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

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Abstract

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

Study design: Multicenter retrospective study of infants born <29 weeks' gestation from 2016 to 2018 without congenital anomalies who received active treatment at delivery and were exposed

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Portions of this study were presented at the Pediatric Academic Societies webinar series, June 19, 2020 (virtual).

Data Sharing: Data reported in this paper may be requested through a data use agreement. Further details are available at https://neonatal.rti.org/index.cfm?fuseaction=DataRequest.Home.

to UCM or DCC. The primary outcome was mortality or severe (grade III or IV) intraventricular hemorrhage (IVH) by 36 weeks postmenstrual age (PMA). Secondary outcomes assessed at 36 weeks 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 two GA strata, 22-24$^{6/7}$ and 25-28$^{6/7}$ weeks.

Results: Among 1,834 infants, 23.6% were exposed to UCM and 76.4% to DCC. The primary outcome, mortality or severe IVH, occurred in 21.1% of infants: 28.3% exposed to UCM and 19.1% exposed to DCC, with an adjusted odds ratio that was similar between groups (aOR 1.45, 95% CI 0.93, 2.26). UCM exposed infants had higher odds of severe IVH (19.8% UCM vs. 11.8% DCC, aOR 1.70 95% CI 1.20, 2.43), as did the 25-28$^{6/7}$ week stratum (14.8% UCM vs. 7.4% DCC, aOR 1.89 95% CI 1.22, 2.95). Other secondary outcomes were similar between groups.

Conclusion: This analysis of extremely preterm infants suggests that DCC is the preferred practice for placental transfusion, as UCM exposure was associated with an increase in the adverse outcome of severe IVH.

Trial registration—ClinicalTrials.gov: NCT00063063

Keywords

Placental transfusion; Intraventricular hemorrhage; Neonatal Research Network

Compared with immediate cord clamping (ICC), delayed cord clamping (DCC) has associated benefit in decreasing mortality, all grades of IVH, and bronchopulmonary dysplasia (BPD) in preterm infants.(1)(2) Multiple professional organizations endorse at least 30 seconds of DCC 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 DCC in this population. In such situations placental transfusion via umbilical cord milking (UCM) is a potential alternative, as it can be performed quickly and may provide similar benefits.(7)

The majority of trials comparing DCC and UCM have either concentrated on establishing the safety profile of UCM or were powered to determine the effect of UCM on initial hematocrit, need for blood transfusions, or hemodynamics.(8–11) Until recently, trials have reported similar rates of intraventricular hemorrhage (IVH) after DCC and UCM.(12–14) The comparative effectiveness of the two modes of placental transfusion remains debatable for some providers, and favorable results from small trials have led to continued use of UCM 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 UCM, specifically among infants 23-27 weeks' gestation.(16) Thus, additional studies assessing the potential benefits or harm after exposure to UCM are needed.

The objective of our retrospective study was to compare the risk-adjusted rates of mortality or severe IVH by 36 weeks postmenstrual age (PMA) after UCM versus DCC among infants born < 29 weeks' gestation in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN). Additionally, we

performed a prespecified, exploratory analysis evaluating severe IVH in two 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$^{0/7}$-28$^{6/7}$ weeks' gestation in NRN centers from January 1st, 2016 to December 31st, 2018. Each participating center obtained institutional review board approval for the NRN GDB registry. Based on the study objective to compare the two modes of placental transfusion, infants exposed to ICC 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 DCC and UCM.

The NRN GDB collects demographic, maternal, and neonatal information from birth until death, hospital discharge, or 120 days postnatal age using pre-specified definitions. (18–19) Antenatal steroid exposure was defined as the administration of at least one 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 >18 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 degree Celsius. 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 PMA was used to diagnose cystic periventricular leukomalacia (cPVL), 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, cPVL, porencephalic cyst or ventriculomegaly diagnosed on cranial ultrasound by the radiologist at each NRN center. Necrotizing enterocolitis (NEC) was defined as modified Bells stage IIA or greater.(21) Bronchopulmonary dysplasia (BPD) was limited to grade three BPD, infants requiring invasive mechanical ventilation at 36 weeks 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 five days or intent to treat but death occurring before five 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 UCM, and DCC exposure served as the reference group. Both were identified in the GDB registry using two 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' PMA. Secondary outcomes were) mortality by 36 weeks' PMA;) severe IVH in those surviving to 36 weeks' PMA; any grade IVH or mortality by 36 weeks' PMA; and a composite outcome of mortality or major morbidity diagnosed by 36 weeks' 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 version 3.5.1 (Feather Spray, Vienna, Austria). Statistical significance was established at $P < .05$. 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 UCM versus DCC 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, GA (in weeks), ANS 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 two GA 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 PMA.(16)

