Effects of Placental Transfusion on Late Preterm Infants Admitted to a Mother Baby Unit

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Abstract

Objective Well-appearing late preterm infants admitted to a mother baby unit may benefit from either delayed cord clamping (DCC) or umbilical cord milking (UCM). However, there are concerns of adverse effects of increased blood volume such as polycythemia and hyperbilirubinemia. The purpose of this study is to examine the short-term effects of placental transfusion on late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation.

Study Design In this pre- and postimplementation retrospective cohort study, we compared late preterm infants who received placental transfusion (161 infants, DCC/UCM group) during a 2-year period after guideline implementation (postimplementation period: August 1, 2017 to July 31, 2019) to infants who had immediate cord clamping (118 infants, ICC group) born during a 2-year period before implementation (preimplementation period: August 1, 2015 to July 31, 2017).

Results The mean hematocrit after birth was significantly higher in the DCC/UCM group. Fewer infants had a hematocrit <40% after birth in the DCC/UCM group compared with the ICC group. The incidence of hyperbilirubinemia needing phototherapy, neonatal intensive care unit (NICU) admissions, or readmissions to the hospital for phototherapy was similar between the groups. Fewer infants in the DCC/UCM group were admitted to the NICU primarily for respiratory distress. Symptomatic polycythemia did not occur in either group. Median hospital length of stay was 3 days for both groups.

Conclusion Placental transfusion (DCC or UCM) in late preterm infants admitted to a mother baby unit was not associated with increased incidence of hyperbilirubinemia needing phototherapy, symptomatic polycythemia, NICU admissions, or readmissions to the hospital for phototherapy.

Keywords
- delayed cord clamping
- umbilical cord milking
- placental transfusion
- hyperbilirubinemia
- phototherapy
- late preterm infants

Key Points

- Placental transfusion was feasible in late preterm infants.
- Placental transfusion resulted in higher mean hematocrit after birth.
- Placental transfusion did not increase the need for phototherapy.
- Fewer admissions to the NICU for respiratory distress were noted in the placental transfusion group.

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The methods, delayed cord clamping (DCC) and umbilical cord milking (UCM), used to increase placental blood transfusion to the newborn are associated with increased hemoglobin levels after birth.[1,2] The result improved iron stores during the first several months of life may lead to a favorable effect on neurodevelopmental outcomes.[3–6] Evidence suggests that umbilical cord clamping should be delayed for at least 1 minute in all births.[7,8] UCM also appears to be safe, especially in a cesarean section scenario, where waiting too long to delay the cord clamping may not be feasible.[9,10]

Previously, published research on DCC has focused either on preterm infants who are admitted to the neonatal intensive care unit (NICU) or healthy term infants. Seldomly, the investigation specifically addressed the effects of placental transfusion on late preterm infants transitioning well in the delivery room and admitted to a mother baby unit.[11,12] These well-appearing infants constitute a majority of preterm births.[13] They may be physically stable, but physiologically and metabolically immature compared with the infants born at term. The late preterm birth has a negative impact on brain development contributing to the future developmental, behavioral, educational, and social disabilities.[14,15] The degree of long-term neurodevelopmental benefits from DCC or UCM in these late preterm infants may be higher or at least comparable to that of healthy term infants. However, there are concerns of short-term adverse effects of increased blood volume such as hyperbilirubinemia and polycythemia contributing to longer hospital length of stay (LOS) or readmission for phototherapy.[16,17]

Previously, our practice of DCC was limited to preterm infants (<35 weeks of gestation) directly admitted to the NICU per hospital policy. After the publication of the updated American College of Obstetrics and Gynecology (ACOG) committee's opinion, we expanded the practice of DCC to include late preterm and term infants who are admitted to the mother baby unit. A guideline was drafted and quality improvement (QI) process implemented at our community hospital starting August 1, 2017. The infants born through vaginal delivery would have DCC performed for at least 3 minutes if placed on mother's abdomen/chest or at least 1 minute if held at or below the level of placenta. The infants born via cesarean section would get UCM performed five times.

