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Routine vs Selective Fortification of Preterm Human Milk in Extremely Preterm Infants

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Abstract

Objective

We studied extremely preterm (EPT) infants fed exclusively preterm milk (mother's own or donor from mother's delivering preterm), comparing routine versus selective fortification guided by growth.

Study Design:

In this prospective randomized trial, infants < 28 weeks' gestation received human milk-derived fortifier routinely when feedings reached 150 mL/kg/day or selectively for weight gain < 15 g/kg/day until study completion (35 weeks post-menstrual age). Outcomes included growth, feeding related morbidities, and neurodevelopment at two-years.

Results

Routine (n = 79) and selective (n = 84) groups were similar for baseline characteristics, weight gain (14.9 ± 5.0 and 14.7 ± 3.7 g/kg/day), linear growth (0.72 ± 0.19 and 0.72 ± 0.17 cm/week), and head growth (0.67 ± 0.11 and 0.68 ± 0.10 cm/week). Necrotizing enterocolitis occurred more frequently in the routine group (6% vs 0%, p = 0.03). Both groups showed rapid catch-up growth after hospital discharge and comparable long-term growth and neurodevelopmental outcome.

Conclusion

These findings support individualized fortification in EPT infants fed preterm milk.

Clinical Trial Registration

The trial was registered in ClinicalTrials.gov as NCT04284280

Contributors Statement Page

S. Murthy conceptualized and designed the study, acquired data, played an important role in interpreting the results, drafted the initial manuscript, revised the manuscript, approved the final version, and agrees to be accountable for all aspects of the work.

B. Bou Aram, and S. Gross conceptualized and designed the study, acquired data, played an important role in interpreting the results, revised the manuscript, approved the final version, and agrees to be accountable for all aspects of the work.

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BACKGROUND

The health benefits of human milk for extremely preterm infants are significant and well-known, with evidence associating feedings of mother's own milk with lower rates of necrotizing enterocolitis (NEC), nosocomial infection, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and neurodevelopmental impairment.[1] Human milk fortifiers were developed with the goal of improving postnatal growth without introducing infant formula. Historically, fortifiers were bovine-based, but more recently human milk-derived fortifier (HMDF) has become available and widely used, allowing for an exclusive human milk diet. However, the optimal timing of fortification, its true risk–benefit profile[2,3], and the long-term advantages remain uncertain [4,5].

Our approach to feeding EPT infants has long relied on using preterm human milk (PTHM), i.e. mother's own milk or donor milk obtained from mothers delivering preterm. Because PTHM is higher in protein than term milk[6], it allows optimal nutrient delivery while minimizing use of fortification. This practice has been accomplished with intensive lactation support and the establishment of an in-hospital milk bank using donors who delivered preterm and are expressing milk in the early stages of lactation. We previously reported a < 1% incidence of NEC in extremely low birth weight infants over an extended period (2010–2015) using a standardized feeding protocol relying on PTHM and selective fortification guided by growth.[7] Based on these observations, we conducted this prospective randomized trial in EPT infants comparing two fortification strategies with HMDF: routine fortification initiated at the time of full feeds verses selective fortification initiated for lagging weight gain. Growth, feeding-related morbidities, and neurodevelopmental outcomes through two years of age were tracked.

METHODS

Study Design

This is a prospective randomized controlled trial of infants born < 28 weeks' gestational age admitted during the first week of life to the Central New York Regional Perinatal Center at Crouse Hospital, February 2020 to June 2023. This center houses the only Level IV NICU serving 14 counties in Central New York. As a result, all EPT infants from the region are cared for at our center. Infants were study eligible if their mothers expressed milk and agreed to use of preterm donor milk from our milk bank if their own milk was unavailable. Exclusion criteria included infants with major congenital anomalies and severe intracranial hemorrhage (grade III-IV and cerebellar).[8,9] Enrolled infants were assigned randomly to begin HMDF once enteral feeds reached 150 mL/kg/day (routine group) or only if they demonstrated weight gain < 15g/kg/day over any week thereafter (selective group). Randomization was done with

sealed opaque envelopes by the study investigators (SM, BB, SG); twins were randomized individually. This study was performed in accordance with the Declaration of Helsinki. The hospital IRB approved this trial (IRB Number 2020.0107) and the trial was registered in ClinicalTrials.gov as NCT04284280 on February 15, 2020. The data safety monitor reviewed data (primarily NEC and mortality) every 6 months during the recruitment period. Written informed consent was obtained from one or both parents.

