Higher- or Usual-Volume Feedings in Infants Born Very Preterm: A Randomized Clinical Trial

Colm P. Travers, MD[1], Timothy Wang, MD[1,2], Ariel A. Salas, MD, MSPH[1], Erin Schofield, MD[1,3], Madeline Dills, MD[1,4], Deborah Laney, RN, MSN[1], Aaron Yee, MD[1,5], Anisha Bhatia, MD[1], Lindy Winter, MD[1], Namasivayam Ambalavanan, MD[1], and Waldemar A. Carlo, MD[1]

Objective To determine whether higher-volume feedings improve postnatal growth among infants born very preterm.
Study design Randomized clinical trial with 1:1 parallel allocation conducted from January 2015 to June 2018 in a single academic medical center in the US. In total, 224 infants with a birth weight 1001-2500 g born at <32 weeks of gestation were randomized to higher-volume (180-200 mL/kg/d) or usual-volume (140-160 mL/kg/d) feedings after establishing full enteral feedings (≥120 mL/kg/d). The primary outcome was growth velocity (g/kg/d) from randomization to study completion at 36 weeks of postmenstrual age or hospital discharge if earlier.
Results Growth velocity increased among infants in the higher-volume group compared with the usual-volume group (mean [SD], 20.5 [4.5] vs 17.9 [4.5] g/kg/d; $P < .001$). At study completion, all measurements were higher among infants in the higher-volume group compared with the usual-volume group: weight (2365 [324] g, z score −0.60 [0.73] vs 2200 [308] g, z score −0.94 [0.71]; $P < .001$); head circumference (31.9 [1.3] cm, z score −0.30 [0.91] vs 31.4 [1.3] cm, z score −0.53 [0.84]; $P = .01$); length (44.9 [2.1] cm, z score −0.68 [0.88] vs 44.4 [2.0], z score −0.83 [0.84]; $P = .04$); and mid-arm circumference (8.8 [0.8] cm vs 8.4 [0.8] cm; $P = .002$). Bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis, or other adverse outcomes did not differ between groups.
Conclusions In infants born very preterm weighing 1001-2500 g at birth, higher-volume feedings increased growth velocity, weight, head circumference, length, and mid-arm circumference compared with usual-volume feedings without adverse effects. *(J Pediatr 2020;224:66-71)*.
Trial registration ClinicalTrials.gov; NCT02377050.

Postnatal growth failure (<10th percentile) occurs in about one-half of infants with very low birth weight and severe postnatal growth failure (<3rd percentile) occurs in about one-quarter.[1] Among infants born preterm at 23-34 weeks of gestation, the prevalence of postnatal growth failure has been reported as 20% for weight, 34% for length, and 16% for head circumference. These rates increase as gestational age decreases.[2] Growth velocities of 14-20 g/kg/d using volumes of approximately 150 mL/kg/d of fortified human milk or preterm formula have been recommended to provide growth rates that approximate a normally growing fetus with a net water balance of 10-15 mL/kg/d.[3,4] International guidelines and expert opinion support a range of routine feeding volumes from 150 to 180 mL/kg/d,[5] with outer limits ranging from 120 to 200 mL/kg/d.[3-6] Current goal feeding recommendations may not account for cumulative nutritional deficits before establishment of full feedings.[7]

Higher-volume feedings may mitigate nutritional deficits, and international surveys suggest that goal feeding volumes of 140-160 mL/kg/d are usual in Canadian neonatal intensive care units (NICUs), 161-180 mL/kg/d are more common in European and Antipodean NICUs, with higher volumes up to 200 mL/kg/d reported in a few NICUs.[8] In 2 small randomized controlled trials, including infants born very preterm (N = 54)[9] and infants with very low birth weight (N = 64),[10] higher-volume feedings increased weight gain compared with usual-volume feedings. However, a meta-analysis concluded that there are insufficient data to determine the effect of higher-volume feedings in infants born preterm.[11] We hypothesized that among infants born at <32 weeks of gestation with birth weights of 1001-2500 g, higher-volume feedings (180-200 mL/kg/d) compared with usual-volume feedings (140-160 mL/kg/d) would increase growth velocity, a valid surrogate of postnatal growth restriction.[12]