Results

Between January 1st, 2016 and December 31st, 2018, 5,332 infants 22$^{0/7}$-28$^{6/7}$ weeks' gestation were born in participating NRN centers and 2,514 infants were exposed to placental transfusion. After applying the exclusion criteria, 1,834 were included in the final analysis, of which 23.6% (n=432) were exposed to UCM and 76.4% (n=1,402) were exposed to DCC (Figure 1). Between 2016 to 2018, DCC was the primary mode of placental transfusion in the majority of centers (Figure 2). Maternal and neonatal characteristics that differed between the two groups were: race, maternal insurance, preterm premature rupture of membranes, maternal antibiotics, antepartum hemorrhage, mode of delivery, multiples, Apgar score ≤ 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 PMA were not statistically different between the two groups (aOR 1.45, 95% CI 0.93, 2.26) (Table 2). UCM exposed infants had increased odds of severe IVH by 36 weeks PMA compared with DCC exposed infants (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 UCM group and 57.3% in the DCC group (aOR 1.16, 95% CI 0.71, 1.89)]. The adjusted odds of the remaining secondary outcomes were also not significantly different (Table 2). There was a significant interaction (p = 0.001) by GA between UCM or DCC and the composite outcome of mortality or major morbidity (Figure 3; available at www.jpeds.com). The interaction by GA reflects infants ≥24 weeks gestation as none of the 22-week GA infants were exposed to UCM and 100% of 23-week GA infants exposed to UCM suffered from mortality or a major morbidity.

In our cohort there were no 22-week GA infants exposed to UCM. Beginning at 23 weeks GA, UCM exposed infants had higher rates of severe IVH compared with those exposed to DCC (Table 3; available at www.jpeds.com). In the 25-$28^{6/7}$-week stratum, UCM exposed infants had two times higher rates of severe IVH than infants exposed to DCC, (14.8% versus 7.3%, aOR 1.89 95% CI 1.22, 2.95) (Table 2). There was not a significant difference in the odds of severe IVH in the younger GA 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 PMA among infants exposed to UCM (Table 4; available at www.jpeds.com).

Discussion

In this large, contemporary, observational study, UCM was not associated with the primary outcome of mortality or severe IVH by 36 weeks PMA but was associated with higher odds of the secondary outcome of severe IVH. These results are similar to the large randomized trial comparing DCC and UCM, which favored DCC.(16) Over the past three years in the NRN, DCC 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 ICC, 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 DCC versus UCM. 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 UCM 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 UCM or DCC, 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 two placental transfusion modalities, which was stopped early due to high rates of severe IVH among infants randomized to UCM.(16) Additionally, these findings parallel those reported in the Canadian Neonatal Network, which similarly found higher rates of severe IVH among infants exposed to UCM compared with DCC.(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 3). 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 UCM 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 UCM are likely contributing to the increase in severe IVH.