Feeding Protocol

All infants were started on parenteral nutrition within the first 24 hours of life and oral care with colostrum once available. Enteral feedings were initiated, advanced, and maintained by strict protocol.[7,10] Trophic feedings of maternal breast milk were started by day 7 of life and continued at 12 mL/kg/day for 7 days. Subsequently, milk intake was advanced by 15 mL/kg/day to 150 mL/kg/day. Thereafter, infants were fed and fortified based on their assigned group. For infants in the routine group, feedings were maintained at 150 mL/kg/day and HMDF was added (Prolacta + 4 H^2MF; Prolacta Bioscience, Inc, City of Industry, CA). For infants in the selective group, feedings were advanced and maintained at 180 mL/kg/day without fortification. Thus, both groups received isocaloric feedings at approximately 120 kcal/kg/day. Subsequently, infants in the selective group were started on HMDF at a feeding volume of 150 mL/kg/day if weight gain was < 15 g/kg/day over any subsequent one week. In both groups, if weight gain was < 15 g/kg/day over a one-week period while receiving fortification, feedings were advanced and maintained at 165 mL/kg/day. If maternal milk was not available at any time, preterm donor milk was used, ensuring that all infants received exclusive PTHM until study completion at 35 weeks' PMA (earliest age of potential hospital discharge). All infants received multivitamins and iron supplementation once receiving full enteral feedings.

Infants were fed by gastric gavage every 2 hours until reaching a weight of 1250g and every 3 hours thereafter. Intralipid and parenteral nutrition were discontinued when enteral feedings reached 100 mL/kg/day. Feedings were decreased or stopped for emesis, bile-stained gastric residuals, or abdominal distension per the care team's discretion. Gastric residuals were generally not re-fed. During red blood cell transfusion, fortification was stopped and feedings were decreased to 100–120 mL/kg/day for 24 hours.

Infants were weighed at birth and then three times weekly. When feedings reached 150 mL/kg/day, weights were obtained daily until study completion. Head circumference and recumbent length measurements were obtained weekly by the study investigators (SM, BB, SG). Head circumference was measured with a paper tape at the largest occipital-parietal diameter using an average of three values. A clear acrylic length-board (Ellard Instrumentation, Monroe, Washington) was used to ensure accuracy.[11]

Preterm Human Milk Bank

The milk bank at Crouse Hospital has been licensed as a Tissue Bank by the New York Department of Health since 1995[12]. The bank accepts milk only from mothers who deliver at < 34 weeks gestational age. Mothers who consent to participate as donors are screened and tested as required by state regulation and educated about proper collection, storage, and transport practices of expressed milk. Donors are required to be rubella immune, and negative for tuberculosis, hepatitis B surface antigen, hepatitis C antibody, human T-lymphotropic virus 1 and 2 antibody, and syphilis. Milk from multiple donors (typically 8–12) is pooled, such that the composition of each batch averages that of week 4–5 postpartum milk. Milk is divided into 60 mL aliquots, Holder pasteurized, and stored at -20^{o}C for use for up to 12 months.