Methods

This was a single center randomized clinical trial with a 1:1 parallel allocation to either higher-volume (180-200 mL/kg/d) or usual-volume (140-160 mL/kg/d)

NICU	Neonatal intensive care unit

From the [1]Division of Neonatology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL; [2]Division of Neonatology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]Division of Neonatology, Department of Pediatrics, University of Maryland, Baltimore, MD; [4]Department of Surgery, Louisiana State University Health Sciences Center, New Orleans, LA; and [5]Division of Neonatology, Department of Pediatrics, Nemours Alfred I. duPont Hospital for Children, Wilmington, DE

Funded by the Perinatal Health and Human Development Research Program of the University of Alabama at Birmingham and the Children's of Alabama Centennial Scholar Fund. The study sponsor(s) had no role in the study design, the collection, analysis, and interpretation of data, the writing of the report; and the decision to submit the manuscript for publication. W.C. serves on the board of MEDNAX, Inc. A.S. received consulting fees from Lockwood Group LLC for participation in Mead Johnson Nutrition advisory board meetings. The other authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.05.033

feedings. The trial was approved by the institutional review board at the University of Alabama at Birmingham academic medical center and registered on ClinicalTrials.gov (NCT02377050). The trial was conducted from January 2015 to June 2018. Infants were included if they had a gestational age of $<32^{0/7}$ weeks, a birth weight of 1001-2500 g, and had achieved a feeding volume of ≥120 mL/kg/d. Both inborn and outborn infants were included. Infants with a hemodynamically significant patent ductus arteriosus, necrotizing enterocolitis stage 2 or greater, a known gastrointestinal or neurologic malformation, terminal illness, or decision to withdraw or limit support were excluded.

Randomization was performed using computer-generated random-block sequences of 2, 4, 6, and 8 placed in sequentially numbered, opaque, sealed envelopes. Stratification was not used. Following parent or legal guardian consent, the infants were randomized after establishment of full enteral feedings defined as ≥120 mL/kg/d.

Interventions

Feedings were advanced daily by 20-30 mL/kg/d until the goal volume was achieved. Human milk was fortified when full enteral feedings were reached, and preterm formula (24 kcal/oz) was used as needed for insufficient human milk supply. Preterm formula was not used to increase milk supply above usual-volume feedings among infants randomized to higher-volume feedings. Feeding volumes routinely are adjusted daily to account for increases in infant weight. Clinicians assessed growth at least once a week to target fortification. Additional increases in caloric density of feedings could be ordered by the attending physician for infants with inadequate growth in either group. Feeding volume was not restricted to 160 mL/kg/d in the usual-volume group once infants were feeding ad lib by mouth. Although the nursery staff were not informed of group assignment, masking could not be performed as staff were aware of volumes ordered and received.

Measures

Weight, head circumference, length, and mid-arm circumference were measured at enrollment and at study completion, which was at the time of discharge home or 36 weeks of postmenstrual age, whichever came first. The primary outcome was growth velocity from randomization to study completion calculated using the exponential method[13,14] and reported in g/kg/d. Weight was measured to the nearest gram by nursery staff using an electronic scale. Length was measured to the nearest millimeter by nursery staff using standard tape measure from stretched heel to top of head. Head circumference was measured to the nearest millimeter by one of the authors as the maximal occipital frontal circumference obtained following 3 consecutive measurements. Mid-arm circumference was measured to the nearest millimeter by one of the authors at the mid-point between the tip of the shoulder and the tip of the elbow. Postnatal growth failure was defined as weight <10th percentile for postmenstrual age, and z scores were determined using Fenton 2013 growth charts.[15]

Bronchopulmonary dysplasia was defined as any respiratory support or oxygen use at 36 weeks of postmenstrual age. Hemodynamically significant patent ductus arteriosus was defined as moderate to large based on a left atrium-to-aorta ratio more than 1.5:1 and diameter ≥1.5 mm diagnosed by echocardiography.[16] Necrotizing enterocolitis was defined as Bell stage 2 or greater.[17] Feeding intolerance was defined as being fed nothing by mouth for >24 hours for feeding or abdominal issues. Other safety outcomes included the duration of respiratory support, culture-proven sepsis after study entry, and mortality before hospital discharge. All outcomes were prespecified.