The majority of trials comparing UCM and DCC have either concentrated on establishing the safety profile for UCM 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 1,500 infants due to increased rates of severe IVH in the UCM group. (16) Although not a clinical trial, our study adds to the growing body of evidence for DCC over UCM as the preferred method of placental transfusion. Compared with DCC, UCM allows for quick placental transfusion in order to initiate resuscitation soon after birth. However, the potential for neurologic injury and harm associated with UCM may outweigh the benefits of early resuscitation. Additionally, trials across the world are examining the ability to perform DCC with concurrent resuscitation (e.g. VentFirst NCT02742454, Baby DUCC Australian Trial Registry 1261800621213). If feasible and successful, these trials may provide further support for DCC 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 UCM as their primary mode of placental transfusion whereas most other centers used DCC. 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 UCM. Neuro-centric 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 methodological limitations leading to unmeasured covariate imbalances and non-differential biases which cannot be corrected in the analysis. Therefore, this observational study cannot infer causation; however, it does demonstrate an association between UCM exposure and severe IVH. Differences in the 5-minute Apgar scores in our bivariate analysis suggest that the subset of infants exposed to UCM required more resuscitation and may have been exposed to UCM in order to expediate 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 data missingness 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 UCM (intact vs cut), the number of times the cord was milked or timing of the onset of infant breathing are not available. The UCM group was much smaller than the DCC group and such comparisons are subject to type 1 error. Finally, large databases that utilize data from multiple centers highlight clinical practice variation, which could either exaggerate or mask study findings.

Although utilizing a database has several limitations, it also has several strengths. The NRN GDB is a robust database which includes multiple centers across the United States. From 2016 to 2018, the NRN GDB provided 1,834 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 UCM group and 4,419 in the DCC 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 < 33 weeks GA and the organization and regionalization of extremely preterm care delivery between Canada and the United States are not the same. Thus, our findings from the NRN may more accurately reflect outcomes in clinical practice in the United States. Previous cohort studies have not exclusively focused on extremely premature infants and randomized trials have inconsistently included infants less than 24 weeks' gestation, populations at high risk for adverse neurologic outcomes. Given that UCM exposure was associated with an adverse event as serious as severe IVH, caution should be exercised before considering use of UCM as a mode of placental transfusion.

In conclusion, in this large, contemporary, observational study comparing short-term outcomes among infants < 29 weeks' gestation following DCC or UCM exposure, UCM 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 UCM-exposed infants were likely sicker, the association of UCM with severe IVH is similar to the largest randomized trial comparing DCC and UCM, which also favored DCC. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

GA	gestational age
PMA	postmenstrual age
IVH	intraventricular hemorrhage
aOR	adjusted odds ratio
CI	confidence interval
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
GDB	Generic Database
cPVL	cystic periventricular leukomalacia
BPD	bronchopulmonary dysplasia
NEC	necrotizing enterocolitis
ROP	retinopathy of prematurity

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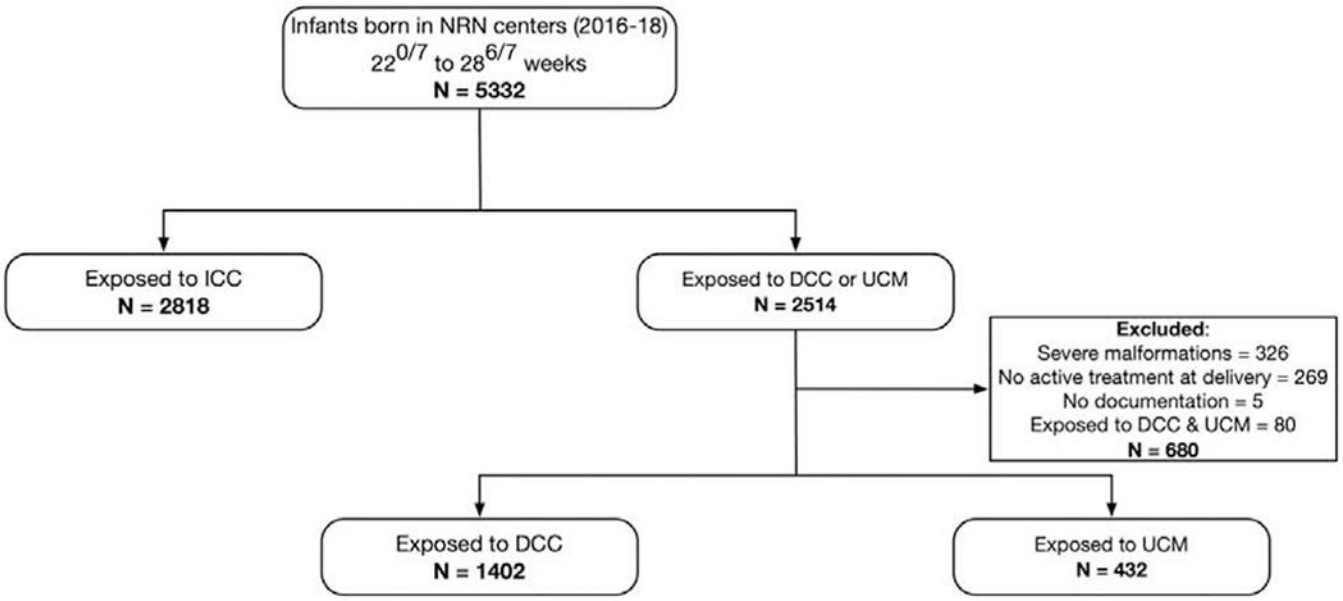