Outcomes

The primary study outcome was weight gain (g/kg/day) after regained birthweight to 35 weeks' PMA. Secondary outcomes included linear and head growth, incidences of NEC, nosocomial infection, BPD, and severe ROP. Longer-term outcomes included death prior to discharge, length of hospitalization, and growth and neurodevelopmental outcomes through two years of age. NEC was defined as clinical symptoms with presence of pneumatosis intestinalis on radiographs or evidence of inflammation, infarction, or necrosis on surgical specimen histology. BPD was defined as supplemental oxygen requirement at 36 weeks' PMA. Infants were classified as having severe ROP if they received laser therapy in one or both eyes. Nosocomial infection was defined as positive blood and/or cerebral spinal fluid culture after 72 hours of life. At post-discharge follow-up, anthropometric measures, health history, neuromotor assessment[13], and developmental evaluation using the Bayley Scales of Infant and Toddler Development–Fourth Edition (Bayley)[14,15] were obtained at 6, 15, and 24 months (age adjusted for prematurity) by an observer (BM) blinded to group assignment.

Statistical Analyses

All randomized subjects were included in the analysis. Absolute measures of growth were converted to Z-scores based on parameters from the 2013 Fenton (birth to 35 weeks), 2006 WHO (6–15 months), and 2000 CDC (24 months) growth charts using the Peditools clinical calculators.[16] Parametric data were analyzed using the student *t-test* and presented as means and standard deviations. Non-parametric data were analyzed using the Mann-Whitney *U-test* and presented as medians and interquartile ranges. Categorical variables were compared using either the chi-square or Fisher exact tests. A sample size of 192 was calculated to show a 1 g/kg/day difference in weight gain with an alpha error of 5% and power of 80%. Planned recruitment was less than two years. With lower EPT infant births, recruitment was stopped after three years with a sample side of 163 infants. An intent-to-treat approach was used and all infants remained in their assigned study group.

RESULTS

Baseline Data

There were 254 infants admitted to our NICU at < 28 weeks' gestational age during the recruitment period and all were screened for study eligibility. Infant exclusions included 32 early deaths (none with NEC), 4 infants with congenital anomalies, 24 infants with severe IVH, and 8 with medical complications (1 with early NEC) delaying enteral feedings. Twelve other infants were excluded because their mothers did not provide expressed milk. Of the remaining 174 infants, all were approached and 163 (94%) were consented in the study. Study groups were comparable for all baseline characteristics (Table 1). Gestational age averaged approximately 26 weeks in both groups. The routine and selective groups were similar at birth for weight (819 ± 220 and 827 ± 187 g, respectively), length (32.8 ± 2.8 and 32.7 ± 2.3 cm), and head circumference (23.1 ± 1.8 and 23.1 ± 1.7 cm). Socioeconomic variables including two-parent household and maternal age and education were also comparable.

Table 1
Baseline Neonatal & Maternal Characteristics

Birth weight, g	**Routine (n = 79)**	**Selective (n = 84)**	**p value**
	819 ± 220	**827 ± 187**	**0.80**
Birth length, cm	32.8 ± 2.8	32.7 ± 2.3	0.84
Birth head Circumference, cm	23.1 ± 1.8	23.1 ± 1.7	0.94
Gestational age, weeks	26.0 ± 1.3	25.7 ± 1.4	0.25
Male sex	45 (57)	50 (60)	0.74
Inborn	73 (92)	69 (82)	0.05
Antenatal Steroids	74 (94)	76 (91)	0.45
Born by cesarean section	59 (75)	63 (75)	0.96
Apgar score at 5 min < 7	20 (26)	18 (21)	0.53
Received surfactant	60 (76)	59 (70)	0.41
Maternal age, years	29 ± 6.4	28 ± 6.2	0.13
Maternal education	14 (18)	19 (23)	0.12
<High school	27 (34)	36 (43)	
High school	38 (48)	29 (35)	
>High school			
Two-Parents Household at Birth	66 (84)	64 (76)	0.24
Values are mean ± SD or number (%).			

