Umbilical Cord Milking vs Delayed Cord Clamping and Associations with In-Hospital Outcomes among Extremely Premature Infants

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Objective To compare in-hospital outcomes after umbilical cord milking vs delayed cord clamping among infants <29 weeks of gestation.

Study design Multicenter retrospective study of infants born <29 weeks of gestation from 2016 to 2018 without congenital anomalies who received active treatment at delivery and were exposed to umbilical cord milking or delayed cord clamping. The primary outcome was mortality or severe (grade III or IV) intraventricular hemorrhage (IVH) by 36 weeks of postmenstrual age (PMA). Secondary outcomes assessed at 36 weeks of PMA were mortality, severe IVH, any IVH or mortality, and a composite of mortality or major morbidity. Outcomes were assessed using multivariable regression, incorporating mortality risk factors identified a priori, confounders, and center. A prespecified, exploratory analysis evaluated severe IVH in 2 gestational age strata, 22-24$^{6/7}$ and 25-28$^{6/7}$ weeks.

Results Among 1834 infants, 23.6% were exposed to umbilical cord milking and 76.4% to delayed cord clamping. The primary outcome, mortality or severe IVH, occurred in 21.1% of infants: 28.3% exposed to umbilical cord milking and 19.1% exposed to delayed cord clamping, with an aOR that was similar between groups (aOR 1.45, 95% CI 0.93, 2.26). Infants exposed to umbilical cord milking had higher odds of severe IVH (19.8% umbilical cord milking vs 11.8% delayed cord clamping, aOR 1.70 95% CI 1.20, 2.43), as did the 25-28$^{6/7}$ week stratum (14.8% umbilical cord milking vs 7.4% delayed cord clamping, aOR 1.89 95% CI 1.22, 2.95). Other secondary outcomes were similar between groups.

Conclusions This analysis of extremely preterm infants suggests that delayed cord clamping is the preferred practice for placental transfusion, as umbilical cord milking exposure was associated with an increase in the adverse outcome of severe IVH. *(J Pediatr 2021;232:87-94)*.

Trial registration ClinicalTrials.gov: NCT00063063.

Compared with immediate cord clamping, delayed cord clamping has associated benefit in decreasing mortality, all grades of intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD) in preterm infants.[1,2] Multiple professional organizations endorse at least 30 seconds of delayed cord clamping for preterm infants who do not require resuscitation.[3-6] However, many preterm infants require some intervention to transition to extrauterine life, which may limit opportunities for delayed cord clamping in this population. In such situations, placental transfusion via umbilical cord milking is a potential alternative, as it can be performed quickly and may provide similar benefits.[7]

The majority of trials comparing delayed cord clamping and umbilical cord milking have either concentrated on establishing the safety profile of umbilical cord milking or were powered to determine the effect of umbilical cord milking on initial hematocrit, need for blood transfusions, or hemodynamics.[8-11] Until recently, trials have reported similar rates of IVH after delayed cord clamping and umbilical cord milking.[12-14] The comparative effectiveness of the 2 modes

BPD	Bronchopulmonary dysplasia
GDB	Generic Database
IVH	Intraventricular hemorrhage
NRN	Neonatal Research Network
PMA	Postmenstrual age
PPV	Positive pressure ventilation
ROP	Retinopathy of prematurity

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of placental transfusion remains debatable for some providers, and favorable results from small trials have led to continued use of umbilical cord milking in clinical practice despite current recommendations.[15] In 2019, a multicenter trial was stopped early due to increased rates of severe IVH among infants exposed to umbilical cord milking, specifically among infants 23-27 weeks of gestation.[16] Thus, additional studies assessing the potential benefits or harm after exposure to umbilical cord milking are needed.

The objective of our retrospective study was to compare the risk-adjusted rates of mortality or severe IVH by 36 weeks of postmenstrual age (PMA) after umbilical cord milking vs delayed cord clamping among infants born <29 weeks of gestation in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN). In addition, we performed a prespecified, exploratory analysis evaluating severe IVH in 2 gestational age strata, 22-24$^{6/7}$ and 25-28$^{6/7}$ weeks.

Methods

This was a retrospective analysis of prospectively collected data from the NRN Generic Database (GDB). The cohort includes infants born between 22$^{0/7}$and 28$^{6/7}$ weeks of gestation in NRN centers from January 1, 2016 to December 31, 2018. Each participating center obtained institutional review board approval for the NRN GDB registry. Based on the study objective to compare the 2 modes of placental transfusion, infants exposed to immediate cord clamping were not included in the analysis. The exclusion criteria were infants with missing exposure documentation; infants with severe congenital malformations, including those with congenital heart disease and/or genetic syndromes; infants who were alive at birth but did not receive active treatment in the form of ventilatory support, including continuous positive airway pressure, positive pressure ventilation (PPV), intubation, chest compressions or epinephrine administration, surfactant therapy or mechanical ventilation and parental nutrition after delivery as previously defined by Rysavy et al[17]; and infants with documented exposure to both delayed cord clamping and umbilical cord milking.