The purpose of the present study was to examine the short-term effects of placental transfusion on well-appearing late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation who are admitted to the mother baby unit. We hypothesized that DCC or UCM was safe and not associated with increased incidence of hyperbilirubinemia needing phototherapy, symptomatic polycythemia, and readmission for phototherapy or increased hospital LOS compared with a historic cohort of immediate cord clamping (ICC).

Materials and Methods

Management of Late Preterm Infants Born between $35^{0/7}$ and $36^{6/7}$ Weeks of Gestation

Prior to August 1, 2017, the general obstetric practice was to clamp and cut the umbilical cord without any intentional delay (ICC). After birth, the infant would stay with the mother and admitted to the mother baby unit unless the birth weight was <2 kg. In that case, the newborn would get directly admitted to the NICU per hospital policy. Usual hospital LOS for these late preterm infants was 3 days. NICU admission was needed in approximately 20% of the infants primarily for respiratory distress. A placental transfusion guideline was drafted for these deliveries and QI process implemented starting August 1, 2017. The exclusion criteria for DCC/UCM were severe maternal hemodynamic instability, severe placental abruption, bleeding vasa previa, cord avulsion, true tight knot of umbilical cord, intent to withhold care, severe congenital anomaly, or severe hydrops fetalis.

Procedures: The infant born via vaginal delivery would have DCC performed for at least 3 minutes if placed skin to skin on the mother's abdomen/chest or at least 1 minute if held at or below the level of placenta. The infant born via cesarean section would have intact UCM performed by the obstetric provider. The cord was pinched as close to the placenta as possible with the thumb and index fingers of left hand and milked with the thumb and index fingers of right hand toward the infant over a 2-second duration. The cord was then released at the placental end and allowed to refill with blood for a brief 2-second pause before the next milking motion. This was repeated for a total of five times. After the DCC/UCM, the cord was clamped and cut followed by routine newborn care. Apgar timing was initiated at the time of birth when the infant was delivered completely.

Education was provided to the obstetric and newborn providers and nursing staff by presentations and demonstrations of the procedures in department and staff meetings. An e-mail communication was also sent which included the video of the procedures. Documentation of the placental transfusion procedure was to be entered in the electronic medical record (EMR) by both obstetric providers and nurses. Obstetric providers documented the procedure in the delivery note, whereas there was a specific place in the EMR for nursing documentation. The QI process was monitored regularly and data presented periodically in the department meetings.

Data Collection

The preimplementation period was chosen to be 2 years (August 1, 2015 to July 31, 2017) and the postimplementation period was also 2 years (August 1, 2017 to July 31, 2019). After approval from the local institutional review board, data were extracted from the EMRs of mothers and late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation. Collected data included maternal demographics, obstetric and fetal complications, and maternal outcomes, such as postpartum hemorrhage (>500 mL for a vaginal delivery or >1,000 mL for a cesarean delivery). Neonatal data included gestational age, birth weight, gender, Apgar's scores, and need for continuous positive airway pressure (CPAP) and/or positive pressure ventilation (PPV) in the delivery room. The newborn outcomes of interest included incidence of moderate hypothermia (first axillary temperature taken within

30 minutes after birth <36°C), exclusive breastfeeding at discharge (no formula exposure during the hospital stay), incidence of phototherapy, symptomatic polycythemia, and NICU admission. Hospital LOS and readmission from home within 1 week of discharge for phototherapy were also recorded. The management of hyperbilirubinemia and treatment with phototherapy were based on the American Academy of Pediatrics clinical practice guidelines.[18,19] Symptomatic polycythemia was defined as a central hematocrit of >65% associated with symptoms, such as hypoglycemia, respiratory distress, poor feeding, or lethargy.