Nutritional Data and Hospital Outcomes

There was strict adherence to the feeding protocol (Table 2). Feedings were initiated at a median of 7 (IQR 7, 8) days and both groups received a median of 7 (7, 8) days of trophic feeds. Full feeds (150 mL/kg/day) were achieved at four weeks of age in both groups. To maintain exclusive feedings of PTHM, about 60% of infants in both study groups received donor milk to supplement inadequate maternal milk supply (Table 2). While all of the infants in the routine group received HMDF (by study design) at a median of 30 days of age, only two-thirds of those in the selective group qualified based on inadequate weight gain and received fortifier significantly later at a median of 47 days ($p < 0.001$). Significantly more infants in the routine fortification group subsequently required increased volume of feeds for continued lagging weight gain compared to the selective group ($p = 0.01$).

Table 2
Nutritional Data

Initiation of enteral feeding, days	**Routine (n = 79)**	**Selective (n = 84)**	**p value**
	7 (7,8)	**7 (7,8)**	**0.79**
Duration of trophic feeding, d	7 (7,8)	7 (7,8)	0.17
Time to 150 mL/kg/day, days	29 (25,34)	28 (26,32)	0.78
Duration of parenteral nutrition, days	26 (22,32)	24.5 (22,30)	0.23
Duration of Central line, days	26 (22,33)	25 (22,30)	0.77
Use of donor milk	48 (60)	54 (64)	0.64
Day of initiation of donor milk, days	21 (14, 32)	26 (16, 44)	0.14
Use of HMDF	79 (100)	55 (66)	< 0.01
Initiation of nutritional fortification, days	30 (25, 34)	47 (42, 56)	< 0.01
Advancement to 165 mL/kg/day with HMDF	39 (49)	15 (27)	0.01
Values are median (interquartile range) or number (%)			

Routine and selective groups were comparable for time to regain birth weight (12.4 ± 8.9 and 12.4 ± 8.3 days, respectively) as well as subsequent weight gain (14.9 ± 5.0 and 14.7 ± 3.7 g/k/day), linear growth (0.72 ± 0.19 and 0.72 ± 0.17 cm/week), and head growth (0.67 ± 0.11 and 0.68 ± 0.10 cm/week) (Table 3). Notably, the 29 (34%) infants in the selective group who never received fortifier demonstrated weight gain (14.6 ± 3.8 g/kg/day), linear growth (0.74 ± 0.20 cm/week), and head growth (0.66 ± 0.10 cm/week) that were almost exactly the same as the remaining study cohort. There were five infants (6%) who developed NEC in the routine group and none in the selective group ($p = 0.03$). Three of the infants with NEC were diagnosed surgically (one died) and two were treated medically (both survived). Two

additional infants died prior to discharge: one infant in the routine group with incarcerated hernia on autopsy and one infant in the selective group who had care withdrawn due to severe BPD. Incidences of other morbidities including infection, BPD, and severe ROP were similar in the two groups (Table 3).

Table 3
Hospital Outcomes

Growth Velocity	**Routine**	**Selective**	**p value**
Weight (birth weight regained to 35 weeks), g/kg/day	**(n = 79)**	**(n = 84)**	
Linear (birth to 35 weeks), cm/week	**14.9 ± 5.0**	**14.7 ± 3.7**	**0.74**
Head Circumference (birth to 35 weeks), cm/week	**0.72 ± 0.19**	**0.72 ± 0.17**	**0.91**
	0.67 ± 0.11	**0.68 ± 0.10**	**0.58**
Growth at 35 weeks' PMA	1579 ± 339	1596 ± 254	0.71
Weight, grams	39.2 ± 3.1	39.3 ± 2.5	0.85
Length, cm	29.2 ± 1.5	29.4 ± 1.3	0.40
Head Circumference, cm			
NEC	5 (6)	0 (0)	0.03
Nosocomial infection	15 (19)	8 (10)	0.08
Infection after randomization	3 (4)	3 (4)	1.00
BPD	54 (68)	59 (70)	0.80
Severe ROP	11 (14)	12 (14)	0.95
Death prior to discharge	2 (3)	1 (1)	0.61
Length of hospitalization, days	95.9 ± 32.1	103.5 ± 48.4	0.24
Values are mean ± SD or number (%). Two infants died prior to 35 weeks' PMA.			

