Cristina Fernández, MD MPH
IRB Protocol Proposal
Pediatrics, PGY-2
8/2/12

Assessment of premature infant post-discharge feeding regimens and growth during the first year

Study Purpose and Rationale

Annually in the United States 13% of infants are born premature at less than 37 weeks gestation[1] and 70% of all low birth weight infants are premature.[2] Prematurity remains associated with significant morbidities, such a vision and hearing deficits, neurocognitive impairment, and developmental delay. Small premature infants in the LBW and VLBW categories are particularly susceptibility to nutritional deficits that subsequently impact growth and neurocognitive development. General principles for feeding hospitalized preterm infants include providing sufficient nutrients and caloric intake to support optimal post-natal growth. Optimal post-natal growth or "catch-up" growth has traditionally meant a growth rate comparable to intra-uterine growth rates for weight, length, and head circumference by fetuses of the same post-conceptional age.[3] Studies by Kashyap et al. showed that hospitalized premature infants can use up to 2.8 g/kg/d of protein and 462-504 kJ (110 to 120 kcal)/kg/d of calories in the absence of metabolic stress to achieve daily growth.[4] These concentrations of protein and calories are higher than the concentrations typically fed to term infants. Several studies have shown that a total metabolic protein and energy intake of 100-125 kcal/kg/day is needed, corresponding to 110-140 kcal intake for an energy absorption rate of 85% with human milk and 90% with a well-absorbed formula.[5] Fortified breast milk is endorsed by many organizations as an strong option to provide the increase in protein and calories needed to achieve optimal post-natal growth rates. Premature infants have also been started on special calorie dense 24 kcal/oz formula or enriched 22 kcal/oz formula in cases where breast milk is unavailable or growth targets are not being met. These formulas contain added whey protein, glucose polymers, medium chain triglycerides, calcium, phosphorus, electrolytes, folate, and fat-soluble vitamins.

In spite of hospital-based comprehensive feeding regimens to optimize growth through use of human milk fortifier and/or enriched formulas, correction of acquired nutrient deficits may not be accomplished prior to discharge. Persistent nutrition and energy deficits occur in hospital and many small premature infants are experiencing extra-uterine growth failure, defined as weight at discharge being less than 10th%ile of intrauterine growth.[6-7] Nutrition deficits and extra-uterine growth failure are partly attributable to extent of immaturity, initial post-natal weight loss, and the documented 1-2 week delay in establishment of adequate dietary intake leading to slower rates of initial growth in the hospital.[8] Average daily weight gain in grams/day in a NICU population of preterm infants (23-34 weeks gestational age) was nearly one-half the projected weight gain calculated from birth weight versus gestational age curves generated from the medical record.[9] The AAP Committee on Fetus and the Newborn reports that the decision to discharge an infant is usually based on whether the infant has a sustained pattern of weight gain rather than attainment of a specific weight, and average weight at hospital discharge for premature infants is 1800-2000 grams.[10] Premature infants being discharged home on lower weights than their term counterparts may also have lower nutrient stores, insufficient bone mineralization, and a significant energy deficit greater than 3000 kJ.[11] As a consequence, these

infants remain small at discharge relative to a fetus of the same post-conceptional age and may continue to have growth retardation with subsequent morbidities.

The community pediatrician or family physician assumes care of the preterm infants upon hospital discharge, and these community providers are tasked with mitigating growth retardation and nutrition deficits over the following months. Many randomized control trials evaluating growth parameters for premature infants on enriched formulas versus term formulas or breast milk have shown improvement in growth and nutrition parameters on enriched formulas post-discharge.[12] Lucas et al. reported that U. K. preterm infants fed an enriched formula until 9 months corrected gestational age had greater weight gain and linear growth than did similar preterm infants fed standard term formula after discharge.[13] Carver et al. saw increased weight by 2 months corrected gestational age and increased length in all preterm infants on enriched formula by 3 months corrected gestational age compared to preterm infants on term formula; specifically for infants < 1250 g birth weight, the investigators saw increased weight and length at 6 months corrected age in infants on enriched formula compared to infants on term formula and more weight gained in g/day.[10] In contrast, Chan et al. showed that there were no significant differences in weight, length, and head circumference for preterm-LBW infants fed a standard term formula, a preterm formula, or an intermediate enriched formula for 8 weeks after discharge.[14] Koo et al. also showed no advantage of enriched formula over term formula for premature infants randomized to receive one or the other over 12 month period.[15] It has also been shown that infants fed enriched formula had greater bone mineral content at 3 and 9 months corrected gestational age than did infants fed standard term formula.[16-17] Cooke et al. demonstrated that premature infants who are fed term formula after reaching 40 weeks gestational age had slowing of z-score for weight and length and that it took the infants almost 2 months to upregulate the volume of term formula consumed to reach caloric intakes comparable to premature infants randomized to receive enriched formula.[18]

