that umbilical cord milking was not inferior, assuming the expected difference in rates ($P_{\text{umbilical cord milking}} - P_{\text{delayed umbilical cord clamping}}$) was −4% and the reference rate in the delayed umbilical cord clamping group was 10%. Using 10.1% as the pilot study reference rate yields 485 per group and rounding the proportional difference down to 10% conferred a conservative estimate.

An adjustment factor of 1.12 derived from the Neonatal Research Network generic database maintained by the Eunice Kennedy Shriver National Institute of Child Health and Human Development allowed for multiple births to be randomized to the same treatment group, introducing a clustering effect.[8] The noninferiority margin of 1% was selected to show that the rate of the primary outcome was less than 1% higher in the umbilical cord milking group compared with the delayed umbilical cord clamping group. A difference of 1% was considered to be clinically meaningful because it would allow minimal discrepancy between the 2 true outcome rates.

In the event that noninferiority was established, the study sample size was sufficient to allow for subsequent superiority testing whether umbilical cord milking provided better outcomes than delayed umbilical cord clamping. Because the sample size estimate was based on cesarean birth data, the final estimate was further inflated to 1500 to include vaginal deliveries.

Statistical Analyses

For the analysis of the primary composite outcome, the study was designed as a noninferiority trial using the sample size calculation described above. However, safety signals observed by the data and safety monitoring board with just under one-third of the total sample size recruited resulted in suspension of enrollment in September 2018. The data and safety monitoring board, which was blinded to treatment assignments, reviewed the event rates for safety outcomes, including severe intraventricular hemorrhage, with meetings scheduled approximately every 6 months. There were no prespecified stopping rules.

At the scheduled April 2018 meeting, the data and safety monitoring board noted an imbalance in the number

of severe intraventricular hemorrhage events across groups. Because the study enrollment and severe intraventricular hemorrhage events at that time were dominated by 1 site and event rates have high variability early in trials, the board requested an additional meeting when at least 400 participants were enrolled. At the September 2018 meeting, 465 participants had been enrolled and there was a lower percentage of severe intraventricular hemorrhage events at the 1 site. The imbalance persisted and the data and safety monitoring board recommended stopping the trial and unmasking the results. Given the early study termination, the originally designed primary analysis was not applicable and is not presented herein.

Maternal, neonatal, and delivery characteristics were compared between groups. The summary statistics included means and SDs for continuous variables and frequencies and percentages for categorical variables. Formal statistical comparisons were based on the *t* test for continuous variables and the χ^2 or Fisher exact test (as appropriate) for categorical variables.

The complete study outcomes were evaluated for all infants that were enrolled up until the time the trial was stopped. For all primary, secondary, and exploratory outcomes, the unadjusted treatment group rates were calculated and presented along with the risk differences and 95% CIs. The risk differences also were calculated within prespecified gestational age strata and by mode of delivery subgroups. The consistency of the associations between the treatment group assignment and the outcomes were assessed across the gestational age strata and the modes of delivery by evaluating interaction terms in multivariable regression models and by the Breslow-Day test (as applicable).

An exploratory multivariable logistic regression model also was generated to further investigate a potential mechanism (inflammation from maternal chorioamnionitis) that could interact with changes in cerebral blood flow by treatment group, leading to severe intraventricular hemorrhage. Sensitivity analyses included generalized estimating equations to estimate the treatment effects while accounting for correlation within sites and multiple gestations. Infants with missing outcome data were excluded from the analyses.

The α level for all hypothesis tests for the main effects was set at .05. All hypothesis tests were 2-sided. Version 9.4 of SAS statistical software (SAS Institute Inc) was used for all analyses. No adjustments were made for multiple comparisons. Because of the post hoc nature of the analyses and the potential for type I error due to multiple comparisons, the study findings should be interpreted as exploratory.

Results

Between June 2017 and September 2018, 474 infants were enrolled (Figure). The adherence rate for umbilical cord milking was 98% and it was 93% for delayed umbilical cord clamping. Maternal demographics were similar between the groups (**Table 1**). However, there was a higher rate of maternal diabetes in the delayed umbilical cord clamping group (19%) vs the umbilical cord milking group (11%), a lower rate of cesarean deliveries (67% vs 76%, respectively), and a lower rate of pregnancy-induced hypertension or preeclampsia (23% vs 34%).