Statistical Analyses

A power calculation showed that a sample size of 224 infants was required to achieve 80% power to detect a 3 g/kg/d difference in growth velocity with a standard deviation of 8 g/kg/d at a 0.05 significance level. Allowance was not made for attrition or noncompliance during the study. All analyses were planned a priori and by intention to treat. The results were analyzed by independent samples t test for continuous data and χ^2 or Fisher exact test for categorical data. A sensitivity analysis was performed for stage 2 necrotizing enterocolitis including data from 1 infant who was withdrawn at parental request.

Results

In total, 224 infants with a mean (SD) gestational age of 30.5 (1.2) weeks and a birth weight of 1445 (256) g were enrolled at a postmenstrual age of 31.7 (1.2) weeks. Birth characteristics including gestational age, weight, sex, race/ethnicity, Apgar scores, head circumference, length, and proportion of infants with a weight <10th percentile at birth did not differ between groups (**Table I**). There was also no difference between groups in weight, head circumference, length, mid-arm circumference, the proportion of infants with a weight <10th percentile, or postmenstrual age at study entry. Seven infants were withdrawn from the study at parental request, which included 6 infants in the higher-volume group and 1 infant in the usual-volume group (**Figure 1**; available at www.jpeds.com). Withdrawals from the higher-volume group included 2 infants with emesis, 1 with stage 2 necrotizing enterocolitis, 1 requiring supplemental oxygen, and 2 with parental concerns about study risks. One infant was withdrawn from the usual-volume group due to parental concern about study risks. No infants were withdrawn by the investigators due to adverse events.

Infants randomized to the higher-volume group had increased growth velocity compared with infants randomized to the usual-volume group (mean [SD], 20.5 [4.5] vs 17.9 [4.5] g/kg/d; $P < .001$) (**Table II**). Infants randomized to the higher-volume group had increased weight, weight z score, head circumference, head circumference z score, length, length z score, and mid-arm circumference at study completion compared with infants randomized to the usual-volume group (**Table II**). The proportion of infants with postnatal growth failure at study completion was 12%

Table I. Baseline characteristics at birth and at study entry

Characteristics	Higher volume (N = 104)	Usual volume (N = 113)
Birth		
Gestational age, wk, mean ± SD	30.5 ± 1.2	30.5 ± 1.2
Birth weight, g, mean ± SD	1445 ± 234	1453 ± 273
Length at birth, cm, mean ± SD	40.1 ± 3.0	40.2 ± 2.4
Head circumference at birth, cm, mean ± SD	27.7 ± 1.5	27.8 ± 1.7
Weight <10th percentile at birth, n (%)	6 (6)	7 (6)
Female sex, n (%)	50 (48)	55 (49)
Race/ethnicity, n (%)		
Black	55 (53)	61 (54)
White	46 (44)	47 (41)
Other	3 (3)	5 (4)
Study entry		
Postmenstrual age, wk, mean ± SD	31.8 ± 1.1	31.6 ± 1.2
Weight, g, mean ± SD	1377 ± 210	1370 ± 256
Head circumference, cm, mean ± SD	27.8 ± 1.4	27.9 ± 1.5
Length, cm, mean ± SD	40.6 ± 2.5	40.6 ± 2.3
Mid-arm circumference, cm, mean ± SD	6.7 ± 0.7	6.8 ± 0.8

in the higher-volume group compared with 21% in the usual-volume group ($P = .07$; Table II).

There was no difference in length of stay, bronchopulmonary dysplasia, duration of respiratory support, hemodynamically significant patent ductus arteriosus, proven necrotizing enterocolitis, feeding intolerance, or other adverse events between the groups (Table II). After inclusion of 1 infant with stage 2 necrotizing enterocolitis who was withdrawn at parental request, there remained no difference in the rates of proven necrotizing enterocolitis ($P = .47$). There was no difference in feeding volume or the proportion of infants receiving human milk between groups at study entry (Table III). The difference in feeding volume received between groups was approximately 15 mL/kg/d at day 7 after study entry and 25 mL/kg/d from day 14 after study entry onwards (Figure 2). Infants randomized to the higher-volume group were receiving a higher volume of feedings compared with infants randomized to the usual-volume group at study completion (181 [16] vs 157 [14]; $P < .001$). The higher-volume group received 6-16 mL/kg/d less milk and the usual-volume group received 2-6 mL/kg/d less milk than what was intended based on documentation.

