Neonatal Nutrition: Defining Growth Outcomes

Deborah Steward, Research Mentor

Stefani Heger, Student Researcher

The Ohio State University

College of Nursing

Table of Contents

Chapter I- Statement of the Problem

Promoting growth in preterm infants, those born before 38 weeks gestation, is a difficult challenge in the neonatal intensive care unit (NICU). By the time these infants are discharged from the NICU, their attained weights are significantly below the 10th percentile (Clark, Thomas, & Peabody, 2003; Fanaroff et al., 2007). Growth faltering begins during the first few weeks of life. One of the most important reasons is the difficulty in providing adequate nutrition to these infants. Researchers have demonstrated that extremely preterm infants are often undernourished and develop significant calorie and protein deficits (Ernst, Radmacher, Rafail, & Adamkin, 2003; Grover, Khashu, Mukherjee, & Kairamkonda, 2008).

An important cause is the lack of agreement with how these infants should be nourished, both parenterally and enterally (Uhing & Das, 2009). Findings from a recent survey indicated that variability exists across NICUs in relation to nutrition practices (Hans et al., 2009; Olsen et al., 2002). This variability may be impeding improvement in neonatal nutrition practices that could benefit preterm infants and their growth.

Chapter II- Review of the Literature

Every year approximately 560,000 preterm infants are born ( ). One of the most important issues for these infants is promoting adequate growth, which is crucial for proper skeletal and neurological development. It has been found that about 97% of extremely preterm infants develop a significant growth deficit by the time they are discharged from the hospital, attaining weights below the 10th percentile (Ehrenkranz, et al., 2006). A growth trajectory below the 10th percentile is consistent with IUGR (intrauterine growth retardation). Proper nutritional intake is viewed as the most

important strategy to promote adequate growth and much is currently being written about defining adequate nutrition (Thureen, 2007; Ziegler, 2007). However, despite the increased attention to this issue, there is a lack of consensus regarding what comprises adequate nutrition. In fact, no established standard measure of growth for the first 28 days of life exists (Olsen et al, 2002). Adding to this dilemma, a national survey and results from nutrition research indicate that variability exists across NICUs regarding nutrition practices including feeding by special routes (Hans et al., 2009; Olsen et al., 2002). Likewise, aggressive nutritional strategies have not resulted in a significant improvement in growth (Thureen, 2007; Ziegler, 2007). An important question, then, is whether this is a function of the variability in how growth is being quantified.

Growth is often used as the primary outcome in nutrition research. However, researchers do not agree on how to define growth. For example, there are discrepancies as to how to calculate growth velocity and which growth reference to use. Until researchers can agree about how to measure growth, nutrition practices will most likely not change, growth for these infants will not improve, and medical costs and morbidity will continue to rise.

Purpose of Study

The purpose of this study was to review neonatal nutrition research from the last ten years and examine how growth was operationalized. Discrepancies and inconsistencies in the data were examined and possible effects on practice considered in order to make a subsequent recommendation.

Significance of Study

After examining these characteristics of growth, implications for neonatal nutrition research were explored. The possibility exists that the applicability of findings from neonatal nutrition research are not generalized and embraced by clinicians due to the way growth outcomes are defined. If this is the case, then it is extremely difficult to make changes to neonatal nutrition regimens and actual nutrition practices in hospital NICUs. Not only does this affect the preterm infants being studied, but it also carries a large financial burden associated with the increased cost accompanying the infant's increased hospital stay and medical expenditures.

Research Questions

The study will attempt to answer the following questions?

- How are researchers measuring growth in neonatal studies?
- How are researchers reporting growth in neonatal studies?
- Are SGA infants included in the studies?
- Are researchers using growth references to categorized infants as SGA?
- If yes, do researchers specify which growth reference was used?
- How much variability actually exists in the literature for measuring and reporting growth in neonatal nutrition studies?

Definition of Terms

Preterm infant- infant born before 38 weeks gestation

Chapter III- Methodology

Research Design

In order to gain information about the variability that exists in reporting growth measures across neonatal nutrition studies, a quantitative study that synthesized

information from existing nutrition studies was conducted. An extensive literature search using PubMed, MEDLINE, and CINAHL spanning the past ten years was conducted in order to find neonatal nutrition studies with following criteria: sample only included preterm infants, nutrition was manipulated as a variable, and growth was included as a primary outcome variable. From this search, twenty-five articles were deemed appropriate for use in this study. A collection grid was then created in order to abstract the data from the article for analysis. Data included: growth parameters (i.e. height, weight, lower leg growth rate, tyrosine and thyroxine levels, and head circumference), how growth velocity was calculated (including starting point), how the researchers defined 'preterm' (i.e. by birth weight and/or gestational age), growth reference used, methods of stratification (i.e. by birth weight or gestational age) if applicable, and whether the sample included small for gestational age infants. It was hypothesized that significant variability would exist across studies in terms of how growth was measured and reported, how 'preterm' was defined, and how the different researchers decided to stratify their samples. Likewise, it was hypothesized that most studies would not identify what growth reference was used to determine whether an infant was 'preterm' and how growth was measured. The data was reported in frequencies and percentages in order to make useful comparisons among the studies.