The NRN GDB collects demographic, maternal, and neonatal information from birth until death, hospital discharge, or 120 days postnatal age using prespecified definitions.[18,19] Antenatal steroid exposure was defined as the administration of at least 1 dose of any corticosteroid (dexamethasone or betamethasone) given during the present pregnancy. Pregnancy induced hypertension was defined as maternal blood pressure >140 systolic or 90 diastolic. Rupture of membranes before onset of labor was defined as preterm premature rupture of membranes and rupture of membranes >8 hours was defined as prolonged rupture of membranes. Antepartum hemorrhage included placental previa, abruption, or threatened abortion resulting in bleeding after 20 weeks. Gestational age was determined by best obstetric estimate based on ultrasonography and/or the date of the last menstrual period. Hypothermia was defined as temperature <36°C. The Papile criteria were used to classify IVH, and severe IVH was defined as grade III and IV.[20] Cranial ultrasound performed closest to 36 weeks of PMA was used to diagnose cystic periventricular leukomalacia, which was defined by the presence of cystic echolucencies in the periventricular white matter, and ventriculomegaly, which was defined by the presence of enlarged ventricles. Severe brain injury was defined as presence of severe IVH, cystic periventricular leukomalacia, porencephalic cyst, or ventriculomegaly diagnosed on cranial ultrasound by the radiologist at each NRN center. Necrotizing enterocolitis was defined as modified Bells stage IIA or greater.[21] BPD was limited to grade 3 BPD, infants requiring invasive mechanical ventilation at 36 weeks of PMA as defined by Jensen et al.[22] This definition was chosen to identify infants with BPD severity that is most closely associated with death or serious respiratory morbidity. Late onset sepsis (≥72 postnatal hours) was defined by positive blood culture for bacteria or fungi and antibiotic therapy for greater than or equal to 5 days or intent to treat but death occurring before 5 days.[23,24] Severe retinopathy of prematurity (ROP) was defined as stage 4 disease or greater with 'plus' disease or ROP receiving treatment.[25]

The exposure of interest was umbilical cord milking and delayed cord-clamping exposure served as the reference group. Both were identified in the GDB registry using 2 yes/no questions: Is there documentation of cord milking; and is there documentation of at least 30 seconds of delayed cord clamping?

The primary outcome was a composite outcome of mortality or severe IVH by 36 weeks of PMA. Secondary outcomes were mortality by 36 weeks of PMA; severe IVH in those surviving to 36 weeks of PMA; any grade IVH or mortality by 36 weeks of PMA; and a composite outcome of mortality or major morbidity diagnosed by 36 weeks of PMA. Major morbidity was defined as severe brain injury, NEC, late onset sepsis, grade 3 BPD, or severe ROP.

Statistical Analyses

The NRN Data Coordinating Center (RTI International) performed the statistical analysis using the R statistical software v 3.5.1 (Feather Spray). Statistical significance was established at P values of <.05. Exposure data were missing for <1% of the cohort which was handled using complete case analysis. Baseline maternal and neonatal characteristics were compared between infants exposed to umbilical cord milking vs delayed cord clamping using t tests for continuous variables and the Fisher exact test for categorical variables. The risk-adjusted association of each mode of placental transfusion with each outcome was assessed using multivariable logistic regression. The following variables were incorporated into the final regression model risk factors for mortality identified a priori: sex, gestational age (in weeks), antenatal steroid exposure (no antenatal steroids or any antenatal steroids), and birth resuscitation (PPV, intubation in

the delivery room, chest compressions, and/or epinephrine administration)[19,26,27]; covariates that were statistically significantly imbalanced between the groups; and NRN center as a random effect.

A prespecified, exploratory analysis evaluated severe IVH in 2 gestational age strata, 22-24$^{6/7}$ and 25-28$^{6/7}$ weeks. Based on the publication of an interim study, a post-hoc, stratified analysis was conducted to understand the effect of mode of delivery and chorioamnionitis on the primary outcome of mortality or severe IVH by 36 weeks of PMA.[16]

Results

Between January 1, 2016 and December 31, 2018, 5332 infants 22$^{0/7}$-28$^{6/7}$ weeks of gestation were born in participating NRN centers and 2514 infants were exposed to placental transfusion. After applying the exclusion criteria, 1834 were included in the final analysis, of which 23.6% (n = 432) were exposed to umbilical cord milking and 76.4% (n = 1402) were exposed to delayed cord clamping (**Figure 1**). Between 2016 and 2018, delayed cord clamping was the primary mode of placental transfusion in the majority of centers (**Figure 2**). Maternal and neonatal characteristics that differed between the 2 groups were race, maternal insurance, preterm premature rupture of membranes, maternal antibiotics, antepartum hemorrhage, mode of delivery, multiples, Apgar score of ≤4 at 5 minutes, PPV, intubation, chest compressions, epinephrine, hypothermia on admission, and surfactant (**Table I**).