The difference in caloric intake received between groups was approximately 9 kcal/kg/d at day 7 after study entry (126 kcal/kg/d vs 117 kcal/kg/d) and 16 kcal/kg/d from day 14 after study entry onwards (139 kcal/kg/d vs 123 kcal/kg/d) (Figure 3; available at www.jpeds.com). Infants randomized to the higher-volume group were receiving a higher caloric intake compared with infants randomized to the usual-volume group at study completion (134 [16] vs 122 [14]; $P < .001$). The difference in calories was primarily driven by the feeding volume, and there was no difference in caloric density between groups at study completion (Table III). In addition, there was no difference in the proportion of infants in each group receiving exclusive human milk at study completion.

Discussion

In this randomized clinical trial, higher-volume feedings increased not only growth velocity but also weight, head circumference, length, and mid-arm circumference compared with usual-volume feedings. However, the risk reduction of postnatal growth restriction observed in the higher-volume group did not reach statistical significance.

International surveys have revealed variation in feeding volumes ranging from 140 to 200 mL/kg/d[8] (typically with fortification), consistent with feeding volume recommendations.[3-6] The current trial defined higher-volume feedings as 180-200 mL/kg/d, similar to the trial by Kuschel et al, which compared feeding volumes of 150 mL/kg/d and 200 mL/kg/d.[9] In the trial by Thomas et al, usual volume feedings were defined as 200 mL/kg/d, whereas higher-volume feedings were defined as 300 mL/kg/d, but neither human milk fortification or fortified preterm formulas were used.[10] As expected, in the current study there was some regression to the mean in volumes received although the average separation was maintained at approximately 25 mL/kg/d between groups from day 14 onwards. Regression to the mean also was seen in the 2 other randomized

Table II. Outcomes at study completion

Outcomes	Higher volume (N = 104)	Usual volume (N = 113)	*P* value	Relative risk (95% CI)
Growth velocity, g/kg/d, mean ± SD	20.5 ± 4.5	17.9 ± 4.5	<.001	–
Weight, g, mean ± SD (z score, mean ± SD)	2365 ± 324 (−0.60 ± 0.73)	2200 ± 307 (−0.94 ± 0.71)	<.001	–
Head circumference, cm, mean ± SD (z score, mean ± SD)	31.9 ± 1.3 (−0.30 ± 0.91)	31.4 ± 1.3 (−0.53 ± 0.84)	.01	–
Length, cm, mean ± SD (z score, mean ± SD)	44.9 ± 2.1 (−0.68 ± 0.88)	44.4 ± 2.0 (−0.83 ± 0.84)	.04	–
Mid-arm circumference, cm, mean ± SD	8.8 ± 0.8	8.4 ± 0.8	.002	–
Weight <10th percentile at completion, n (%)	12 (12)	24 (21)	.07	0.54 (0.29-1.03)
Length of stay after randomization, d, mean ± SD	38 ± 16	38 ± 19	.91	–
Bronchopulmonary dysplasia, n (%)	3 (3)	5 (4)	.72	0.65 (0.16-2.66)
Hemodynamically significant patent ductus arteriosus, n (%)	3 (3)	2 (2)	.67	1.63 (0.28-9.56)
Days on respiratory support, mean (range)	6 (0-85)	6 (0-85)	.81	–
Necrotizing enterocolitis stage 2 or greater, n (%)	0 (0)	0 (0)	1.00	1.09 (0.02-54.23)
Feeding intolerance, n (%)	2 (2)	3 (3)	1.00	0.72 (0.12-4.25)

Table III. Feeds at study entry and study completion

Outcomes	Higher volume (N = 104)	Usual volume (N = 113)	*P* value
Study entry			
Feeding volume, mL/kg/d, mean ± SD	134 ± 16	131 ± 15	.14
Calorie density, kcal/oz (mean, range)	21, 20-24	21, 20-24	.99
Exclusive human milk, n (%)	64 (62)	67 (59)	.78
Calories, kcal/kg/d	94 ± 13	92 ± 13	.21
Study completion			
Feeding volume, mL/kg/d, mean ± SD	181 ± 16	157 ± 14	<.001
Calorie density, kcal/oz, mean (range)	23 (20-27)	23 (20-30)	.52
Exclusive human milk, n (%)	37 (36)	44 (39)	.58
Calories, kcal/kg/d	134 ± 16	122 ± 14	<.001