Data Analysis

In this pre- and postimplementation retrospective cohort study, two groups from two different study periods were compared. For the purpose of this study, a convenience sample of 100 late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation in each group was deemed appropriate on the basis of our previous study.[20] This sample size was feasible with a 2-year study period for each arm. Continuous data were presented as mean and standard deviation if parametrically distributed or median and range if nonparametric and categorical variables as counts (percent). Data were compared between two groups with the use of two-tailed Student's *t*-test for continuous variables and Pearson's Chi-square test or Fisher's exact test for categorical variables. Data were analyzed by using SPSS version 25 (IBM corporation, Armonk, NY). Statistical significance was set at probability value of <0.05.

Results

During the preimplementation period, out of the 203 infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation, 71 infants had DCC/UCM performed. Hence, they were excluded from the analysis. Fourteen infants excluded were either born with a birth weight <2 kg (7, admitted directly to NICU) or met one of the exclusion criteria (7). The remaining 118 infants were eligible for DCC/UCM, but had ICC performed (ICC group). During the postimplementation period, out of the 198 infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation, 161 infants had DCC/UCM performed (DCC/UCM group). Ten infants were born with a birth weight of <2 kg, and 27 infants had ICC (4 had documented exclusion criteria and 23 had no reason documented). ►**Fig. 1** shows the distribution of study population.

No significant differences were noted either in the maternal characteristics or the incidence of obstetric or fetal complications between the groups (►**Table 1**). The mean difference of hematocrit before and after delivery and the incidence of postpartum hemorrhage were similar between the groups. There were no differences in the newborn characteristics such as gestational age, birth weight, or gender. Apgar's scores and other resuscitation variables,

