Enteral Feeding with Human Milk Decreases Time to Discharge in Infants following Gastroschisis Repair

Brian C. Gulack, MD[1,2], Matthew M. Laughon, MD, MPH[3], Reese H. Clark, MD[4], Terrance Burgess, MA Ed[2], Sybil Robinson[2], Abdurrauf Muhammad[2], Angela Zhang[2], Adrienne Davis[2], Robert Morton[2], Vivian H. Chu, MD, MHS[5], Christopher J. Arnold, MD[5], Christoph P. Hornik, MD, MPH[2,6], and P. Brian Smith, MD, MHS, MPH[2,6]

Objective To assess the effect of enteral feeding with human milk on the time from initiation of feeds to discharge after gastroschisis repair through review of a multi-institutional database.

Study design Infants who underwent gastroschisis repair between 1997 and 2012 with data recorded in the Pediatrix Medical Group Clinical Data Warehouse were categorized into 4 groups based on the percentage of days fed human milk out of the number of days fed enterally. Cox proportional hazards regression modeling was performed to determine the adjusted effect of human milk on the time from initiation of feeds to discharge.

Results Among 3082 infants, 659 (21%) were fed human milk on 0% of enteral feeding days, 766 (25%) were fed human milk on 1%-50% of enteral feeding days, 725 (24%) were fed human milk on 51%-99% of enteral feeding days, and 932 (30%) were fed human milk on 100% of enteral feeding days. Following adjustment, being fed human milk on 0% of enteral feeding days was associated with a significantly increased time to discharge compared with being fed human milk on 100% of enteral feeding days (hazard ratio [HR] for discharge per day, 0.46; 95% CI, 0.40-0.52). The same was found for infants fed human milk on 1%-50% of enteral feeding days (HR, 0.37; 95% CI, 0.32-0.41) and for infants fed human milk on 51%-99% of enteral feeding days (HR, 0.51; 95% CI, 0.46-0.57).

Conclusion The use of human milk for enteral feeding of infants following repair of gastroschisis significantly reduces the time to discharge from initiation of feeds. *(J Pediatr 2016;170:85-9)*.

Multiple studies have demonstrated the benefits of human milk over formula for the newborn infant[1,2]; these include improved absorption of nutrients, immunologic defenses, and maternal–infant bonding.[3-5] Such benefits are of great importance in the preterm infant, who is at a much higher risk for a host of complications, including respiratory difficulties, infections, and in-hospital mortality.[6,7] Human milk use is associated with a decreased incidence of necrotizing enterocolitis (NEC), a complication associated with substantial morbidity and mortality.[8]

The incidence of gastroschisis, a congenital defect in the para-umbilical abdominal wall associated with evisceration of abdominal organs, is much higher in preterm infants compared with full-term infants.[9] Previous work has demonstrated that enteral feeding with human milk after gastroschisis repair is beneficial and may help prevent NEC[10]; however, additional benefits from the use of human milk in these infants have not been explored fully. In the present study, we investigated the association of enteral feeding with human milk and time to discharge after gastroschisis repair, using time to discharge as a surrogate for the incidence of complications and the infant's ability to tolerate feeds. We hypothesized that human milk use would be associated with reduced time to discharge.

Methods

The study population was drawn from an electronic medical record that prospectively captures information generated by clinicians on all infants cared for by the Pediatrix Medical Group in neonatal intensive care units (NICUs) in North America. This information includes data on multiple aspects of care obtained from admission notes, daily progress notes, and discharge summaries and includes maternal history, demographic data, medications, laboratory results, diagnoses, and procedures. The data are then transferred to the Pediatrix Clinical Data Warehouse for quality improvement and research purposes.[11] Permission

HR	Hazard ratio
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit

From the [1]Department of Surgery and [2]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC; [3]Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Pediatrix Medical Group, Inc, Sunrise, FL; Departments of [5]Medicine and [6]Pediatrics, Duke University Medical Center, Durham, NC

Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; HHSN275201000003I for the Pediatric Trials Network and 1R25HD076475). B.G. receives support from the National Institutes of Health–funded Cardiothoracic Surgery Trials Network (5U01HL088953-05). M.L. receives support from the US government for his work in pediatric and neonatal clinical pharmacology (HHSN267200700051C under the Best Pharmaceuticals for Children Act [PI: Daniel K. Benjamin Jr]) and NICHD (K23HD068497). P.S. receives salary support for research from the National Center for Advancing Translational Sciences (UL1TR001117), NICHD (HHSN2752010000031 and 1R01-HD081044-01), the Food and Drug Administration (1R18-FD005292-01), and Cempra Pharmaceuticals (subaward to HHS0100201300009C); and serves as a paid consultant for AbbVie, Astellas Pharma US, GlaxoSmithKline, and MissionPharma. C.H. receives salary support from the National Center for Advancing Translational Sciences (UL1TR001117). The other authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.11.046

to conduct this analysis was provided by Duke University's Institutional Review Board.

We included infants who had a report of gastroschisis in the diagnosis table between 1997 and 2012. Infants were excluded who did not receive human milk or formula at any point after gastroschisis repair, who were discharged to home on day of feeding 0 or 1, or had missing postnatal age data at discharge. The remaining infants were categorized a priori into 4 groups based on the percentage of days on which they received human milk out of their total days of enteral feeds: 0%, 1%-50%, 51%-99%, and 100%.

Definitions

Percentage of days fed was defined as the percentage of days after gastroschisis repair during which an infant received any amount of enteral nutrition. Percentage of human milk exposure was defined as the percentage of days fed during which an infant received any human milk. Human milk included both mother and donor human milk. Daily inotropic support was considered to be any exposure to amrinone, dobutamine, dopamine, epinephrine, milrinone, or norepinephrine on a given day. Daily mechanical ventilation was defined as any exposure to conventional or high-frequency ventilation on a given day. The percentage of days of inotropic and mechanical ventilator support was calculated as the number of days of inotropic or mechanical ventilator support after the first feed divided by the number of days from first feed until discharge. A positive blood culture was defined as any blood culture positive for an organism not typically considered a contaminant obtained on a day after the first feed. Small for gestational age status was defined as described previously.[12]

Statistical Analyses

Baseline characteristics and outcomes were compared between groups using standard summary statistics including median (IQR) and frequency (percentage). Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using the Fisher exact test or χ^2 test of association as appropriate. We used Kaplan-Meier estimators, censoring infants lost to follow-up and death, to determine the association of human milk and time from first enteral feed to discharge. Time to discharge among groups was compared using the log-rank test. Cox proportional hazards regression modeling was performed to determine the adjusted association between human milk use and time from first feed to discharge. Covariates included in the model were postnatal age at first feed, number of days during which the infant was not being fed after starting feeds, gestational age, small for gestational age status, percentage of days the infant was on inotropes, percentage of days the infant was on the ventilator, and any positive blood culture after feeds began. The proportional hazards assumption was tested using goodness-of-fit tests based on Schoenfeld residuals, and all potential covariates were inspected for linearity using visual inspection and goodness-of-fit tests. We also conducted a sensitivity analysis limited to infants who were discharged within 3 weeks of their first feed, to better ensure that our findings were not the result of unobserved confounding.

All statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas). A P value of .05 was used to determine statistical significance.

Results

Among the 3082 infants who met study criteria, 659 (21%) were fed human milk on 0% of enteral feeding days, 766 (25%) were fed human milk on 1%-50% of enteral feeding days, 725 (24%) were fed human milk on 51%-99% of enteral feeding days, and 932 (30%) were fed human milk on 100% of enteral feeding days. An infant was fed both human milk and formula during 1 day on only 2.9% of feeding days. Infants in the 0% human milk group were more likely to be born preterm and African American (**Table I**). Infants fed 0% human milk were also significantly older on their first day of feeding compared with infants fed 100% human milk (median, 13 days vs 12 days; $P < .01$).

Median (IQR) time from first feed to discharge was shorter in infants fed human milk on 100% of enteral feeding days compared with those fed human milk on 51%-99%, 1%-50%, and 0% of enteral feeding days (12 [8-17] days vs 19 [13-34] days vs 31 [15-60] days vs 20 [11-38] days, respectively; $P < .01$). Compared with the other groups, infants fed 100% human milk also had a significantly lower rate of positive blood cultures and a lower percentage of days on inotropes after beginning feeds (**Table II**). Finally, infants who were fed 0% human milk had a significantly higher mortality compared with the other 3 groups.