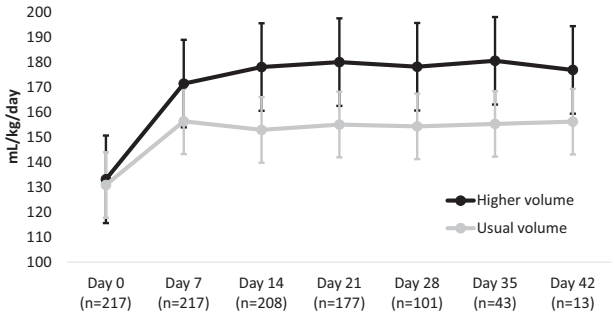

Figure 2. Mean (SD) feeding volumes (mL/kg/d) received at study entry and every 7 days until completion.

controlled trials of higher-volume feedings.[9,10] In the current study, regression to the mean in feeding volumes may have been partly explained by infants "outgrowing" their intended volumes faster in the higher-volume group compared with the usual-volume group. Daily adjustment in feeding volume based on weight, which is the current practice in our center, may have improved adherence and growth but were not mandated in the current study.

Early fortification has not been shown to significantly improve growth in infants born preterm,[18] and this strategy was not used in this trial. Infants in the usual-volume group received feedings with up to 30 kcal/oz at study completion, indicating that caloric density was increased to target growth. Fortification of human milk and caloric density of preterm formula was standardized and continued until discharge in the current trial. Although adjustments in fortification and caloric density were permitted to treat growth failure at the discretion of the attending neonatologist, there were no differences in caloric density or protein density between groups. By study design, infants in the higher-volume group received more calories and protein than infants in the usual-volume group because of the difference in volumes targeted. In the trial by Kuschel et al, fortification was routinely discontinued at 1800-2000 g, which may have contributed to the regression to the mean in that study.[9] In the trial by Thomas et al, fortification was not used.[10] In the current study, despite the difference in volumes between groups, there were no differences in the rates of exclusive breast milk use at discharge.

In previous studies of higher-volume feedings from 200 mL/kg/d to 300 mL/kg/d no significant differences were noted in adverse outcomes.[9,10,19-22] In the current study, there was no difference in adverse events between groups. The trial by Kuschel et al found no differences in fluid retention or edema.[9] The trial by Thomas et al showed no difference in rates of patent ductus arteriosus or tachypnea.[10] The current study did not assess edema or tachypnea, but it is reassuring that there were no differences in rates of bronchopulmonary dysplasia or hemodynamically significant patent ductus arteriosus, or in the duration of respiratory support. The current study results are also consistent with the results of other higher-volume feeding trials, which found no difference in rates of necrotizing enterocolitis[10,19] or feeding intolerance.[9,10,19]

There was a concern that higher-volume feedings might increase the length of stay, as infants might take longer to achieve the higher volumes by mouth. It is reassuring that there were no differences in the length of stay between groups in the current study. Similarly, there were no differences in length of stay in the trial by Kuschel et al.[9] In a trial of higher-volume feedings in 72 small for gestational age infants born preterm at 32-36 weeks of gestation with birth weights of ≥1500 g, the group randomized to higher-volume feedings (200 mL/kg/d) had a decreased length of stay compared with the group randomized to usual-volume feedings (170 mL/kg/d) likely due to the different rates of feeding advancement between groups.[19]

Previous higher-volume feeding trials have shown inconsistent postnatal growth benefits but were limited by small sample sizes. In a trial of higher-volume feedings in 54 infants born at 24-29 weeks of gestation, higher-volume feedings increased growth velocity (18.6 g/kg/d vs 16.5 g/kg/d; $P = .047$), weight gain, and arm fat area at study completion.[9] However, head circumference and length did not differ significantly. The trial of higher-volume feedings among small for gestational age infants born moderately preterm found improved weight and length z scores from study entry to completion but the change in head circumference z scores did not differ between groups.[19] In a trial of 64 infants born preterm with birth weights <1500 g, higher-volume feedings increased growth velocity but length and head circumference were not reported.[10]