Follow-Up

Follow-up was completed in November 2025. One infant in the routine group died after hospital discharge at 18 months of age of unexplained cause. There were no deaths in the selective group. Follow-up was obtained at a mean of 6.3 ± 0.5 months in 154 (96%) infants, again at 15.6 ± 1.5 months in 144 (90%) infants, and finally at 24.5 ± 1.1 months in 143 (90%) infants. Absolute measures of growth were converted to Z-scores to allow comparison to normative data and are depicted in the Figure. Weight, length, and head growth were similar over time in the two groups. Both groups demonstrated similar growth delay at 35 weeks' PMA (mean Z-scores for weight − 2.4 in both groups, length − 2.8 in both groups, and head circumference − 1.9 in both groups). There was similar and dramatic catch-up growth by six months of age. Weight and length continued further catch-up through 24 months at which

time both groups had mean Z-scores that were within 1 standard deviation of the norm (for weight, routine group − 0.8 and selective group − 0.6; and for length − 0.7 in both groups). Head growth normalized more rapidly and mean Z-scores were within 0.5 standard deviations of the norm by 6 months (routine group − 0.5 and selective group − 0.2) and remained in the normal range through two-years. Three children had accidental bone fractures secondary to trauma: one child in the routine group (left humerus at 6 months of age) and two children in the selective group (skull fracture shortly after discharge and wrist fracture at 13 months). There were no differences in neurodevelopmental outcomes at 24 months (Table 4). Neurological abnormalities occurred in 3 (4%) of children in the routine group and 1 (1%) in the selective group. Mean Bayley scores for cognition, language, and motor were not different between groups. Rates of survival without severe neurodevelopmental impairment (normal neurologic exam and Bayley cognitive and motor score > 70) were about 80% percent in both groups.

Table 4
Neurodevelopmental Outcome at 24 months

Abnormal Neurologic Examination [1]	**Routine (n = 71)**	**Selective (n = 72)**	**p value**
	3 (4)	**1 (1)**	**0.31**
Bayley Scales of Infant Development [2]	89 ± 18	85 ± 17	0.27
Cognitive Score	81 ± 22	80 ± 23	0.29
Language Score	89 ± 14	87 ± 14	0.39
Motor Score			
Survival Without Severe Neurodevelopmental Impairment [3]	57 (80)	57 (79)	0.87
Values are mean ± SD or number (%)			
[1] Motor dysfunction with GMFCS > 2 [13]			
[2] Bayley normative mean ± SD = 100 ± 15 [14]			
[3] Survival with normal neurologic examination, and Bayley Cognitive and Motor scores > 70.			

DISCUSSION

Providing optimal nutrition for the EPT infant is challenging. Maximizing extrauterine growth must be balanced against risk of feeding related morbidities. Our results demonstrate that in infants fed PTHM, routine fortification offers no growth advantage over selective fortification guided by lagging weight gain, and is associated with a significantly higher incidence of NEC. Importantly, routine fortification also resulted in no benefit in longer-term growth and neurodevelopmental outcome through two years. A notable observation is that one-third of infants assigned to selective fortification never received fortifier,

yet achieved growth velocities equivalent to that of the routinely fortified group. These data question the assumption that all EPT infants fed PTHM benefit from nutritional fortification.