After adjustment, infants fed 0% human milk continued to have a significantly prolonged length of stay following the start of enteral feeding compared with infants fed 100% human milk (adjusted hazard ratio [HR] for discharge per day, 0.46; 95% CI, 0.40-0.52), as did infants fed human milk on 1%-50% of feeding days (adjusted HR, 0.37; 95% CI, 0.32-0.41) and those fed human milk on 51%-99% of feeding days (adjusted HR, 0.51; 95% CI, 0.46-0.57) (**Figure**). However, infants fed human milk on 1%-50% of feeding days had a longer adjusted time to discharge than infants fed 0% human milk (adjusted HR, 0.80; 95% CI, 0.71-0.90).

In the sensitivity analysis, which grouped infants by percentage of enteral feed days on which the infant was fed human milk during the first 21 days of feeds, infants fed human milk on 0% of feeding days continued to have a significantly longer time to discharge compared with those fed human milk on 100% of feeding days (adjusted HR for discharge per day, 0.59; 95% CI, 0.50-0.69). The same was true for infants fed human milk on 1%-50% of enteral feeding days (adjusted HR, 0.61; 95% CI, 0.52-0.72) and those fed human milk on 51%-99% of enteral feeding days (adjusted HR, 0.59; 95% CI, 0.52-0.68).

Discussion

Gastroschisis is associated with a long hospital stay following surgical repair.[13] Previous studies have demonstrated a beneficial effect in feeding these infants with human milk

Table I. Baseline characteristics by group

Variables	Overall (n = 3082)	Human milk on 0% of enteral feeding days (n = 659)	Human milk on 1%-50% of enteral feeding days (n = 766)	Human milk on 51%-99% of enteral feeding days (n = 725)	Human milk on 100% of enteral feeding days (n = 932)	*P* value
Gestational age, wk, n (%)						<.01
≤28	20 (0.7)	5 (0.8)	6 (0.8)	5 (0.7)	4 (0.4)	
29-32	155 (5.0)	43 (6.5)	40 (5.2)	40 (5.5)	32 (3.4)	
33-36	1822 (59)	400 (61)	478 (62)	427 (59)	517 (56)	
≥37	1084 (35)	211 (32)	242 (32)	253 (35)	378 (41)	
Birth weight <1500 g, n (%)	96 (3.1)	18 (2.7)	36 (4.7)	25 (3.4)	17 (1.8)	<.01
SGA, n (%)	598 (19)	135 (21)	155 (20)	141 (19)	167 (18)	.55
Female sex, n (%)	1506 (49)	303 (46)	378 (49)	360 (50)	465 (50)	.42
Race/ethnicity, n (%)						<.01
White	1622 (55)	349 (55)	368 (50)	382 (55)	523 (58)	
Black	212 (7.2)	74 (12)	48 (6.6)	50 (7.2)	40 (4.5)	
Hispanic	957 (32)	183 (29)	276 (38)	227 (33)	271 (30)	
Other	159 (5.4)	26 (5.3)	39 (5.3)	33 (4.8)	61 (6.8)	
Postnatal age at first feed, d, n (%)						<.01
<8	256 (8.3)	46 (7.0)	71 (9.3)	86 (12)	53 (5.7)	
8-14	1141 (37)	191 (29)	233 (30)	246 (34)	471 (51)	
15-21	946 (31)	180 (27)	242 (32)	241 (33)	283 (30)	
>21	739 (24)	242 (37)	220 (29)	152 (21)	125 (13)	

SGA, small for gestational age.

compared with formula after repair; however, those studies involved single-center retrospective reviews and were limited by small sample sizes.[14] Using a database containing data from more than 300 NICUs, we have demonstrated that feeding with human milk is associated with significantly decreased time to discharge following repair of gastroschisis, after adjusting for patient characteristics and other factors related to severity of illness.