The improvement in head and length measurements in the current study may have important clinical implications. Head circumference and brain volume are closely correlated.[23] Both postnatal head[24-28] and linear growth failure[24,29] are associated with neurodevelopmental impairment in infants born preterm. However, these findings are from observational studies with possible biases. Neurodevelopmental outcomes were not included in the current study, as we assessed outcomes before discharge only. In the trial by Kuschel et al, there was no difference in the rate of any neurodevelopmental impairment or severe neurodevelopmental impairment at 12 months of corrected age, but the trial was not powered for neurodevelopmental outcomes.[9]

It has been suggested that postnatal growth failure may be unavoidable in infants born preterm,[7] as the recommended growth velocity[3,4] is insufficient to allow catch up growth after the expected postnatal weight loss.[11] In the current study, the average growth velocity among infants in the higher-volume group was higher than the recommended growth velocity of 14-20 mL/kg/d[3], which could promote catch-up growth. A clinically meaningful decrease in the proportion of infants with postnatal growth failure at study completion did not reach statistical significance, although our study was not powered for this outcome. Postnatal growth failure has been associated with increased rates of adverse outcomes, including neurodevelopmental impairment, cerebral palsy, bronchopulmonary dysplasia, necrotizing enterocolitis, and sepsis.[24,30,31] However, these data are observational and are likely confounded by illness severity. In the current study, we did not assess biochemical differences between groups and the long-term metabolic effect of a higher-volume feeding strategy is unknown.

This single-center study of infants born very preterm has a number of limitations that should be noted. Although staff were not informed of the group assignment, it was possible for staff to calculate daily volumes based on the volume administered at each feeding. Lack of masking may have resulted in attrition bias and more withdrawals from the trial in the higher-volume group, although the effect size for most outcomes was positive despite the resultant loss of power. One infant from a multiple birth receiving preterm formula developed stage 2 necrotizing enterocolitis and was withdrawn at parental request, but inclusion of this infant in a sensitivity analysis did not alter the significance for this outcome. Length was measured to the nearest millimeter using a standard measuring tape from heel to top of head. This may be less accurate than measurements using a length board, but would lead to a nondifferential bias between groups. Furthermore, the difference in length between groups was consistent with the differences noted in weight and head circumference. In this unmasked trial, it is possible that differences in measurements for length, head circumference, and mid-arm circumference were due to performance bias. However, these differences were consistent with the observed difference in weight. Although it was reassuring that there was no difference in morbidities before discharge among study participants, the study was not powered for these outcomes and is not generalizable to infants with birth weights <1000 g with higher risk for mortality and major morbidities.

Higher-volume feedings increased growth velocity, weight, head circumference, length, and mid-arm circumference compared with usual-volume feedings in infants born very preterm with a birth weight 1001-2500 g. Higher-volume feedings may be a safe and effective way to improve postnatal growth in infants born very preterm. ■

Submitted for publication Jan 15, 2020; last revision received May 5, 2020; accepted May 15, 2020.

Reprint requests: Colm P. Travers, MD, 9380 Women and Infants Center, 1700 6th Ave South, Birmingham, AL 35249. E-mail: ctravers@peds.uab.edu