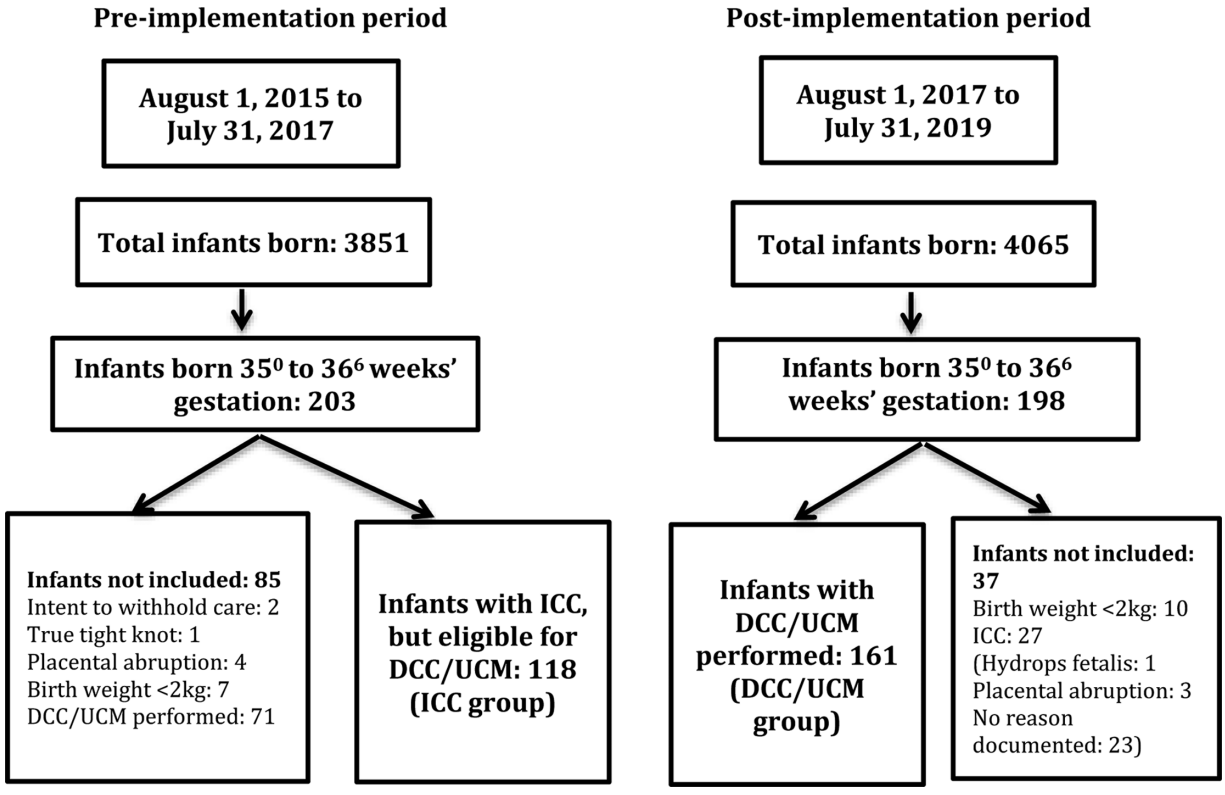

Fig. 1 Distribution of the study groups. During the preimplementation period, out of 203 infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation, 118 were eligible for DCC/UCM, but had ICC performed (ICC group). During the postimplementation period, out of 198 infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation, 161 infants had DCC/UCM performed (DCC/UCM group). DCC, delayed cord clamping; ICC, immediate cord clamping; UCM, umbilical cord milking.

Table 1 Maternal characteristics

Variable, *n* (%)	ICC (*n* = 100)	DCC/UCM (*n* = 140)	*p*-Value
Maternal age (y)[a]	29.0 ± 5.4	26.6 ± 5.5	0.42
Maternal race			0.54
White	89 (89)	116 (82.9)	
Non-White	11 (11)	22 (17.1)	
Primipara	29 (29)	51 (36.4)	0.26
Hypertensive disorders of pregnancy	17 (17)	32 (22.9)	0.27
Maternal diabetes	10 (10)	21 (15)	0.33
Twin gestation	20 (20)	27 (19.3)	>0.99
Fetal distress	6 (6)	17 (12.1)	0.13
Meconium-stained amniotic fluid	3 (3)	5 (3.6)	>0.99
Rupture of membranes ≥18 h	9 (9)	19 (13.6)	0.31
Chorioamnionitis	0 (0)	0 (0)	NA
Cesarean section	52 (52)	59 (42.1)	0.15
Hematocrit change pre- and postdelivery[a]	5.0 ± 3.0	5.1 ± 2.8	0.93
Postpartum hemorrhage	13 (13)	16 (11.4)	0.84

Abbreviations: DCC, delayed cord clamping; ICC, immediate cord clamping; UCM, umbilical cord milking.
[a]Data given as mean ± standard deviation.

such as need for CPAP and/or PPV, were similar between both groups. Moderate hypothermia was not observed in either group. Hematocrit at birth was obtained in 37 infants of ICC group and 59 infants of DCC/UCM group. The mean hematocrit was significantly higher in DCC/UCM group compared with the ICC group. Fewer infants in the DCC/UCM group had hematocrit <40% after birth compared with the ICC group. Symptomatic polycythemia was not noted in either group. There were no significant differences in the incidence of phototherapy, exclusive breastfeeding, or readmission from home for phototherapy. Although there was no difference in the incidence of NICU admission, the need primarily for respiratory distress was significantly lower in the DCC/UCM group. The median hospital LOS was 3 days for both the groups (►Table 2). ►Table 3 depicts the characteristics and outcomes among infants born by twin gestation. Monochorionic twins comprised 16% among ICC group and 28% in DCC/UCM group. Compared with the ICC twin group, DCC/UCM twin group had significantly higher need for CPAP in delivery room. No differences were noted in the incidence of phototherapy or NICU admission. Exclusive breastfeeding was significantly higher in the DCC/UCM twin group compared with the ICC twin group.