The mean time to umbilical cord clamping was higher in the delayed umbilical cord clamping group (57.5 seconds) compared with the umbilical cord milking group (22.8 seconds). There were 25 infants randomized for whom deferred consent was not obtained (13 in the delayed umbilical cord clamping group and 12 in the umbilical cord milking group). Three infants died shortly after birth (2 in the delayed umbilical cord clamping group and 1 in the umbilical cord milking group) and the parents were not available to provide consent. No missing data were identified for the primary outcome of incidence of death or severe intraventricular hemorrhage at 6 months' corrected gestational age. For the secondary outcomes, data on hemoglobin and hematocrit levels collected at 4 hours of life were missing for 18% of the newborns.

Data for the primary outcome at the time the study was stopped appear in **Table 2**. In the umbilical cord milking group, 29 of 236 infants (12%) died or developed severe intraventricular hemorrhage compared with 20 of 238 infants (8%) in the delayed umbilical cord clamping group (risk difference, 4% [95% CI, −2% to 9%]; *P* = .16). There was no statistically significant difference in death between the groups (7% [17/236] of the umbilical cord milking group vs 6% [15/238] of the delayed umbilical cord clamping group; risk difference, 1% [95% CI, −4% to 5%]; *P* = .70).

Umbilical cord milking was associated with a statistically significantly higher rate of severe intraventricular hemorrhage compared with delayed umbilical cord clamping (8% [20/236] vs 3% [8/238], respectively; risk difference, 5% [95% CI, 1% to 9%], *P* = .02). The secondary outcomes for the entire cohort appear in **Table 3** and the prespecified adverse events appear in **Table 4**. There were no statistically significant differences between groups.

The test for interaction between gestational age strata and treatment group for death or severe intraventricular hemorrhage was not statistically significant, but it was statistically significant for severe intraventricular hemorrhage only (*P* = .003). Among infants born at 23 to 27 weeks' gestation, umbilical cord milking was associated with a higher rate of severe intraventricular hemorrhage compared with delayed umbilical cord clamping (22% [20/93] vs 6% [5/89], respectively; risk difference, 16% [95% CI, 6% to 26%]; *P* = .002). This association was not found in infants born at 28 to 32 weeks' gestation (0% [0/143] in the umbilical cord milking group vs 2% [3/149] in the delayed umbilical cord clamping group; risk difference, −2% [95% CI, −4% to 1%]; *P* = .24).

The test for interaction between treatment group and mode of delivery for the outcome of death or severe intraventricular hemorrhage was not statistically significant (*P* = .17). The test for interaction between treatment group and mode of delivery for the outcome of severe intraventricular hemorrhage only yielded a value of *P* = .06. For infants delivered by cesarean delivery, the incidence of severe intraventricular

Table 1. Maternal and Neonatal Demographics by Treatment Group

	Umbilical Cord Milking (n = 236)	Delayed Umbilical Cord Clamping (n = 238)
Maternal age, mean (SD), y	30.4 (5.7)	29.9 (5.6)
Gestational age at birth, mean (SD), wk	28.4 (2.4)	28.4 (2.5)
Gestational age at birth strata, No. (%)		
23 wk 0 d through 27 wk 6 d	93 (39)	89 (37)
28 wk 0 d through 31 wk 6 d	143 (61)	149 (63)
Infant sex, No. (%)		
Female	113 (48)	106 (45)
Male	123 (52)	132 (55)
Infant race/ethnicity, No./total No. (%)		
White	134/219 (61)	137/229 (60)
Black or African American	42/219 (19)	33/229 (14)
Asian	13/219 (6)	27/229 (12)
American Indian or Alaskan Native	9/219 (4)	10/229 (4)
Native Hawaiian or other Pacific Islander	3/219 (1)	1/229 (<1)
>1 Race	18/219 (8)	21/229 (9)
Hispanic or Latino	67/228 (29)	63/234 (27)
Cesarean delivery, No. (%)	180 (76)	159 (67)
Maternal diabetes, No. (%)	27 (11)	45 (19)
Maternal chorioamnionitis, No. (%)	67 (28)	84 (35)
Pregnancy-induced hypertension or preeclampsia, No. (%)	80 (34)	55 (23)
Labor or uterotonics before delivery, No. (%)	132 (56)	149 (63)
Duration of rupture of membranes before delivery, median (IQR), h	0 (0-41)	0 (0-34)
Steroids given before delivery, No. (%)	211 (89)	209 (88)
Prenatal magnesium, No. (%)	179 (76)	177 (74)
General anesthesia, No. (%)	36 (15)	39 (16)
Small for gestational age, No. (%)	32 (14)	18 (8)

Abbreviation: IQR, interquartile range.