Primary and Secondary Outcomes

The adjusted odds of mortality or severe IVH by 36 weeks of PMA were not statistically different between the 2 groups (aOR 1.45, 95% CI 0.93, 2.26) (**Table II**). Infants exposed to umbilical cord milking had increased odds of severe IVH by 36 weeks of PMA compared with infants exposed to delayed cord clamping (aOR 1.70, 95% CI 1.20, 2.43). The rates for the secondary composite outcome of mortality or major morbidity by 36 weeks PMA were not statistically different (75.1% in the umbilical cord milking group and 57.3% in the delayed cord clamping group [aOR 1.16, 95% CI 0.71, 1.89]). The adjusted odds of the remaining secondary outcomes were also not significantly different (**Table II**). There was a significant interaction (P = .001) by gestational age between umbilical cord milking or delayed cord clamping and the composite outcome of mortality or major morbidity (**Figure 3**; available at www.jpeds.com). The interaction by gestational age reflects infants ≥24 weeks of gestation as none of the 22-week gestational age infants were exposed to umbilical cord milking and 100% of 23-week gestational age infants exposed to umbilical cord milking suffered from mortality or a major morbidity.

In our cohort there were no 22-week gestational age infants exposed to umbilical cord milking. Beginning at 23 weeks of gestational age, infants exposed to umbilical cord milking had higher rates of severe IVH compared with those exposed to delayed cord clamping (**Table III**; available at www.jpeds.com). In the 25-28$^{6/7}$-week stratum, infants exposed to umbilical cord milking had 2 times higher rates of severe IVH than infants exposed to delayed cord clamping (14.8% vs 7.3%, aOR 1.89 95% CI 1.22, 2.95) (**Table II**). There was not a significant difference in the odds of severe IVH in the younger gestational age stratum (aOR 1.19 95% CI 0.65, 2.19).

An interim publication suggested an association of both mode of delivery and chorioamnionitis with severe IVH.[16] Therefore, the associations of both were assessed in a post-hoc analysis. The mode of delivery (aOR 1.26 95% CI 0.70, 2.28) and presence of maternal chorioamnionitis (aOR 1.20 95% CI 0.77, 1.89) were not associated with mortality or severe IVH by 36 weeks of PMA among infants exposed to umbilical cord milking (**Table IV**; available at www.jpeds.com).

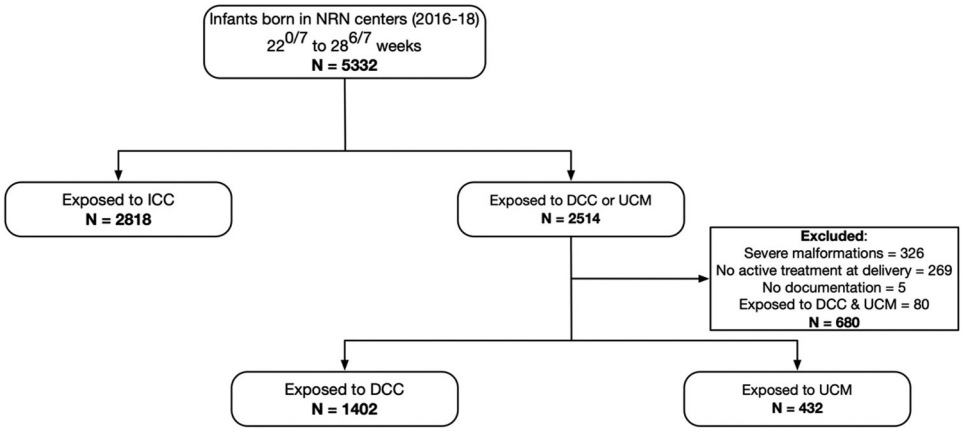

Figure 1. Study flow diagram. *DCC*, delayed cord clamping; *ICC*, immediate cord clamping; *UCM*, umbilical cord milking.