Figure 1. Study Flow Diagram

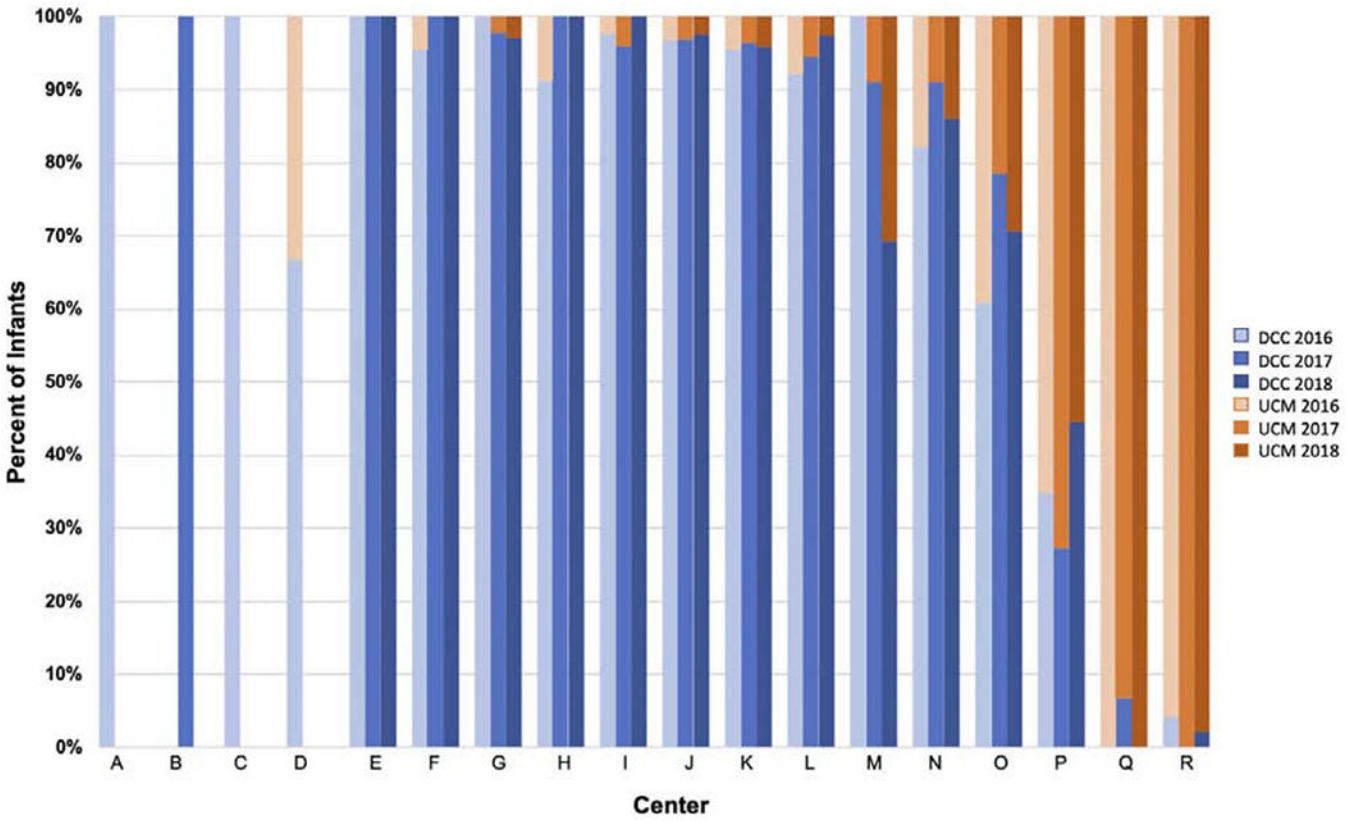

Figure 2. Number of Infants Exposed to DCC or UCM per year (2016-2018) by Center

The y-axis shows percentage of preterm infants exposed to DCC (blue) or UCM (orange) and the x-axis shows the NRN centers. The years are differentiated by the shading which gets darker with each subsequent year (e.g., light blue represents the number of DCC exposed infants in 2016 and the darkest blue the number of DCC exposed infants in 2018). Centers A, B, C, D were no longer a part of the NRN centers in 2017 and 2018.