Discussion

After the publication of ACOG committee's initial opinion suggesting the single most important clinical benefit of DCC as reduction in intraventricular hemorrhage, the very preterm infants were given priority to receive DCC.[21–23] Similarly, our practice of 60 seconds delay in cord clamping was initially limited to very preterm infants. It was later extended to <35 weeks of gestation which was the threshold of direct NICU admission as per hospital policy.[24] Subsequently, after the publication of updated ACOG committee's opinion recommending DCC in all the births, we further expanded the policy to include the healthy late preterm and term infants directly admitted to the mother baby unit.[8] Because these late preterm infants are at higher risk for hyperbilirubinemia compared with the term infants, there were concerns for increased incidence of phototherapy and longer hospital LOS. Very few small trials specifically addressed the short-term effects of increased blood volume due to placental transfusion in the otherwise healthy late preterm population.[11,12] Therefore, we monitored our data in a quality improvement process and presented the findings in this cohort study. We demonstrated that DCC/UCM in the late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation was feasible, and not associated with increased incidence of phototherapy for hyperbilirubinemia, symptomatic polycythemia, NICU admissions, or readmissions for phototherapy compared with the historic cohort of infants who received ICC.

ACOG recommends a delay in cord clamping of at least 30 to 60 seconds, whereas World Health Organization defines DCC as at least 1 minute.[7,8] In stable late preterm and term infants born by vaginal delivery, a longer delay of at least 3 minutes is needed if placed on mother's abdomen/chest soon after birth.[25] It may take up to three uterine contractions for optimal placental transfusion to occur. There is no rush to cut the cord in these stable infants.[26] Currently, ACOG and other major societies neither support nor refute UCM due to insufficient evidence.[8] In a recently published randomized controlled trial, harm was identified with UCM compared with DCC in extremely preterm infants.[27] However, in multiple studies, UCM has been shown to be safe and beneficial for late preterm and term infants.[9] This

Table 2 Newborn characteristics and outcomes

Variable, *n* (%)	ICC (*n* = 118)	DCC/UCM (*n* = 161)	*p*-Value
Gestational age (wk)[a]	36.1 ± 0.5	36.1 ± 0.6	0.97
Birth weight (g)[a]	2,748.2 ± 396	2,746.1 ± 416	0.97
Female	52 (44.1)	83 (51.6)	0.22
Small for gestational age	3 (2.5)	7 (4.3)	0.50
Apgar's score[b]			
1 min	8 (1–9)	8 (3–9)	0.38
5 min	9 (6–10)	9 (5–9)	0.74
Apgar's score ≤7 at 5 min	4 (3.4)	6 (3.7)	>0.99
Need for CPAP in delivery room	15 (12.7)	13 (8.1)	0.20
Need for PPV in delivery room	2 (1.7)	8 (5.0)	0.20
First temperature after birth (°C)[a]	36.7 ± 0.1	36.7 ± 0.1	0.30
Moderate hypothermia	0 (0)	0 (0)	NA
Hematocrit after birth (%)[a]	47.6 ± 6.2 (*n* = 37)	53.8 ± 6.6 (*n* = 59)	<0.01
Hematocrit <40%	5 (13.5)	1 (1.7)	0.03
Hematocrit >65%	0 (0)	3 (5.1)	0.28
Symptomatic polycythemia	0 (0)	0 (0)	NA
Serum bilirubin at 48 h[a]	9.5 ± 4.0 (*n* = 37)	10.6 ± 3.8 (*n* = 47)	0.24
TCB high intermediate or high risk	37 (31.4)	47 (29.2)	0.75
Phototherapy	15 (12.7)	17 (10.6)	0.58
Exclusive breastfeeding	29 (24.6)	56 (34.8)	0.07
IV dextrose bolus for hypoglycemia	4 (3.4)	5 (3.1)	>0.99
Culture positive sepsis	0 (0)	0 (0)	NA
Need for NICU admission	24 (20.3)	24 (14.9)	0.24
Respiratory distress	20 (83.3)	12 (50)	0.03
Length of hospital stay[b]	3 (1–33)	3 (1–23)	0.08
Readmission for phototherapy	3 (2.5)	2 (1.2)	0.65