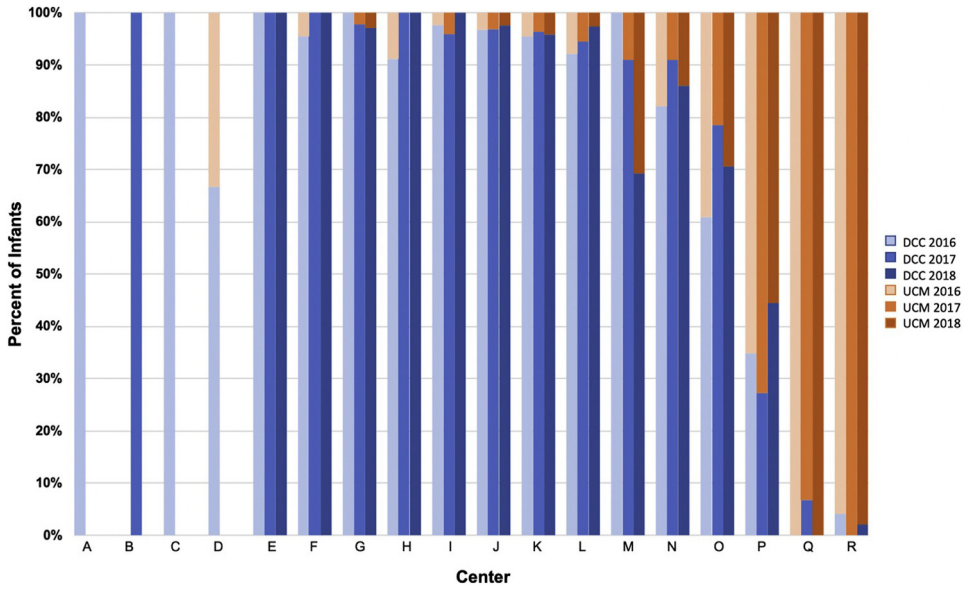

Figure 2. Number of infants exposed to delayed cord clamping or umbilical cord milking per year (2016-2018) by center. The y-axis shows percentage of preterm infants exposed to delayed cord clamping (*blue*) or umbilical cord milking (*orange*) and the x-axis shows the NRN centers. The years are differentiated by the shading, which gets darker with each subsequent year (eg, light blue represents the number of infants exposed to delayed cord clamping in 2016 and the darkest blue the number of infants exposed to delayed cord clamping in 2018). Centers A, B, C, and D were no longer a part of the NRN centers in 2017 and 2018.

Discussion

In this large, contemporary, observational study, umbilical cord milking was not associated with the primary outcome of mortality or severe IVH by 36 weeks of PMA but was associated with higher odds of the secondary outcome of severe IVH. These results are similar to the large randomized trial comparing delayed cord clamping and umbilical cord milking, which favored delayed cord clamping.[16] Over the past 3 years in the NRN, delayed cord clamping was the more frequently used mode of placental transfusion, as may be expected based on professional organizational guidelines.[3-6]

We previously reported that compared with immediate cord clamping, infants exposed to any mode of placental transfusion had a lower odds of mortality.[28] The current study was motivated by the need to differentiate between the outcomes of infants exposed to delayed cord clamping vs umbilical cord milking. Although we did not find an association with the composite outcome of mortality or severe IVH, the key finding of the current study was a statistically significant and clinically relevant increased odds of severe IVH following umbilical cord milking exposure. This signal persisted in the stratified analysis of infants $25^{0/7}$-$28^{6/7}$ weeks but not in the $22^{0/7}$-$24^{6/7}$-week subgroup. The high rate of severe IVH among infants in the $22^{0/7}$-$24^{6/7}$-week subgroup, regardless of exposure to umbilical cord milking or delayed cord clamping, in combination with the small sample size (n = 400) may have contributed to our inability to detect a difference in this stratum. Findings from our observational study are similar to the results of a recent trial comparing the 2 placental transfusion modalities, which was stopped early due to high rates of severe IVH among infants randomized to umbilical cord milking.[16] In addition, these findings parallel those reported in the Canadian Neonatal Network, which similarly found higher rates of severe IVH among infants exposed to umbilical cord milking compared with delayed cord clamping.[29]

In our cohort, 13% of infants had severe IVH, which is similar to the previously reported rates of 16% among extremely premature infants.[30,31] As expected, rates of severe IVH were higher among infants with lower gestational age (**Table III**). The inverse relationship between gestational age and severe IVH risk has been attributed to limited cerebral autoregulation, capillary fragility, and fluctuations in cerebral blood flow.[32] Animal data show that umbilical cord milking causes large oscillating swings in both arterial pressure and cerebral blood flow, further increasing fluctuations in cerebral perfusion.[33] The combination of extreme immaturity and large oscillating swings in arterial pressure and cerebral blood flow secondary to umbilical cord milking are likely contributing to the increase in severe IVH.