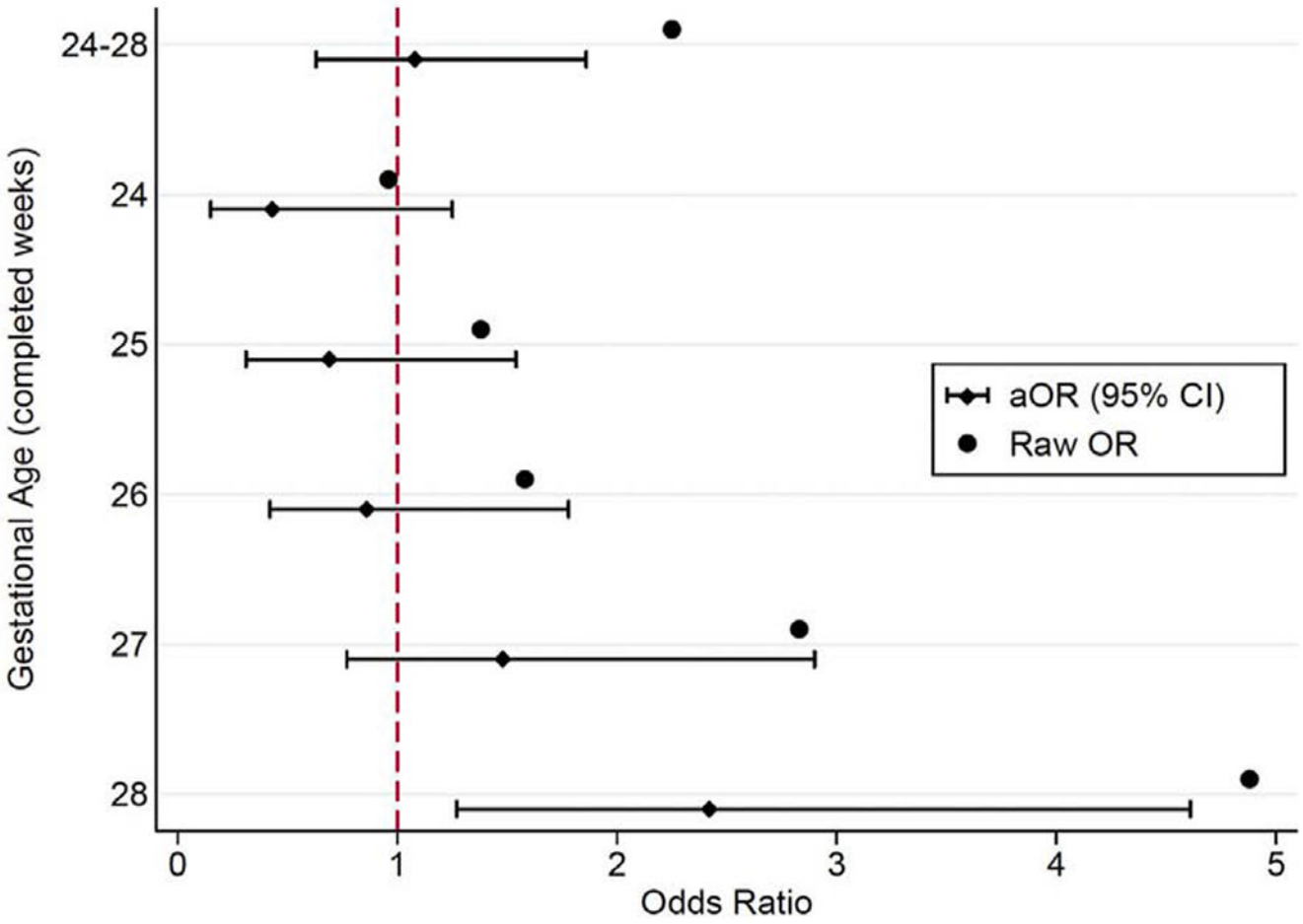

Figure 3. Raw and Adjusted Odds Ratio for Mortality or Severe Morbidity by Gestational Age.

Variables in the model include sex, antenatal steroids, positive pressure ventilation, intubation, resuscitation (PPV, intubation, chest compressions and/or epinephrine), race, 1-minute Apgar < = 4, antenatal hemorrhage, cesarean delivery, the interaction of GA and exposure to DCC or UCM, and center as a random effect.

Only infants ≥24 weeks gestation were included in the model as there were no 22-week infants exposed to UCM and 100% of 23-week infants exposed to UCM experienced mortality or major morbidity.

The four sites (A-D in Figure 1) that did not have exposed infants all three years were excluded from the model.

Table 1:

Maternal and Neonatal Characteristics

Characteristics	UCM (N = 432)	DCC (N = 1402)	*p value* *
Maternal characteristics			
Maternal age (years), mean (SD)	28.8 (5.7)	28.4 (6.1)	0.17
Race/Ethnicity			< 0.0001
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			< 0.0001
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%)	0.24
Received antenatal steroids **	416 (96.3%)	1359 (97.1%)	0.42
No steroids	16 (3.7%)	40 (2.9%)	0.58
Partial steroid course	96 (22.4%)	304 (21.8%)	
Complete steroid course	317 (73.9%)	1054 (75.4%)	
Antenatal MgSo4	398 (92.1%)	1281 (91.6%)	0.77
Diabetes prior to pregnancy	20 (4.6%)	48 (3.5%)	0.31
Gestational diabetes	20 (4.7%)	69 (5.0%)	0.90