It was important to adjust for patient factors because at baseline, patients who received only human milk appeared to be less sick than those who had some enteral feeding days with only formula. This was supported by the findings that infants fed human milk were fed at an earlier postnatal age, and that infants in the no human milk group experienced greater weight gain from birth to discharge. We attempted to take this into account by adjusting for surrogates for severity of illness, including time to first feed, days on inotropes, and days on ventilation. Despite these baseline differences, after adjustment, we still found that the increasing utilization of human milk was associated with reduced time to discharge.

The use of time to discharge as our outcome of interest is important for many reasons. First, it serves as a composite for the real variables of interest, including the incidence of complications and the tolerability of enteral feeds. Second, time to discharge is also related to hospital costs, an important

Table II. Outcomes by group

Variables	Overall (n = 3082)	Human milk on 0% of enteral feeding days (n = 659)	Human milk on 1%-50% of enteral feeding days (n = 766)	Human milk on 51%-99% of enteral feeding days (n = 725)	Human milk on 100% of enteral feeding days (n = 932)	*P* value
Days from first feed to discharge or death, n (%)						<.01
<8	179 (5.8)	45 (6.8)	20 (2.2)	16 (2.2)	98 (10)	
8-14	949 (31)	166 (25)	140 (18)	187 (28)	456 (49)	
15-21	629 (20)	121 (18)	95 (12)	187 (26)	226 (24)	
>21	1325 (43)	327 (50)	511 (67)	335 (46)	152 (16)	
Days infant not fed after first feed, median (IQR)	3 (0-13)	4 (0-16)	12 (3-27)	3 (0-13)	0 (0-4)	<.01
Weight gain from birth to discharge, g/d, median (IQR)	19 (14-24)	20 (14-26)	20 (16-25)	19 (14-24)	17 (11-22)	<.01
Positive blood culture after first feed	318 (10)	78 (12)	138 (18)	70 (10)	32 (3.4)	<.01
Percentage of days on ventilator after first feed, n (%)						<.01
<25%	1317 (43)	290 (45)	302 (40)	277 (39)	448 (48)	
25%-49%	920 (30)	203 (31)	230 (31)	205 (29)	282 (30)	
50%-100%	803 (26)	155 (24)	221 (29)	228 (32)	199 (21)	
Percentage of days on inotrope after first feed, n (%)						.02
<25%	2838 (93)	604 (93)	695 (92)	655 (92)	844 (95)	
25%-49%	145 (4.8)	25 (3.9)	45 (6.0)	38 (5.4)	37 (4.0)	
50%-100%	57 (1.9)	19 (2.9)	13 (1.7)	17 (2.4)	8 (0.9)	
NEC, n (%)	1 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	.30
Mortality, n (%)	31 (1.1)	16 (2.6)	5 (0.7)	6 (0.9)	4 (0.4)	<.01

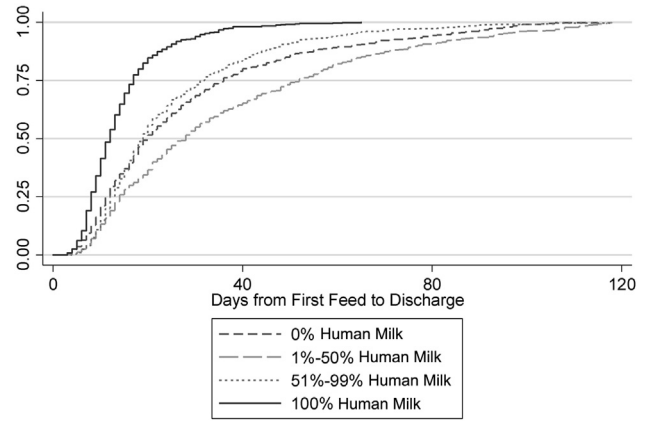

Figure. Time to discharge by percentage of enteral feeding days on which the infant was given human milk. $P < .01$.

concern in the current health care environment. Caring for infants in the NICU is expensive, especially for preterm and low birth weight infants.[15] Reductions in NICU length of stay by a day or 2 can result in large savings. Finally, using time to discharge allowed us to perform an analysis that included censoring for death, which prevented bias from early mortality.