The majority of trials comparing umbilical cord milking and delayed cord clamping have either concentrated on establishing the safety profile for umbilical cord milking or were powered to determine the effect on hemodynamics.[8-11] Four trials that assessed IVH as an outcome were small, with a median enrollment of 106 infants (range 40-474).[12-16] The largest trial was prematurely stopped after enrolling 474 of the planned 1500 infants because of increased rates of severe IVH in the umbilical cord milking group.[16] Although not a

Table I. Maternal and neonatal characteristics

Characteristics	Umbilical cord milking (n = 432)	Delayed cord clamping (n = 1402)	*P* value*
Maternal characteristics			
Maternal age (y), mean (SD)	28.8 (5.7)	28.4 (6.1)	.17
Race/ethnicity			<.0001
Black, non-Hispanic	31 (7.2%)	569 (40.6%)	
White, non-Hispanic	252 (58.5%)	592 (42.3%)	
Hispanic	93 (21.6%)	153 (10.9%)	
Asian	24 (5.6%)	51 (3.6%)	
Other	29 (6.7%)	26 (1.9%)	
Unknown/not reported	2 (0.5%)	10 (0.7%)	
Maternal insurance			<.0001
Private	620 (44.29%)	241 (55.79%)	
Public	744 (53.14%)	148 (34.26%)	
Other	36 (2.57%)	43 (9.95%)	
Limited or no prenatal care	37 (8.6%)	150 (10.7%)	.24
Received antenatal steroids†	416 (96.3%)	1359 (97.1%)	.42
No steroids	16 (3.7%)	40 (2.9%)	.58
Partial steroid course	96 (22.4%)	304 (21.8%)	
Complete steroid course	317 (73.9%)	1054 (75.4%)	
Antenatal $MgSo_4$	398 (92.1%)	1281 (91.6%)	.77
Diabetes prior to pregnancy	20 (4.6%)	48 (3.5%)	.31
Gestational diabetes	20 (4.7%)	69 (5.0%)	.90
Hypertension during pregnancy	112 (25.9%)	414 (29.6%)	.16
Pregnancy induced hypertension	64 (14.8%)	229 (16.3%)	.50
Preterm premature rupture of membranes	200 (46.6%)	739 (53.0%)	.02
Prolonged rupture of membranes	117 (27.3%)	390 (28.0%)	.81
Chorioamnionitis	194 (44.9%)	712 (50.8%)	.04
Maternal antibiotics	385 (89.1%)	1139 (81.4%)	<.001
Antepartum hemorrhage	116 (26.9%)	220 (15.8%)	<.0001
Cesarean delivery	320 (74.1%)	843 (60.1%)	<.0001
Neonatal characteristics			
Gestational age (wk)			.91
22 wk	0 (0%)	39 (2.8%)	
23 wk	43 (10%)	99 (7.1%)	
24 wk	54 (12.5%)	165 (11.8%)	
25 wk	71 (16.4%)	202 (14.4%)	
26 wk	64 (14.8%)	251 (17.9%)	
27 wk	84 (19.4%)	284 (20.3%)	
28 wk	116 (26.9%)	362 (25.8%)	
Gestational age in wk (continuous), mean (SD)	26.5 (1.7)	26.4 (1.7)	.94
Multiples	143 (33.1%)	340 (24.3%)	<.001
Birth weight (g), mean (SD)	880.5 (247.9)	873.1 (247.2)	.65
SGA	37 (8.6%)	125 (8.9%)	.92
Male	216 (50.0%)	700 (49.9%)	1.0
Apgar scores			
≤4 at 1 min	236 (54.8%)	669 (47.9%)	.01
≤4 at 5 min	82 (19.0%)	208 (14.9%)	.04
Delivery room interventions			
PPV	378 (87.5%)	1103 (78.7%)	<.0001
Intubation	322 (74.5%)	723 (51.6%)	<.0001
Chest compressions	22 (5.1%)	36 (2.6%)	.01
Epinephrine	13 (3.0%)	21 (1.5%)	.06
Admission temperature (°C)	36.5 (0.7)	36.7 (0.7)	<.0001
Hypothermia on admission	68 (16.0%)	159 (11.4%)	.01
Surfactant	359 (84.9%)	1011 (73.0%)	<.0001

SGA, small for gestational age.
Data presented as % for categorical variables and mean (SD) for continuous variables.
**P* values based on *t* test/Wilcoxon rank-sum test for continuous variables and Fischer exact test for 2-level categorical variables, and for multilevel categorical variables a Cochran-Mantel-Haenszel mean score test using rank scores performed.
†Data for antenatal steroid subgroup missing for one infant in the umbilical cord milking exposed group.

clinical trial, our study adds to the growing body of evidence for delayed cord clamping over umbilical cord milking as the preferred method of placental transfusion. Compared with delayed cord clamping, umbilical cord milking allows for quick placental transfusion to initiate resuscitation soon after birth. However, the potential for neurologic injury and harm associated with umbilical cord milking may outweigh the benefits of early resuscitation. In addition, trials across the world are examining the ability to perform delayed cord clamping with concurrent resuscitation (eg, VentFirst NCT02742454, Baby DUCC Australian Trial Registry 1261800621213). If feasible and successful, these trials may provide further support for delayed cord clamping as the optimal approach to placental transfusion.