Hypertension during pregnancy	112 (25.9%)	414 (29.6%)	0.16
Pregnancy induced hypertension	64 (14.8%)	229 (16.3%)	0.50
Preterm premature rupture of membranes	200 (46.6%)	739 (53.0%)	0.02
Prolonged rupture of membranes	117 (27.3%)	390 (28.0%)	0.81
Chorioamnionitis	194 (44.9%)	712 (50.8%)	0.04
Maternal antibiotics	385 (89.1%)	1139 (81.4%)	< 0.001
Antepartum hemorrhage	116 (26.9%)	220 (15.8%)	< 0.0001
Cesarean delivery	320 (74.1%)	843 (60.1%)	<0.0001
Neonatal characteristics			
Gestational age (weeks)			0.91
22 weeks	0 (0%)	39 (2.8%)	
23 weeks	43 (10%)	99 (7.1%)	
24 weeks	54 (12.5%)	165 (11.8%)	
25 weeks	71 (16.4%)	202 (14.4%)	
26 weeks	64 (14.8%)	251 (17.9%)	

Characteristics	UCM (N = 432)	DCC (N = 1402)	*p value**
27 weeks	84 (19.4%)	284 (20.3%)	
28 weeks	116 (26.9%)	362 (25.8%)	
GA in weeks (continuous), mean (SD)	26.5 (1.7)	26.4 (1.7)	0.94
Multiples	143 (33.1%)	340 (24.3%%)	<0.001
Birth weight (grams), mean (SD)	880.5 (247.9)	873.1(247.2)	0.65
SGA	37 (8.6%)	125 (8.9%)	0.92
Male	216 (50.0%)	700 (49.9%)	1.0
Apgar scores			
≤4 at 1 minute	236 (54.8%)	669 (47.9%)	0.01
≤4 at 5 minutes	82 (19.0%)	208 (14.9%)	0.04
Delivery room interventions			
PPV	378 (87.5%)	1103 (78.7%)	<0.0001
Intubation	322 (74.5%)	723 (51.6%)	<0.0001
Chest compressions	22 (5.1%)	36 (2.6%)	0.01
Epinephrine	13 (3.0%)	21 (1.5%)	0.06
Admission temperature (degrees Celsius)	36.5 (0.7)	36.7 (0.7)	<0.0001
Hypothermia on admission	68 (16.0%)	159 (11.4%)	0.01
Surfactant	359 (84.9%)	1011 (73.0%)	<0.0001