Table 2. Primary Composite Outcome Overall and in Prespecified Subgroups

	Death or Severe Intraventricular Hemorrhage, No./Total No. (%)				
	Umbilical Cord Milking	Delayed Umbilical Cord Clamping	Risk Difference, % (95% CI)	*P* Value[a]	*P* Value for Interaction[b]
Overall	29/236 (12)	20/238 (8)	4 (−2 to 9)	.16	
By gestational age at birth strata					
23 wk 0 d through 27 wk 6 d	26/93 (28)	17/89 (19)	9 (−3 to 21)	.16	.61
28 wk 0 d through 31 wk 6 d	3/143 (2)	3/149 (2)	0 (−3 to 3)	.99	
By mode of delivery subgroups					
Cesarean	17/180 (9)	13/159 (8)	1 (−5 to 7)	.68	.17
Vaginal	12/56 (21)	7/79 (9)	12 (0 to 25)	.04	

[a] Tests the null hypothesis that the risk difference within each subgroup is equal to 0.

[b] Tests the null hypothesis that the treatment group effect on the outcome is the same for each gestational age at birth strata or mode of delivery subgroup. For these binary outcomes and binary covariates, the Breslow-Day test for the homogeneity of odds ratios was used.

hemorrhage was 6% in the umbilical cord milking group and 4% in the delayed umbilical cord clamping group (risk difference, 2% [95% CI, −3% to 6%]; *P* = .44). For vaginal births, the incidence of severe intraventricular hemorrhage was 18% in the umbilical cord milking group compared with 3% in the delayed umbilical cord clamping group (risk difference, 15% [95% CI, 5% to 26%]; *P* = .004). The test for interaction between treatment group and mode of delivery was statistically significant for the secondary outcome of increased hemoglobin level at 4 hours among vaginal deliveries in the umbilical cord milking group (*P* = .007).

In an exploratory post hoc analysis, a statistically significant interaction indicated that the association of umbilical cord milking with severe intraventricular hemorrhage was modified in the presence of maternal chorioamnionitis (*P* = .008; eFigure in Supplement 3) after controlling for gestational age at birth. The sensitivity analyses for the primary outcome and its components that used generalized

Table 3. Secondary Outcomes by Treatment Group, Overall, and Within Specified Subgroups

	Umbilical Cord Milking	Delayed Umbilical Cord Clamping	Risk Difference, % (95% CI)	*P* Value[a]	*P* Value for Interaction[b]
Infant Death, No./Total No. (%)					
Overall	17/236 (7)	15/238 (6)	1 (−4 to 5)	.70	
By gestational age at birth strata					
23 wk 0 d through 27 wk 6 d	14/93 (15)	13/89 (15)	0 (−10 to 11)	.93	.68
28 wk 0 d through 31 wk 6 d	3/143 (2)	2/149 (1)	1 (−2 to 4)	.68	
By mode of delivery subgroups					
Cesarean	11/180 (6)	10/159 (6)	0 (−5 to 5)	.95	.43
Vaginal	6/56 (11)	5/79 (6)	5 (−5 to 14)	.36	
Severe Intraventricular Hemorrhage (Grade 3 or 4), No./Total No. (%)					
Overall	20/236 (8)	8/238 (3)	5 (1 to 9)	.02	
By gestational age at birth strata					
23 wk 0 d through 27 wk 6 d	20/93 (22)	5/89 (6)	16 (6 to 26)	.002	.003
28 wk 0 d through 31 wk 6 d	0/143	3/149 (2)	−2 (−4 to 1)	.24	
By mode of delivery subgroups					
Cesarean	10/180 (6)	6/159 (4)	2 (−3 to 6)	.44	.06
Vaginal	10/56 (18)	2/79 (3)	15 (5 to 26)	.004	
Any Grade of Intraventricular Hemorrhage, No./Total No. (%)					
Overall	57/236 (24)	50/238 (21)	3 (−4 to 11)	.41	
By gestational age at birth strata					
23 wk 0 d through 27 wk 6 d	34/93 (37)	31/89 (35)	2 (−12 to 16)	.81	.67
28 wk 0 d through 31 wk 6 d	23/143 (16)	19/149 (13)	3 (−5 to 11)	.42	
By mode of delivery subgroups					
Cesarean	33/180 (18)	25/159 (16)	3 (−5 to 11)	.52	.52
Vaginal	24/56 (43)	25/79 (32)	11 (−5 to 28)	.18	
Hemoglobin Level at a Mean of 4 (SD, 2) h of Life, Mean (SD), g/dL					
Overall	16.5 (3.1)	16.4 (2.7)	0.06 (−0.52 to 0.65)	.83	
By gestational age at birth strata					
23 wk 0 d through 27 wk 6 d	15.0 (2.8)	14.9 (2.4)	0.10 (−0.69 to 0.90)	.80	.88
28 wk 0 d through 31 wk 6 d	17.6 (2.9)	17.4 (2.5)	0.18 (−0.53 to 0.90)	.62	
By mode of delivery subgroups					
Cesarean	16.7 (3.0)	16.2 (2.6)	0.54 (−0.12 to 1.19)	.11	.007
Vaginal	15.6 (3.1)	16.9 (3.1)	−1.26 (−2.46 to −0.05)	.04	
Hematocrit Level at a Mean of 4 (SD, 2) h of Life, Mean (SD), %					
Overall	48.6 (8.2)	48.6 (7.9)	0.05 (−1.55 to 1.64)	.95	
By gestational age at birth strata					
23 wk 0 d through 27 wk 6 d	45.1 (8.0)	44.5 (6.7)	0.63 (−1.67 to 2.93)	.59	.66
28 wk 0 d through 31 wk 6 d	51.2 (7.4)	51.3 (7.4)	−0.04 (−1.95 to 1.88)	.97	
By mode of delivery subgroups					
Cesarean	49.1 (8.1)	48.0 (7.5)	1.11 (−0.71 to 2.93)	.23	.03
Vaginal	47.0 (8.5)	49.9 (8.5)	−2.89 (−6.20 to 0.42)	.09	