Despite current recommendations, there was some variation in the application of approaches to cord management and placental transfusion over the study period (**Figure 2**). Two centers used umbilical cord milking as their primary mode of placental transfusion, whereas most other centers used delayed cord clamping. These data were collected before 2019 and we hypothesize that placental transfusion across NRN centers today may be changing in response to the increasing evidence of harm after exposure to umbilical cord milking. Neurocentric care practices for extremely preterm infants vary between units, which may also influence outcomes.[34] To account for unmeasured differences, we included center as a random effect in our model; however, by itself it is unlikely to account for all variations in clinical practice which may contribute to our findings.

We pursued a post-hoc analysis to examine 2 additional risk factors (chorioamnionitis and mode of delivery) associated with severe IVH. A meta-analysis in 2018 reported that chorioamnionitis is a risk factor for IVH.[35] The inflammatory response seen with chorioamnionitis results in an increase of cytokines that cause hemodynamic alterations and systemic vasculitis, which both increase the risk for IVH.[36,37] In our stratified analysis, the presence of chorioamnionitis did not affect the exposure and primary composite outcome relationship. Previous studies have also reported that infants born via vaginal delivery are at increased risk of IVH.[38] A similar stratified analysis found that the mode of delivery had no effect on the relationship between placental transfusion and the primary composite outcome. This study was not powered for these analyses, and we examined the primary composite outcome, not severe IVH alone, both of which may contribute to the absence of a detectable association.

This study has the following limitations. Retrospective studies are subject to inherent methodologic limitations leading to unmeasured covariate imbalances and nondifferential biases, which cannot be corrected in the analysis. Therefore, this observational study cannot infer causation; however, it does demonstrate an association between umbilical cord milking exposure and severe IVH.

Table II. Neonatal outcomes among infants exposed to umbilical cord milking vs delayed cord clamping

Outcomes	Umbilical cord milking (n = 432)	Delayed cord clamping (n = 1402)	aOR (95% CI)
Primary outcomes			
Composite of mortality or severe IVH at 36 wk of PMA	122 (28.3%)	266 (19.1%)	1.45 (0.93, 2.26)
Secondary outcomes			
Mortality by 36 wk of PMA	63 (14.6%)	153 (10.9%)	0.98 (0.52, 1.83)
Severe IVH by 36 wk of PMA	82 (19.8%)	159 (11.8%)	1.70 (1.20, 2.43)
Severe IVH among 22-24 wk (n = 400)	34 (38.2%)	80 (28.9%)	1.19 (0.65, 2.19)
Severe IVH among 25-28 wk (n = 1434)	48 (14.8%)	79 (7.4%)	1.89 (1.22, 2.95)
Any IVH or mortality by 36 wk of PMA	188 (43.6%)	466 (33.5%)	1.01 (0.45, 1.59)
Composite of mortality or major morbidity by 36 wk of PMA*	319 (75.1%)	774 (57.3%)	1.16 (0.71, 1.89)
Other outcomes			
Death <12 h	9 (2.1%)	17 (1.2%)	1.47 (0.40, 5.39)
Hypotension therapy or mortality in 12 h	144 (33.3%)	250 (17.8%)	1.31 (0.73, 2.36)
Other outcomes, restricted to survivors of first 12 h			
Severe brain injury			
Severe IVH	82 (19.8%)	159 (11.8%)	1.66 (1.07, 2.55)
Cystic PVL	21 (5.1%)	48 (3.5%)	1.45 (0.80, 2.65)
Porencephalic cyst	11 (2.6%)	21 (1.5%)	1.35 (0.53, 3.43)
Ventriculomegaly	44 (10.4%)	94 (6.8%)	1.45 (0.94, 2.24)
NEC†	38 (9.0%)	121 (8.7%)	1.04 (0.57, 1.90)
Severe BPD	221 (60.7%)	541 (44.1%)	1.17 (0.71, 1.91)
Late onset sepsis	68 (16.1%)	232 (16.8%)	0.94 (0.64, 1.38)
Severe ROP‡	30 (8.4%)	99 (8.2%)	0.86 (0.35, 2.12)
Length of stay mean (SD)	86 (19.1)	82 (19.9)	0.62 (−2.94, 4.18)