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000-2013. Pediatrics 2015;136:84-92.
2. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 2003;111:986-90.
3. Fusch C, Jochum F. Water, sodium, potassium and chloride. In: Tsang RC, Uauy R, Koletzko B, Zlotkin SH, eds. Nutrition of the preterm infant: scientific basis and practice guidelines. 2nd ed. Cincinnati (OH): Digital Education Publishing, Inc; 2005. p. 201-44.
4. Poindexter BB, Martin CR. Nutrient requirements/nutritional support in premature neonate. In: Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff and Martin's neonatal-perinatal medicine: disease of the fetus and infant. 11th ed. Philadelphia (PA): Elsevier, Inc; 2019. p. 670-89.
5. Agostoni C, Buonocore G, Carnielli VP, DeCurtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary for the European society for pediatric gastroenterology, hepatology, and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr 2010;50:85-91.
6. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman RE, Greer FR, eds. Pediatric nutrition. 7th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2014. p. 83-122.
7. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270-3.
8. Klingenberg C, Embleton ND, Jacobs SE, O'Connell LAF, Kuschel CA. Enteral feeding practices in very preterm infants: an international survey. Arch Dis Child Fetal Neonatal Ed 2012;97:F56-61.
9. Kuschel CA, Evans N, Askie L, Bredemeyer S, Nash J, Polverino J. A randomized trial of enteral feeding volumes in infants born before 30 weeks gestation. J Paediatr Child Health 2000;36:581-6.
10. Thomas N, Cherian A, Santhanam S, Jana AK. A randomized controlled trial comparing two enteral feeding volumes in very low birth weight babies. J Trop Pediatr 2012;58:55-8.
11. Abiramalatha T, Thomas N, Gupta V, Viswanathan A, McGuire W. High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants. Cochrane Database Syst Rev 2017;9:CD012413.
12. Martin CR, Brown YF, Ehrenkranz RA, O'Shea TM, Allred EN, Belfort MB, et al. Extremely Low Gestational Age Newborns Study Investigators. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 2009;124:649-57.
13. Patel AL, Engstrom JL, Meier PP, Kimura RE. Accuracy of methods for calculating postnatal growth velocity for extremely low birth weight infants. Pediatrics 2005;116:1466-73.
14. Fenton TR, Anderson D, Groh-Wargo S, Hoyos A, Ehrenkranz RA, Senterre T. An attempt to standardize the calculation of growth velocity of preterm infants-evaluation of practical bedside methods. J Pediatr 2018;196:77-83.
15. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
16. El-Khuffash A, James AT, Corcoran JD, Dicker P, Franklin O, Elsayed YN, et al. A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. J Pediatr 2015;167:1354-61.e2.
17. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201.
18. Alyahya W, Simpson J, Garcia AL, Mactier H, Edwards CA. Early versus delayed fortification of human milk in preterm infants: a systematic review. Neonatology 2019;19:1-9.
19. Zecca E, Costa S, Barone G, Giordano L, Zecca C, Maggio L. Proactive enteral nutrition in moderately preterm small for gestational age infants: a randomized clinical trial. J Pediatr 2014;165:1135-9.e1.

20. Lewis MA, Smith BA. High volume milk feeds for preterm infants. Arch Dis Child 1984;59:779-81.
21. Klingenberg C, Muraas FK, Isaksen CE, Nilsen T, Torgersen M, Melum-Hansen C. Growth and neurodevelopment in very preterm infants receiving a high enteral volume-feeding regimen—a population-based cohort study. J Matern Fetal Neonatal Med 2019;32:1664-72.
22. Valman HB, Heath CD, Brown RJ. Continuous intragastric milk feeds in infants of low birth weight. Br Med J 1972;3:547-50.
23. Cooke RW, Lucas A, Yudkin PL, Pryse-Davies J. Head circumference as an index of brain weight in the fetus and newborn. Early Hum Dev 1977;1:145-9.
24. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253-61.
25. Neubauer V, Griesmaier E, Pehböck-Walser N, Pupp-Peglow U, Kiechl-Kohlendorfer U. Poor postnatal head growth in very preterm infants is associated with impaired neurodevelopment outcome. Acta Paediatr 2013;102:883-8.
26. Raghuram K, Yang J, Church PT, Cieslak Z, Synnes A, Mukerji A, et al. Canadian Neonatal Network; Canadian Neonatal Follow-Up Network Investigators. Head Growth Trajectory and Neurodevelopmental Outcomes in Preterm Neonates. Pediatrics 2017;140.
27. Hack M, Breslau N, Fanaroff AA. Differential effects of intrauterine and postnatal brain growth failure in infants of very low birth weight. Am J Dis Child 1989;143:63-8.
28. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 1991;325:231-7.
29. Belfort MB, Rifas-Shiman SL, Sullivan T, Collins CT, McPhee AJ, Ryan P, et al. Infant growth before and after term: effects on neurodevelopment in preterm infants. Pediatrics 2011;128:e899-906.
30. Kan E, Roberts G, Anderson PJ, Doyle LW. Victorian Infant Collaborative Study Group. The association of growth impairment with neurodevelopmental outcome at eight years of age in very preterm children. Early Hum Dev 2008;84:409-16.
31. Latal-Hajnal B, Von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr 2003;143:163-70.