Several studies listed above demonstrate a significant benefit to preterm infant growth and nutrient stores in using enriched formula or milk fortifier post-discharge. However, there are currently no post-discharge feeding standards for preterm infants compared to term infants and optimal duration for using enriched 22 kcal/oz formula or human milk fortifier after hospital discharge remains unknown. Various authoritative agencies have provided different recommendations on post-discharge feeding of premature infants. In 2007, the American Academy of Family Physicians (AAFP) endorsed fortifying breast milk for infants less than or equal to 1500 g birth weight for families wanting to breastfed. For infants discharged from the hospital on formula, the AAFP recommended high caloric density 22 kcal/oz formula until catch up growth is obtained or until 12 months corrected age; if catch up growth was obtained before 12 months corrected age, the AAFP recommends continuing on standard full term infant 20 kcal/oz formula until 1 year corrected age.[19] In 2006 the Committee on Nutrition of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHN) reported that premature infants with a subnormal discharge weight for post-conceptional age are at increased risk of long-term growth failure. These infants should be discharged on human milk fortifier for supplementation if breastfed and on special post-discharge formula with high contents of protein, minerals and trace elements, and long chain polyunsaturated fatty acids at least until a post-conceptional age of 40 weeks, but possibly until about 52 weeks.[20] The Committee recognizes that further research is needed to evaluate the effects of nutritional interventions on long-term

growth. The American Academy of Pediatrics (AAP) has no official policy statement for post-discharge feeding of premature infants. In 2009 the AAP Committee on Nutrition reported that generally post-discharge formulas are often continued until 9 to 12 months' corrected age or until the baby's weight for length is maintained above the 25th%ile.[21] At the Morgan Stanley Children's Hospital of New York, administrative guidelines for post-discharge feeding of premature infants have been developed from interpretation of the literature. Premature infants of less than or equal to 34 weeks gestational age who were admitted to the Neonatal ICU are recommended post-discharge 22 kcal/oz formula. Outpatient providers are charged to monitor weight, length, and head circumference and to consider changing to term formula if catch-up growth is achieved.

The literature more consistently shows an improvement of growth and nutrition parameters on enriched formula or milk fortifier but the challenge remains interpreting the data for best practice and there continues to be no post-discharge feeding standard for premature infants. The most optimal duration at which to keep premature infants on enriched formula or human milk fortifier remains unknown, and variability in community practices for premature infant feeding can be expected. Determination of outpatient management of premature infant nutrition and evaluation of growth parameters through 1 year corrected age will lead to future development of community-based education and interventions to support best possible growth and developmental outcomes.

Hypothesis

Premature infants less than or equal to 34 weeks gestational age discharged from the CHONY NICU on premature formula 22 kcal/oz or human milk fortifier to receive outpatient follow-up in the NYP Ambulatory Care Network who are no longer on enriched formula or human milk fortifier by 4 months of age corrected will not meet target weight, length, and head circumference by 12 months of age corrected.

Study Design

I will conduct a retrospective chart review of premature infants less than or equal to 34 weeks gestational age born who were born at CHONY or the Allen Pavilion between January 2010 and January 2011 and discharged from the NYP-CHONY NICU. Two study groups will be identified:

- "On enrichment": premature infants who are documented on nutrient enriched formula or human milk fortifier by 4 months corrected age
- "Off enrichment": premature infants who are not on enriched formula or human milk fortifier (documented as either being on term formula or exclusively breastfeeding without fortification).

The primary outcome is weight at 12 months corrected age. Secondary outcomes include length and head circumference. For the purposes of analysis and comparison of groups, subjects will be considered as "on enrichment" if documented on enriched formula or human milk fortifier by 4 months of age corrected regardless of changes to nutrition at future follow-up visits. Subjects will be considered "off enrichment" if documented on term formula or exclusively breastfeeding without fortification by 4 months corrected age. Type of nutrition fed at 4 months corrected age, whether enriched formula or term formula or milk fortifier, will be confirmed by review of

nutrition items dispensed by local WIC offices as a majority of subjects followed in the NYP ACN are enrolled in WIC.

Statistical Analysis

An unpaired t-test will be calculated to compare the mean weight (and mean length and mean head circumference as secondary outcomes) at 12 months corrected age between the two defined subject groups "on enrichment" and "off enrichment." Assuming power of 80% and α=0.05, the sample size necessary to show a statistically significant effect size was calculated using mean weights with standard deviations from peer-reviewed published literature comparing preterm infants fed enriched formula to preterm infants fed term formula through 12 months. Sample size was calculated to be 120 subjects per group. A multivariate linear regression model will then be constructed to identify associations between mean weight at 12 months corrected age and birth weight categories (greater than 1500 g birth weight, less than or equal to 1500 g birth weight), sex, number of ED visits between initial hospital discharge and 12 months corrected age, and primary language spoken by a guardian.

Study Subjects

The subjects are premature infants less than or equal to 34 weeks gestation who were discharged from the CHONY NICU between January 2010 and January 2011 and followed as outpatient in the NYP Ambulatory Care Network through first year of life. Approximately 350-400 infants less than or equal to 34 weeks gestation are admitted annually to the NICU. Of those infants, approximately 150-200 have birth weight less than or equal to 1500 grams.