DCC = Delayed cord clamping, UCM = Umbilical cord milking, SD = Standard deviation, PPV = Positive pressure ventilation, SGA = Small for gestational age.

* p-values based on t-test/Wilcoxon rank sum test for continuous variables and Fischer's exact test for two level categorical variables, and for multi-level categorical variables a Cochran-Mantel-Haenszel mean score test using rank scores performed.

Data presented as % for categorical variables and mean (SD) for continuous variables.

** Data for ANS subgroup missing for one infant in the UCM exposed group.

Table 2:

Neonatal outcomes among infants exposed to UCM versus DCC

Outcomes	UCM (n = 432)	DCC (n = 1402)	Adjusted OR (95% CI)
Primary Outcome			
Composite of mortality or severe IVH at 36 weeks PMA	122 (28.3%)	266 (19.1%)	1.45 (0.93, 2.26)
Secondary Outcomes			
Mortality by 36 weeks PMA	63 (14.6%)	153 (10.9%)	0.98 (0.52, 1.83)
Severe IVH by 36 weeks PMA	82 (19.8%)	159 (11.8%)	1.70 (1.20, 2.43)
Severe IVH among 22-24 weeks (n = 400)	34 (38.2%)	80 (28.9%)	1.19 (0.65, 2.19)
Severe IVH among 25-28 weeks (n = 1434)	48 (14.8%)	79 (7.4%)	1.89 (1.22, 2.95)
Any IVH or mortality by 36 weeks' PMA	188 (43.6%)	466 (33.5%)	1.01 (0.45, 1.59)
Composite of mortality or major morbidity by 36 weeks' PMA *	319 (75.1%)	774 (57.3%)	1.16 (0.71, 1.89)
Other outcomes			
Death < 12 hours	9 (2.1%)	17 (1.2%)	1.47 (0.40, 5.39)
Hypotension therapy or mortality in 12 hours	144 (33.3%)	250 (17.8%)	1.31 (0.73, 2.36)
Other outcomes, restricted to survivors of first 12 hours			
Severe brain iniury			
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)

DCC = Delayed cord clamping, UCM=Umbilical cord milking, BPD Bronchopulmonary dysplasia, IVH = Intraventricular hemorrhage, PVL = Periventricular leukomalacia, NEC = Necrotizing enterocolitis, ROP = retinopathy of prematurity.

Data presented as n (%) for categorical variables and mean (SD) for continuous varables.

Variables in the model include: GA, 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)

Data presented as n (%) for categorical variables and mean (SD) for continuous variables.

Table 3:

Severe IVH stratified by GA and exposure.

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

DCC = delayed cord clamping, UCM = Umbilical cord milking, IVH = Intraventricular hemorrhage

Data presented as n (%) for categorical variables

Table 4:

Stratified analysis by mode of delivery and chorioamnionitis

	UCM (n = 432)	DCC (n = 1402)	aOR (95% CI)	p value	p for interaction
Mode of delivery					
Cesarean	320 (74.1%)	843 (60.1%)	1.26 (0.70, 2.28)	0.45	0.87
Vaginal	112 (25.9%)	559 (39.9%)	1.68 (0.95, 2.97)	0.08	
Chorioamnionitis					
Yes	194 (44.9%)	712 (50.8%)	1.20 (0.77, 1.89)	0.42	0.17
No	238 (55.1%)	690 (49.2%)	1.93 (1.00, 3.73)	0.05	

DCC = Delayed cord clamping, UCM = umbilical cord milking

Data presented as n (%) for categorical variables and mean (SD) for continuous variables.

Variables in the model include: GA, 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.