50 Years Ago in *The Journal of Pediatrics*

Tolubtamide-Mediated Dysregulation of Apoptosis

Schiff D, Aranda JV, Stern L. Neonatal thrombocytopenia and congenital malformations associated with administration of tolbutamide to the mother. J Pediatr 1970;77:457-58.

A male infant born after 37 weeks gestation to a 28-year-old woman with a history of diabetes for 3 years before delivery treated with tolbutamide during pregnancy was described by Schiff et al. The infant had dysmorphic features, including large ears, a right preauricular skin tag, and an accessory right thumb. The infant also had thrombocytopenia, with a platelet count of 25 000/mm^3, a hemoglobin of 13.3 g, and a reticulocyte count of 13.6%. The tolbutamide level was 7.2 mg/dL in the infant and 2.7 mg/dL in the mother. The pattern of anomalies was thought to be more consistent with fetal tolbutamide exposure as opposed to diabetic embryopathy.

The mechanism through which tolbutamide exerts its teratogenicity is not fully understood. Tolbutamide enables insulin release through closure of ATP-regulated K^+ (K_{ATP}) channels, followed by opening of voltage-dependent Ca^{2+} channels located on the β-cell surface. This prevents K^+ efflux, resulting in depolarization of cell membranes and release of insulin from storage granules. One hypothesis for tolbutamide's teratogenicity is through its effect on (K_{ATP}) channels.

Tolbutamide exposure with concentrations comparable with those in human serum in cultured rat embryos resulted in decreases of growth and developmental measures at 100 and 1000 μg/mL. There were no observed changes in embryonic growth and development at 10 μg/mL. During programmed cell death (apoptosis), Ca^{2+}- and Mg^{2+}-activated endonucleases create double-strand breaks between linker regions of nucleosome, resulting in multiples of approximately 180 bp DNA fragments. There is also experimental evidence that tolbutamide exposure to developing rat embryos increases apoptosis-mediated markers, including annexin V binding and DNA fragmentation, in a dose-dependent fashion.[1] Although apoptosis is a necessary mechanism for normal embryologic development, based on this experimental evidence, it is hypothesized that tolbutamide-mediated teratogenesis occurs through dysregulated apoptosis.

Philip F. Giampietro, MD, PhD
Division of Medical Genetics
Rutgers Robert Wood Johnson Medical School
New Brunswick, New Jersey

Reference

1. Singh G, Kumar A, Sinha N. Studying significance of apoptosis in mediating tolbutamide-induced teratogenesis in vitro. Fundam Clin Pharmacol 2012;26:484-94.

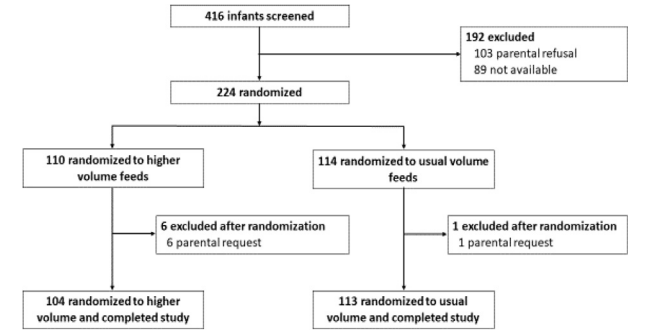

Figure 1. Flow diagram showing screening, randomization, and the number of infants included in the final data analysis.

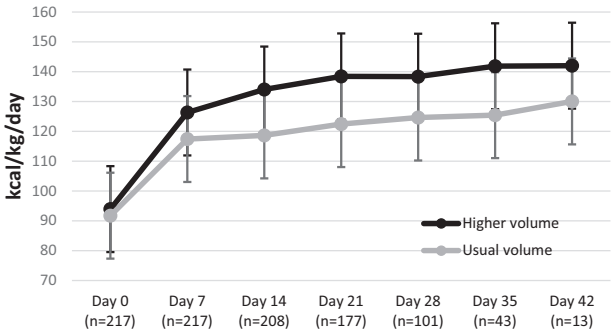

Figure 3. Caloric intake (kcal/kg/d) among infants randomized to the higher-volume or usual-volume groups. Infants randomized to the higher-volume group had higher caloric intake compared with infants randomized to the lower-volume group.