Infants with bronchopulmonary dysplasia, severe respiratory abnormalities and disease, cardiac abnormalities and severe complications, gastrointestinal abnormalities and disease, and other systemic diseases requiring extensive follow-up by specialty services will be excluded from the study.

Recruitment of Subjects

No subject recruitment is necessary as data will be collected via retrospective chart review.

Study Procedures

N/A

Study Questionnaire

N/A

Confidentiality of Study Data

Data will be de-identified after extraction from the medical record and each subject will be assigned a unique study ID number. A separate password-protected and encrypted spreadsheet that can match patients to their study ID numbers will be maintained by one person. All data will be encrypted on a password-protected computer with plan to securely dispose of subject identifiers at the end of the study. All data and results that are published will be stripped of any identifiers.

Potential Conflict of Interest

None.

Location of Study
The study site will be within the CUMC.

Potential Risks
There is no risk to subjects as the data will be collected via retrospective chart review.

Potential Benefits
There will be no immediate benefit to subjects as the study is a retrospective chart review. However the data evaluated could inform nutrition management for future premature infants cared for in our community.

Compensation to Subjects
No plans are made to compensate subjects as the data will be collected via retrospective chart review.

Alternative Therapies
N/A

Radiation and Radioactive Substances
N/A

References
1. Centers for Disease Control. Premature Birth. http://www.cdc.gov/Features/PrematureBirth.
2. Kaiser Family Foundation. State Health Facts, 2009. http://www.statehealthfacts.org/comparemaptable.jsp?ind=42&cat=2. Accessed July 2012.
3. Brandt I, Sticker EJ, Gausche R, Lentze MJ. Catch-up growth of supine length/height of very low birth weight, small for gestational age preterm infants to adulthood. *J Pediatr.* 2005;147:662-668.
4. Kashyap S, Schulze KF, Forsyth M, et al. Growth, nutrient retention, and metabolic response in low birth weight infants fed varying intakes of protein and energy. *J Pediatr* 1988;113:713–21.
5. Agostini C., Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants. A comment of the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2010;50(1):85-91.
6. O'Connor D, Khan S, Weishuhn K, et al. Growth and Nutrient Intakes of Human Milk-Fed Preterm Infants Provided With Extra Energy and Nutrients After Hospital Discharge. *Pediatrics* 2008;121:766-776.
7. Heird, William.(2008). "Nutritional Management of Preterm Infants Postdischarge." Chapter 34. In Duggan C., et al. (eds) *Nutrition in Pediatrics*. 4th ed. Hamilton, Ontario, Canada: BC Decker Inc; pg. 395-402.
8. Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104:280–9.

9. Clark RH, Wagner CL, et al. Nutrition in the neonatal intensive care unit: how do we reduce the incidence of extrauterine growth restriction? *J Perinatol*. 2003 Jun;23(4):337-44.
10. Carver J, Wu P, et al. Growth of Preterm Infants Fed Nutrient-Enriched or Term Formula After Hospital Discharge. *Pediatrics* 2001:107(4):683-689.
11. Fenton TR, McMillan DD, Sauve RS. Nutrition and growth analysis of very low birthweight infants. *Pediatrics*. 1990;86:378-383
12. Henderson G, Fahey T, McGuire W. Calorie and protein-enriched formula versus standard term formula for improving growth and development in preterm or low birth weight infants following hospital discharge. *Cochrane Database Syst Rev* 2005;(2):CD004696.
13. Lucas A, King F, and Bishop NB. Postdischarge formula consumption in infants born preterm. *Arch Dis Child* 1992;67:691-692.
14. Chan, G. M., Borschel, M. W. & Jacobs, J. R. Effects of human milk or formula feeding on the growth, behavior, and protein status of preterm infants discharged from the newborn intensive care unit. *Am. J. Clin. Nutr*. 1994;60:710–716.
15. Koo W and Hockman E. Posthopsital discharge feeding for preterm infants: effects of standard compared with enriched milk formula on growth, bone mass, and body composition. *Am J Clin Nutr* 2006;84:1357-1364.
16. Bishop, N. J., King, F. J. & Lucas, A. Increased bone mineral content of preterm infants fed with a nutrient enriched formula after discharge from hospital. *Arch. Dis. Child*. 1993;68: 573–578.
17. Lapillone A, Salle BL, et al. Bone mineralization and growth are enhanced in preterm infants fed an isocaloric, nutrient-enriched preterm formula through term. *Am J Clin Nutr*. 2004;80:1595-1603.
18. Cooke R, Griffin I, and McCormick K. Adiposity Is Not Altered in Preterm Infants Fed With a Nutrient-Enriched Formula After Hospital Discharge. *Pediatric Research* 2010;67(6):660-664.
19. Lahood A and Bryant C. Outpatient Care of the Premature Infant. *American Family Physician.* 2007:76(8):1159-1164. http://www.aafp.org/afp.
20. Aggett PJ, Agostoni C, Axelsson I, et al. Feeding preterm infants after hospital discharge: a commentary by ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2006;42(5):596-603.
21. AAP Committee on Nutrition, Kleinman R. Pediatric Nutrition Handbook, 6th Edition. American Academy of Pediatrics, 2009.