NEC, necrotizing enterocolitis; *PVL*, periventricular leukomalacia.
Data presented as n (%) for categorical variables and mean (SD) for continuous variables.
Variables in the model include gestational age, male, multiples, antenatal steroids (no antenatal steroid exposure or any antenatal steroid exposure), PPV, intubation, chest compressions and/or epinephrine, race, maternal insurance, preterm premature rupture of membranes, maternal antibiotics, antepartum hemorrhage, mode of delivery, hypothermia on admission, surfactant, and center as random effect.
*Morbidities include severe brain injury, NEC, grade 3 BPD, late onset sepsis, and severe ROP.
†NEC stage II or greater.
‡Severe ROP (stage 4 or requiring treatment).

Differences in the 5-minute Apgar scores in our bivariate analysis suggest that the subset of infants exposed to umbilical cord milking required more resuscitation and may have been exposed to umbilical cord milking to expedite initiation of resuscitation. This scenario leads to confounding by indication, or treatment-selection bias, which could persist despite model adjustments and influence study results.[39] Although missing data in the GDB is quite low, infants with incomplete data (eg, missing exposure or outcome data) were excluded which leads to selection bias. Another limitation of the dataset is the lack of granular data surrounding placental transfusion; details regarding the duration of the delay, type of umbilical cord milking (intact vs cut), the number of times the cord was milked, or timing of the onset of infant breathing are not available. The umbilical cord milking group was much smaller than the delayed cord clamping group and such comparisons are subject to type 1 error. Finally, large databases that use data from multiple centers highlight clinical practice variation, which could either exaggerate or mask study findings.

Although using a database has several limitations, it also has several strengths. The NRN GDB is a robust database that includes multiple centers across the US. From 2016 to 2018, the NRN GDB provided 1834 infants for assessment, making this one of the larger studies comparing outcomes following placental transfusion. A recently published retrospective study from the Canadian Neonatal Network included 394 infants in umbilical cord milking group and 4419 in the delayed cord clamping group with similar findings.[29] Although the Canadian Neonatal Network's study reflects a larger cohort, the generalizability differs from this study as it includes infants of <33 weeks of gestational age and the organization and regionalization of extremely preterm care delivery between Canada and the US are not the same. Thus, our findings from the NRN may more accurately reflect outcomes in clinical practice in the US. Previous cohort studies have not exclusively focused on extremely premature infants and randomized trials have inconsistently included infants less than 24 weeks of gestation, populations at high risk for adverse neurologic outcomes. Given that umbilical cord milking exposure was associated with an adverse event as serious as severe IVH, caution should be exercised before considering use of umbilical cord milking as a mode of placental transfusion.

In conclusion, in this large, contemporary, observational study comparing short-term outcomes among infants <29 weeks of gestation following delayed cord clamping or umbilical cord milking exposure, umbilical cord milking was not associated with improvements in the primary composite outcome of mortality or severe IVH and was associated with an increase in the adverse outcome of severe IVH. Although infants exposed to umbilical cord milking were likely sicker, the association of umbilical cord milking with severe IVH is similar to the largest randomized trial comparing delayed cord clamping and umbilical cord milking, which also favored delayed cord clamping. Results of this study add to

the emerging literature surrounding placental transfusion modalities and outcomes and provide complementary data to published clinical trials. Future studies describing long-term neurodevelopmental outcomes following placental transfusion are required. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

50 Years of Growth in the Assessment of Short Stature

Root AW, Bongiovanni AM, Eberlein WR. Diagnosis and management of growth retardation with special reference to the problem of hypopituitarism. J Pediatr 1971;78:737-53.

Concerns about growth and stature are common indications for referral to pediatric endocrinology. Root et al reviewed the evaluation of short stature, and many aspects of the growth evaluation hold true today. As was described 50 years ago, the assessment of growth aberrations requires accurate plotting of growth data to identify downward trends in growth percentiles. A thorough history and physical examination, and a bone age radiograph, also remain key aspects of the growth evaluation.

The authors described classic growth patterns, including genetic forms of short stature, such as familial short stature, constitutional delay of growth and development, and slow growth with delayed bone age, with or without deviation away from the growth curve, in children with chronic disease. They also described initial laboratory studies to identify causes of slowed growth and provided details about growth hormone (GH) stimulation testing. The gold standard for GH stimulation remains insulin-induced hypoglycemia; however, given the risks of severe hypoglycemia and the availability of alternative provocative agents, it is used less frequently than in the past. Once GH insufficiency is identified, screening for additional pituitary hormone deficiencies is necessary. An addition to the workup for GH insufficiency is MRI of the brain to identify anatomic causes.