These findings are similar to those reported in previous studies. Kohler et al[14] performed a single-center study of 90 infants born with gastroschisis and, as in our study, separated them into 4 groups, with 1 group receiving no human milk, 1 group receiving exclusively human milk, and the other 2 groups receiving mixed amounts of formula and human milk. On unadjusted analysis, they found that the infants fed exclusively human milk had a significantly decreased time from initiation of feeds to full feeding; however, after adjusting for other factors, no significant differences between groups remained, likely owing to the small sample size. We used a much larger sample size to show significant differences in time from feeding initiation to discharge between groups, even after adjustment for other factors. In this type of retrospective analysis, this adjustment is extremely important, because sicker children will be much less likely to continually tolerate feeds, making it much more difficult to keep a continuous supply of human milk on hand. Our ability to control for days during which an infant was not being fed helps decrease this risk of bias.

There are many reasons why human milk may be beneficial over formula in this population. Preterm infants are at extremely high risk for infections, and human milk contains important antibodies and other immunologic factors that may help decrease the incidence of these infections.[3] Furthermore, it improves the absorption of vital nutrients and may be important for gastrointestinal health.[4] Jayanthi et al[10] performed a single-center review of their outcomes following repair of gastroschisis and found that 8 of 60 infants developed NEC. None of the infants who developed NEC had been fed exclusively human milk.

Although we found a clear benefit from being fed exclusively human milk or being fed human milk on 51%-99% of feeding days over receiving no human milk, being fed human milk on 1%-50% of feeding days was associated with an even longer time from initiation of feeds to discharge than being fed 0% human milk. This is likely related to incomplete adjustment for severity of illness, as evidenced by the significantly higher number of days that infants in this group were not fed enterally after feeding initiation compared with the other groups. Holding feeds after initiation may be a sign of poor tolerance but often is secondary to an underlying medical problem, and although we adjusted for the holding of feeds, we likely did not fully adjust for the underlying cause.

Our results show a significantly higher mortality among infants fed no human milk compared with those fed any amount of human milk. Our inability to adjust for important characteristics, such as the complexity of gastroschisis, must be taken into account, however. Whether mortality is associated directly with human milk or just a marker of more severe baseline disease in this patient population is unclear.

Although our results are important for the care of preterm infants following gastroschisis repair, some study limitations should be acknowledged. First, as a retrospective review of a multicenter database, there are missing variables that would aid adjustment for patient-related factors, because the data were not collected specifically for this study. These include reasons for holding feeds, postrepair complications, reasons for not using human milk, feeding methods, and fortification strategies. Second, although donor human milk can provide many of the same advantages as maternal human milk, it likely does not have the same magnitude of effect, and, unfortunately, we could not differentiate the two. Finally, there may be other covariates that could not be adjusted for that may be partially responsible for the differences in outcomes between groups. For instance, socioeconomic status has been associated with the use of human milk in newborn infants.[16]

In conclusion, after adjustment for patient characteristics and factors related to severity of illness, the use of human milk for enteral feeding of preterm infants following repair for gastroschisis significantly decreased the time from feeding initiation to discharge. This outcome is likely a surrogate for a reduction in postrepair complications and improved tolerability of enteral feeding. Future research should focus on methods for increasing the use of human milk among these infants. ■

Submitted for publication Jul 20, 2015; last revision received Oct 26, 2015; accepted Nov 16, 2015.

Reprint requests: P. Brian Smith, MD, MHS, MPH, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail: brian.smith@duke.edu

References

1. Andres A, Cleves MA, Bellando JB, Pivik RT, Casey PH, Badger TM. Developmental status of 1-year-old infants fed breast milk, cow's milk formula, or soy formula. Pediatrics 2012;129:1134-40.
2. Walker A. Breast milk as the gold standard for protective nutrients. J Pediatr 2010;156(2 Suppl):S3-7.