There are no previously published controlled trials comparing routine versus selective human milk fortification in EPT infants. Therefore, we benchmarked our results to randomized trials looking at early verses late fortification. Three prior trials compared growth and feeding tolerance in preterm infants who received early (at human milk intake ≤ 40 mL/kg/day) or delayed (at intakes 75–100 mL/kg/day) fortification.[17–19] Although the trials differed in fortifier used (bovine or HMDF), study subject selection and feeding protocols, none demonstrated a growth advantage with earlier fortification. A subsequent meta-analysis of the three trials totaling 309 infants, confirmed no growth advantage, no decrease in duration of total parenteral nutrition, and a trend towards increased feeding intolerance and NEC with early fortification.[20] Only one of these prior trials studied infants receiving an exclusive human milk diet with HMDF.[18] In that study, infants 500-1250g at birth (n = 138) were randomized to receive early fortification at enteral intakes of 40 mL/kg/day or delayed fortification at intakes of 100 mL/kg/day, with donor milk used when maternal milk was unavailable. Infants in the early and late fortified groups had similar rates of weight gain (14.2 and 14.2 g/kg/day, respectively), linear growth (0.88 and 0.86 cm/week), and head growth (0.75 and 0.76 cm/week). These growth velocities were similar to those in our cohort despite their earlier routine fortification in a more mature population (mean gestational age > 27 weeks and birth weight > 900g). The incidence of NEC was 8% in their early fortified group (intake 40 mL/kg/day), and 6% in their later fortified group (100 mL/kg/day), not unlike that in our routine group (150 mL/kg/day). These rates of NEC substantially exceeded the low-rate observed in our group receiving selective fortification.

A mechanism relating early fortification to NEC is unclear. Fortification alters both the nutrient density and osmolality of expressed human milk, which may affect intestinal peristalsis, gut microbiome and feeding tolerance.[21] Regardless, NEC remains a too frequent complication in EPT infants and independent risk factor for adverse neurodevelopmental outcomes.[22,23]

Data linking early postnatal growth in EPT infants to neurodevelopmental outcomes are conflicting. While some studies suggest a relationship between extrauterine growth restriction and later poor outcome,[24] other studies have not found such an association.[25] No prior trial of fortification strategy has provided growth or developmental outcomes after NICU discharge. We extended our observations through two-years of age and found rapid catch-up growth regardless of neonatal fortification strategy. At 24 months our two groups were comparable in size to a national cohort of EPT infants, which similarly demonstrated substantial but incomplete catch-up growth from NICU discharge.[26] Neurodevelopmental outcomes for our cohort were also consistent with large network findings with 80% of children surviving to two-years without severe neurodevelopmental impairment.[27]

Strengths of this study include its randomized prospective design, standardized feeding protocol with rigorous adherence, and 90% follow-up through two-years. We acknowledge that this small single-center

trial was powered to detect difference in growth, rather than NEC, so the observed NEC reduction in the selective group should be confirmed in large multicenter trials.

We did not directly evaluate bone mineralization and therefore cannot exclude differences in skeletal mineral accretion between fortification strategies. However, in a prior randomized controlled trial we measured bone mineral content using photon absorptiometry in preterm infants fed PTHM with and without fortification.[28] In that study, substantially increasing calcium and phosphorous intakes did not improve bone mineral content despite measurable biochemical differences in mineral metabolism. Furthermore, bone mineral content more than doubled by 44 weeks' PMA and was similar regardless of early mineral supplementation or post-discharge feeding (formula vs. breastmilk). These historical findings have been substantiated by a more recent systematic review.[29] In the current study, we are reassured as selective fortification resulted in comparable linear growth and there was no increase in clinically apparent fractures.

Despite intensive lactation support with 95% of our EPT infant mothers initially successfully expressing milk, most could not provide sufficient volume for extended exclusive human milk feedings. Our hospital-based bank provides preterm milk, a more nutritionally appropriate alternative that may enable conservative fortifier use. This model is cost-saving: accounting for donor health screening, personnel, and pasteurization and storage equipment, our program produces milk at $14.50 per 100 mL, roughly half the cost of commercially available donor milk (Prolacta HM; Prolacta Bioscience, Inc, City of Industry, CA). Together, the availability of preterm donor milk and a selective fortification strategy allowed us to achieve growth comparable to routinely fortified cohorts, while reducing both fortifier and NEC.

Abbreviations

BPD
bronchopulmonary dysplasia
HMDF
human milk–derived fortifier
NEC
necrotizing enterocolitis
NICU
neonatal intensive care unit
PTHM
preterm human milk
PMA
post–menstrual age
ROP
retinopathy of prematurity

Declarations

Competing Interests: The authors have no competing interests, financial or otherwise, to disclose.