Abbreviations: CPAP, continuous positive airway pressure; DCC, delayed cord clamping; ICC, immediate cord clamping; IV, intravenous; PPV, positive pressure ventilation; TCB, transcutaneous bilirubin; UCM, umbilical cord milking.
[a]Data given as mean ± standard deviation.
[b]Data given as median (range).

procedure can be completed in <30 seconds and may be favorable in situations where waiting longer for DCC is not possible, such as cesarean deliveries.[10] Our previous study established the feasibility and safety of UCM in term infants delivered by cesarean section.[20]

In a previously published randomized controlled trial, term infants who received DCC/UCM demonstrated lower residual placental volume and higher hemoglobin levels at 24 to 48 hours of life without an increase in hyperbilirubinemia or symptomatic polycythemia.[2] At 4 months of age, these infants had higher ferritin levels and increased brain myelin in the internal capsule and other early maturing brain regions associated with motor, visual, and sensory processing/function.[6] Extra red blood cells from placental transfusion may provide early critical iron, a necessary component for the maturation and function of myelin producing oligodendrocytes.[28] By improving iron stores during the first several months of life, DCC may prevent iron deficiency anemia and improve neurodevelopmental outcomes.[29,30] As late preterm infants are at a higher risk for iron deficiency anemia, the magnitude of benefits from placental transfusion may be higher or at least comparable to relatively mature term infants.

A large cross-sectional study showed an inverse "dose response" relationship between the developmental delay risk and gestational age at birth. Compared with term infants, late preterm infants had 2.58 times higher odds of developmental delay risk.[31] Evidence suggests that there is a significant measurable difference in brain size, myelination, and gyral folding between late-preterm and term newborns after correcting for gestational age at birth. Relatively immature microstructural cerebral white matter has been reported in preterm infants at term ages compared with term infants.[32] Similar to autologous stem cell transfusion DCC/UCM may offer protection for this immature nervous system and help decrease adverse neurodevelopmental and neurobehavioral outcomes.[33]

Table 3 Newborn characteristics and outcomes among twins

Variable, *n* (%)	ICC (*n* = 38)	DCC/UCM (*n* = 47)	*p*-Value
Gestational age (wk)[a]	36.1 ± 0.4	36.1 ± 0.6	0.71
Birth weight (g)[a]	2,551.2 ± 348	2,525.5 ± 304	0.72
Female	16 (42.1)	29 (61.7)	0.07
Small for gestational age	2 (5.3)	5 (10.6)	0.45
Monochorionic twin	6 (15.8)	13 (27.7)	0.20
Second twin	19 (50)	22 (46.8)	0.78
Cesarean section	32 (84.2)	34 (72.3)	0.30
Apgar's score[b]			
1 min	8 (8–9)	8 (4–9)	0.14
5 min	9 (8–9)	9 (6–9)	0.60
Apgar's score ≤7 at 5 min	0 (0)	2 (4.3)	0.50
Need for CPAP in delivery room	1 (2.6)	8 (17)	0.04
Need for PPV in delivery room	1 (2.6)	5 (10.6)	0.22
First temperature after birth (°C)[a]	36.7 ± 0.1	36.7 ± 0.1	0.50
Hematocrit after birth (%)[a]	46.3 ± 8 (*n* = 3)	55 ± 6 (*n* = 15)	0.03
Serum bilirubin at 48 h[a]	6 ± 2.4 (*n* = 6)	8.1 ± 3 (*n* = 13)	0.11
TCB high intermediate or high risk	6 (15.8)	13 (27.7)	0.20
Phototherapy	0 (0)	1 (2.1)	>0.99
Exclusive breastfeeding	5 (13.2)	15 (31.9)	0.04
Need for NICU admission	2 (5.3)	7 (14.9)	0.20
Respiratory distress	2 (100)	5 (71.4)	0.55
Length of hospital stay[b]	3 (2–6)	3 (2–9)	0.13
Readmission for phototherapy	0 (0)	1 (2.1)	>0.99

Abbreviations: CPAP, continuous positive airway pressure; DCC, delayed cord clamping; ICC, immediate cord clamping; PPV, positive pressure ventilation; TCB, transcutaneous bilirubin; UCM, umbilical cord milking.
[a]Data given as mean ± standard deviation.
[b]Data given as median (range).