The most significant development in treatment of short stature has been the pharmaceutical production of recombinant human GH, which began in 1985. Use of cadaver-derived GH was halted in 1985 after identification of transmission of Creutzfeldt-Jakob disease in patients who received cadaveric GH.[1] The widespread availability of recombinant human GH, free of the risk of disease transmission, has expanded GH treatment to groups beyond those with hypopituitarism.

The diagnostic evaluation of short stature has expanded significantly over the past 50 years with extensive genetic studies to identify syndromic and nonsyndromic causes of short stature. Testing and treatments will continue to advance with a better understanding of the genetics of growth. However, as recognized in 1971, a thorough examination and an assessment of the growth chart remain cornerstones of the growth evaluation.

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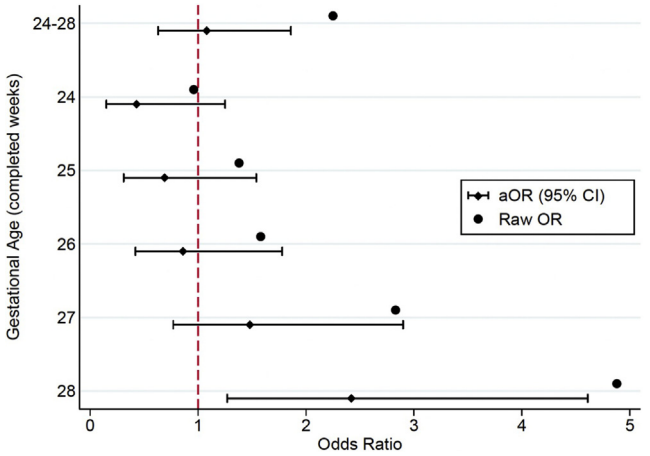

Figure 3. Raw and aOR for mortality or severe morbidity by gestational age. Variables in the model include sex, antenatal steroids, PPV, intubation, resuscitation (PPV, intubation, chest compressions, and/or epinephrine), race, 1-minute Apgar ≤4, antenatal hemorrhage, cesarean delivery, the interaction of gestational age and exposure to delayed cord clamping or umbilical cord milking, and center as a random effect. Only infants ≥24 weeks of gestation were included in the model as there were no 22-week infants exposed to umbilical cord milking and 100% of 23-week infants exposed to umbilical cord milking experienced mortality or major morbidity. The 4 sites (A-D in **Figure 1**) that did not have exposed infants all three years were excluded from the model.

Table III. Severe IVH stratified by gestational age and exposure

	Infant exposed to umbilical cord milking (n = 432)		Infants exposed to delayed cord clamping (n = 1402)	
Gestational age	Severe IVH (n = 82)	No severe IVH (n = 332)	Severe IVH (n = 159)	No severe IVH (n = 1192)
22 wk	0 (NA)	0 (NA)	10 (27.0%)	27 (73.0%)
23 wk	21 (52.5%)	19 (47.5%)	35 (40.2%)	52 (59.7%)
24 wk	13 (26.5%)	36 (73.5%)	35 (23.0%)	118 (77.0%)
25 wk	16 (22.5%)	55 (77.5%)	27 (13.8%)	169 (86.2%)
26 wk	14 (22.2%)	49 (77.8%)	26 (10.7%)	217 (89.3%)
27 wk	6 (7.9%)	70 (92.1%)	16 (5.7%)	263 (94.3%)
28 wk	12 (10.4%)	103 (89.6%)	10 (2.8%)	346 (97.2%)

Data presented as n (%) for categorical variables.

Table IV. Stratified analysis by mode of delivery and chorioamnionitis

Characteristics	Umbilical cord milking (n = 432)	Delayed cord clamping (n = 1402)	aOR (95% CI)	*P* value	*P* for interaction
Mode of delivery					
Cesarean delivery	320 (74.1%)	843 (60.1%)	1.26 (0.70, 2.28)	.45	.87
Vaginal delivery	112 (25.9%)	559 (39.9%)	1.68 (0.95, 2.97)	.08	
Chorioamnionitis					
Yes	194 (44.9%)	712 (50.8%)	1.20 (0.77, 1.89)	.42	.17
No	238 (55.1%)	690 (49.2%)	1.93 (1.00, 3.73)	.05	

Data presented as n (%) for categorical variables and mean (SD) for continuous variables.
Variables in the model include gestational age, male, multiples, antenatal steroids, PPV, intubation, chest compressions and/epinephrine, race, maternal insurance, preterm premature rupture of membranes, maternal antibiotics, antepartum hemorrhage, mode of delivery, hypothermia on admission, surfactant, and center as random effect.