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DATASET AVAILABILITY

The datasets generated during this study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors have no competing interests, financial or otherwise, to disclose.

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Figures

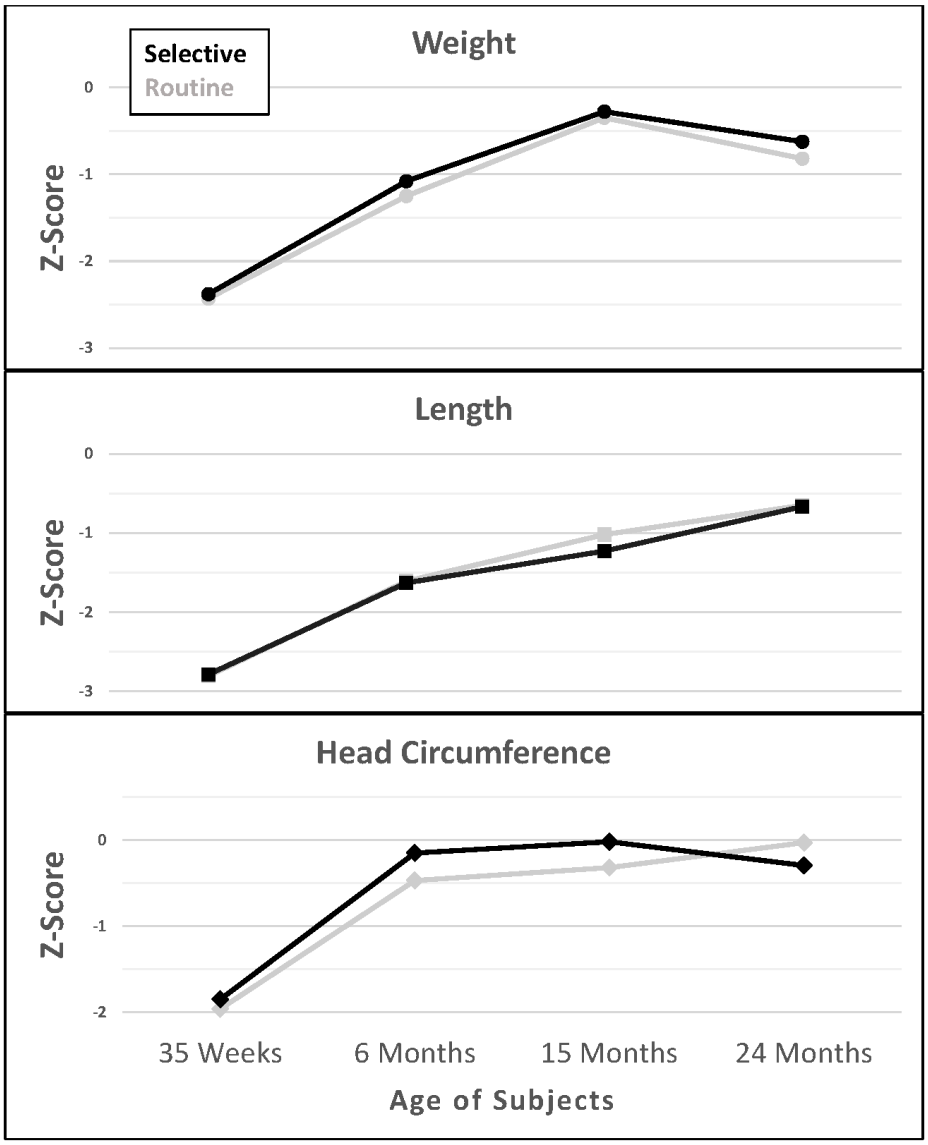


Figure 1

Growth at Study Completion through 24 Months of Age. Age adjusted for prematurity. Values were converted to z-scores and presented as means. There were no difference in growth measurements between time periods.