[a] Tests the null hypothesis that the risk difference within each subgroup is equal to 0.

[b] Tests the null hypothesis that the treatment group effect on the outcome is the same for each gestational age at birth strata or mode of delivery subgroup. For binary outcomes, such as any grade of intraventricular hemorrhage, the Breslow-Day test for the homogeneity of odds ratio was used. For continuous outcomes, such as hemoglobin level, linear regression including an interaction term was used.

Table 4. Expected and Serious Adverse Events by Treatment Group

	Expected and Serious Adverse Events, No. (%)		
	Umbilical Cord Milking (n = 236)	Delayed Umbilical Cord Clamping (n = 238)	Risk Difference, % (95% CI)[a]
Type of delivery room intervention			
Compressions	7 (3)	8 (3)	0 (−4 to 3)
Epinephrine	2 (1)	1 (<1)	0 (−1 to 2)
Polycythemia during first 7 d of life	4 (2)	10 (4)	−3 (−6 to 1)
Sepsis			
Early onset (≤72 h of life)	4 (2)	7 (3)	−1 (−4 to 1)
Late onset (>72 h of life)	22 (9)	19 (8)	1 (−4 to 6)
Any	25 (11)	24 (10)	1 (−5 to 6)
Patent ductus arteriosus	42 (18)	46 (19)	−1 (−8 to 5)
Retinopathy of prematurity requiring treatment	10 (4)	19 (8)	−4 (−8 to 1)
Exchange transfusion for hyperbilirubinemia	1 (<1)	3 (1)	0 (−2 to 1)
Chronic lung disease	47 (20)	44 (18)	2 (−6 to 9)
Necrotizing enterocolitis	8 (3)	13 (5)	−2 (−6 to 2)
Spontaneous intestinal perforation	1 (<1)	5 (2)	−2 (−4 to 1)
Periventricular leukomalacia	17 (7)	9 (4)	3 (−1 to 8)
Maternal death	1 (<1)	0	0 (−1 to 1)
Intraventricular hemorrhage (grade 1 or 2)	37 (16)	42 (18)	−2 (−9 to 5)

[a] Calculated as umbilical cord milking minus delayed umbilical cord clamping. The risk differences are displayed for binary outcomes with asymptotic Wald 95% CIs.

estimating equations to account for study site and multiple gestations were evaluated and the results were consistent (eTable 1 and eTable 2 in Supplement 3).

Discussion

In this randomized clinical trial of umbilical cord milking vs delayed umbilical cord clamping among preterm infants born at less than 32 weeks' gestation, there was no statistically significant difference in the rate of the composite outcome of death or severe intraventricular hemorrhage, but a signal of harm of a statistically significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group led to early termination of the study. There are biologically plausible explanations for the adverse effect with umbilical cord milking that are related to the fragile highly vascularized germinal matrix, which may be prone to bleeding.[9]