Although residual placental blood volume was not measured in the current study, the significant increase in mean hematocrit after birth in the DCC/UCM cohort compared with the ICC cohort suggests placental transfusion. Moreover, fewer infants who received DCC/UCM were born with hematocrit <40% compared with infants with ICC. Low hemoglobin level at birth has been shown to be associated with increased mortality in very preterm infants.[34] In general as late preterm are at increased risk for hyperbilirubinemia compared with term infants, there is a theoretical concern of DCC increasing red blood cell volume and contributing to higher levels of bilirubin needing phototherapy. Our study demonstrated that DCC/UCM performed on the late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation was not associated with a significant increase in serum bilirubin levels at 48 hours or incidence of phototherapy for hyperbilirubinemia. There was a possibility of physiologic increase in bilirubin levels within normal limits due to increased blood volume. This phenomenon has been reported to be neuroprotective than being harmful.[35] In the present study, we did not notice symptomatic polycythemia in either DCC/UCM or ICC groups. Our observation of significantly fewer infants getting admitted to the NICU primarily for respiratory distress supports the reports of better cardiopulmonary transition to extrauterine life among infants receiving DCC/UCM. The easy transition may have resulted in decreased amount of retained lung fluid among these late preterm infants.[36,37] Even though this study establishes the safety of placental transfusion in twin gestation similar to our previous publication on very preterm twins, further research is needed in monochorionic multiple gestations.[38]

This pre- and postimplementation retrospective cohort study is not without limitations. This is not a randomized controlled trial. However, at this time, there is limited equipoise to randomize preterm infants away from placental transfusion. We cannot validate the exact details of the intervention as we depended on the nursing and obstetric provider documentation of cord management. The compliance with the practice of DCC/UCM was excellent, as only 23 infants during postimplementation period had ICC performed without a reason documented. This was possible by multidisciplinary involvement in the QI process and stepwise approach to implementation.[39] DCC/UCM was

performed on 71 infants during the pre-implementation period. Most of these deliveries occurred in the 6-month period between the publication of the updated ACOG committee opinion and our guideline implementation. This could be due to discussions in the department meetings and the belief among the obstetric providers regarding the safety and benefits of the process. In this observational study, neither the residual placental volume was measured nor hematocrit performed on all the well late preterm newborns. Hematocrits were available on the infants who needed complete blood count per guidelines due to risk factors for sepsis.[40] As we tracked readmissions to our hospital only, we could not rule out admissions to other hospitals for problems other than phototherapy, such as sepsis or stroke. Majority of mothers reported their race as white raising a question regarding the generalizability as the study reports observational data from a single community hospital. This study may be underpowered to detect differences in short-term outcomes and not all possible adverse effects of increased blood volume have been reported in this study. However, despite all the limitations, the primary objective of this large cohort study to address the main barriers for placental transfusion was met by reporting our experience with clinically important short-term functional outcomes.

Conclusion

The process of DCC/UCM was feasible and safe in the late preterm infants born between $35^{0/7}$ and $36^{6/7}$ weeks of gestation. Specifically, placental transfusion was not associated with increased incidence of hyperbilirubinemia needing phototherapy, symptomatic polycythemia, hospital LOS, NICU admissions, or readmissions to the hospital for phototherapy compared with the cohort of infants who received ICC. Further studies are needed to report both short- and long-term outcomes of these infants.

Note

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None.

Conflict of Interest

None declared.

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