3. Narayanan I, Prakash K, Bala S, Verma RK, Gujral VV. Partial supplementation with expressed breast milk for prevention of infection in low-birth-weight infants. Lancet 1980;2:561-3.
4. McMillan JA, Oski FA, Lourie G, Tomarelli RM, Landaw SA. Iron absorption from human milk, simulated human milk, and proprietary formulas. Pediatrics 1977;60:896-900.
5. Feldman R, Eidelman AI. Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. Dev Psychobiol 2003;43:109-19.
6. Gould S, Smith N. Complications of prematurity. In: Cohen MC, Scheimberg I, eds. The pediatric and perinatal autopsy manual. Cambridge, UK: Cambridge University Press; 2014. p. 284.
7. Regev RH, Lusky A, Dolfin T, Litmanovitz I, Arnon S, Reichman B. Excess mortality and morbidity among small-for-gestational-age premature infants: a population-based study. J Pediatr 2003;143:186-91.
8. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet 1990;336:1519-23.
9. Hunter AG, Stevenson RE. Gastroschisis: clinical presentation and associations. Am J Med Genet C Semin Med Genet 2008;148C:219-30.
10. Jayanthi S, Seymour P, Puntis JW, Stringer MD. Necrotizing enterocolitis after gastroschisis repair: a preventable complication? J Pediatr Surg 1998;33:705-7.
11. Spitzer AR, Ellsbury DL, Handler D, Clark RH. The Pediatrix BabySteps Data Warehouse and the Pediatrix QualitySteps improvement project system: tools for "meaningful use" in continuous quality improvement. Clin Perinatol 2010;37:49-70.
12. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010;125:e214-24.
13. Driver CP, Bruce J, Bianchi A, Doig CM, Dickson AP, Bowen J. The contemporary outcome of gastroschisis. J Pediatr Surg 2000;35:1719-23.
14. Kohler JA Sr, Perkins AM, Bass WT. Human milk versus formula after gastroschisis repair: effects on time to full feeds and time to discharge. J Perinatol 2013;33:627-30.
15. Russell RB, Green NS, Steiner CA, Meikle S, Howse JL, Poschman K, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. Pediatrics 2007;120:e1-9.
16. Merewood A, Brooks D, Bauchner H, MacAuley L, Mehta SD. Maternal birthplace and breastfeeding initiation among term and preterm infants: a statewide assessment for Massachusetts. Pediatrics 2006;118:e1048-54.

50 Years Ago in *The Journal of Pediatrics*

Perinatal Stress and the Premature Neonate. II. Effect of Fluid and Calorie Deprivation on Blood Glucose

Beard AG, Panos TC, Marasigan BV, Eminians J, Kennedy HF, Lamb J. J Pediatr 1966;68:329-43

Fifty years ago, Beard et al challenged the notion that small and premature infants were not compromised by withholding calories for up to 72 hours. They measured glucose and other biochemical variables in premature infants who had feeding and fluids withheld for 72 hours and in premature infants who were fed beginning at 6 hours of age. In the 72 hours fasted group, blood glucose concentrations progressively declined to levels that would be worrisome to many current clinicians. However, none of their subjects developed symptoms and it is apparent in their discussion that the debate over the significance of asymptomatic hypoglycemia was as alive then as it is today.

Importantly, the glycemic response to glucagon was close to normal in the fed premature infants and none had urinary ketones present at 48-72 hours of age. In the fasted premature infants there was a significantly lower glycemic response to glucagon and almost two-thirds developed ketonuria. It was clear that prolonged withholding of calories resulted in hyperketotic hypoglycemia. Over time, the results of this study and others like it led to a change in practice as the duration and degree of calorie and carbohydrate deprivation in premature infants began to decrease.

Today, our goal is early and aggressive enteral and parenteral nutrition of the premature infant. Evolution of this practice has been based on pioneering work investigating fetal and perinatal amino acid metabolism, gastrointestinal developmental biology and minimal enteral nutrition, and the short- and long-term benefits of breast milk for premature infants. Undoubtedly, the nutritional care of these patients will continue to change. These changes will be based on current studies focusing on the importance of the microbiome, oligosaccharide derivatives, and other milk components, to name just a few areas. As current and future research continues to refine parenteral and enteral nutritional approaches to premature infants, it is worthwhile to remember that the field of perinatal carbohydrate metabolism gave us our first push towards early and aggressive nutrition in this vulnerable population.

Paul Joseph Rozance, MD
Perinatal Research Center
University of Colorado School of Medicine
Aurora, Colorado
http://dx.doi.org/10.1016/j.jpeds.2015.10.055