First, extremely premature infants lack adequate cerebral autoregulation compared with more mature preterm infants. Beausoleil et al[10] analyzed cerebral autoregulation, as assessed by near infrared spectroscopy, and demonstrated that cerebral perfusion can fluctuate based on systemic blood pressure greater than 50% of the time in extremely preterm infants compared with 20% of the time in very preterm infants.[11] Changes in systemic blood flow with umbilical cord milking may be transferred to the cerebral blood flow causing rupture. A study in anesthetized 128-day-old preterm lambs (equivalent to a human at 26 weeks' gestation) demonstrated that repeated umbilical cord milking caused substantial fluctuations in carotid artery flow.[12] Second, the interactions of maternal chorioamnionitis and extreme prematurity with treatment group are consistent with inflammatory mediators crossing the blood-brain barrier, promoting a neuroinflammatory cascade, and increasing the fragility of the germinal matrix and the cerebral blood vessels.[13]

The pilot trial demonstrated that, compared with delayed umbilical cord clamping, umbilical cord milking at cesarean birth improved blood flow and organ perfusion by providing greater placental transfusion, as measured by improved superior vena cava flow (by echocardiography) and higher admission hemoglobin level.[3] However, improved blood flow in a very immature fragile brain may lead to an adverse outcome. Several large cohort studies also have shown an increased incidence of severe intraventricular hemorrhage in preterm infants delivered vaginally compared with cesarean delivery.[14,15]

There are also some important differences between the pilot trial[3,4] and this study. First, the pilot trial compared umbilical cord milking vs 45-second delayed umbilical cord clamping. A recent cohort study has suggested that a longer time to umbilical cord clamping (30-45 seconds vs 60-75 seconds) may result in improved neonatal outcomes.[16] Second, the pilot study only included half the number of infants born at 23 to 27 weeks' gestation as the current trial (75 vs 182, respectively), and was possibly underpowered to detect differences in severe intraventricular hemorrhage. Third, the current trial has the highest rate of adherence to delayed umbilical cord clamping of any multicenter umbilical cord management trial to date. The greater than 90% adherence rate for infants randomized to delayed umbilical cord clamping may explain why the rates of severe intraventricular hemorrhage with delayed umbilical cord clamping

were lower than in the pilot study (adherence rate of 81%)[3] or in the Australian Placental Transfusion Study trial (adherence rate of 75%).[1]

Restricting delivery room trials to prenatal consent may allow bias; mothers who were not approached were in advanced labor and delivered infants with poor short- and long-term outcomes.[17] Two-thirds (6 of 9) of the trial sites used deferred consent approved by the local institutional review board. Thus, in the absence of deferred consent, a substantial proportion of infants at risk for severe intraventricular hemorrhage may not have been enrolled. At the outset of this randomized clinical trial, delayed umbilical cord clamping or umbilical cord milking practices had no reported harms, and both practices were associated with short-term clinical benefits, suggesting the interventions were associated with minimal risk. Given the statistically significant risk identified in infants born at 23 to 27 weeks' gestation in this study, the use of deferred consent for future studies would no longer be appropriate.

Umbilical cord milking compared with delayed umbilical cord clamping in a smaller randomized clinical trial was associated with higher cognitive and language scores at 22 to 26 months' corrected gestational age.[4] Because of the importance of long-term neurodevelopment, all surviving infants will be followed up to determine developmental outcomes at 22 to 26 months' corrected gestational age. In addition, because the increased rate of severe intraventricular hemorrhage appeared to be limited to infants born at 23 to 27 weeks' gestational age, the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the data and safety monitoring board approved a new trial of umbilical cord milking compared with delayed umbilical cord clamping in older gestational age infants (30-32 weeks' gestational age), with a primary outcome of cognitive status at 2 years, and allowed data from infants at 30 to 32 weeks from this trial to be included.

Limitations

This study has several limitations. First, the study was terminated early, leading to some of the analyses being post hoc and some secondary outcome results being underpowered due to the diminished sample size. Second, there may be selection bias introduced by the postrandomization exclusions from the deferred consent process.

Conclusions

In this post hoc analysis of a prematurely terminated randomized clinical trial of umbilical cord milking vs delayed umbilical cord clamping among preterm infants born at less than 32 weeks' gestation, there was no statistically significant difference in the rate of a composite outcome of death or severe intraventricular hemorrhage, but there was a statistically significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group. The early study termination and resulting post hoc nature of the analyses preclude definitive conclusions.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Cutter reported being the president of Pythagoras Inc, a private consulting company; serving on data and safety monitoring boards for AMO Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Galmed Pharmaceuticals, Horizon Pharmaceuticals, Hisun Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva pharmaceuticals, the National Heart, Lung, and Blood Institute (protocol review committee), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (OPRU oversight committee); and serving as a consultant or serving on advisory boards for Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Medday, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion Pharmaceuticals, Roche, Somahlution, and TG Therapeutics. No other disclosures were reported.

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