Chapter IV- Research Results

Twenty-five neonatal nutrition articles were included in this research study. The articles were deemed representative of all neonatal nutrition studies since they span the past ten years and include all studies where growth was measured, reported, and considered an important outcome variable. Anthropometric indices of growth included in

the research, aside from weight, were: head circumference, length, lower leg length, middle arm circumference, and triceps. Across the twenty-five studies, seven different indicators of weight were reported, including: z-scores, grams, grams/day, grams/kilogram/day, % change, attained weight, and EUGR (extra uterine growth retardation). It was also determined that across studies, researchers used a mean of 2.84 +/- 1.7 indicators and a range of 1-8 indicator(s) to analyze growth.

SGA infants were included in 56% of studies, while they were excluded from 16% of the studies. In 28% of the studies, researchers were unclear or did not specify whether or not SGA infants were included. Of the 56% of studies that did include SGA infants, only 14.3% specified that a growth reference was used to determine whether birth weight was appropriate for gestational age or not.

Chapter V- Summary, Conclusions, and Recommendations

It is clear from the literature that growth is an important outcome variable being examined in neonatal nutrition studies, with weight being the primary measure. Across studies, significant variability exists in relation to measuring and reporting growth. This was particularly true for indicators of weight gain. The result is that this variability will, and is, limiting the ability to compare findings across studies, as well as to replicate studies. The inclusion of SGA infants in these studies is also an important factor affecting measures of growth, since infants who are SGA grow differently than infants who are AGA. Most infants born SGA have experienced intrauterine growth restriction and have the potential for catch-up growth, the return towards one's original growth channel. However, the extent, speed, and time of onset of catch-up growth are variable and unpredictable, leading to altered growth trajectories (Ziegler, 2007).

A possible limitation of this study is the small sample size. However, this could not be corrected since limited research exists, in general, related to neonatal nutrition and growth.

Recommendations

It is evident that nutritional intake and growth of preterm infants will not improve if there continues to be a lack of uniformity in relation to measuring growth. Growth measures across neonatal studies should be standardized. Likewise standardization needs to exist in defining the term 'preterm', calculating growth velocity, measuring and reporting growth and weight gain, and in the use of growth references and how they are reported in the literature.

Several of these needs can be fulfilled by NICU nurses. The growth of the infant is ultimately the responsibility of the health care team that is caring for him/her. Use of a growth chart to consistently monitor the infant's growth can provide more substantial information about the infant's overall health in the long run. Likewise, the NICU nurse is in an ideal position to educate the family of the infant, as well as to advocate for the patient if appropriate growth is not being achieved.

The American Academy of Pediatrics recommends that preterm infants grow at a rate of 15 g/kg/day, a rate that duplicates the intrauterine growth velocity of a normal fetus during the 3rd trimester (Steward, 2002). Therefore, in order to produce clinically meaningful data and positively impact clinical practice, it is our recommendation that future neonatal nutrition studies use g/kg/day as the primary indicator of growth.

References

Anchieta, L.M., Xavier, C.C., Colosimo, E.A., & Souza, M.F. (2003). Weight of preterm newborns during the first twelve weeks of life. *Brazilian Journal of Medical and Biological Research, 36*, 761-770.

Arslanoglu, S., Moro, G.E., & Ziegler, E.E. (2006). Adjustable fortification of human milk fed to preterm infants: does it make a difference? *Journal of Perinatology, 26*, 614-621.

Clark, R.H., Chace, D.H., & Spitzer, A.R. (2007). Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: a randomized, controlled trial. *Pediatrics, 120* (6), 1286-1296).

Cormack, B.E., & Bloomfield, F.H. (2006). Audit of feeding practices in babies <1200g or 30 weeks gestation during the first month of life. *Journal of Paediatrics and Child Health, 42*, 458-463.

Donovan, R., Puppala, B., Angst, D., & Coyle, B.W. (2006). Outcomes of early nutrition support in extremely low-birth-weight infants. *Nutrition in Clinical Practice, 21* (4), 395-400.

Dsilna, A., Christensson, K., Alfredsson, L., Lagercrantz, H., & Blennow, M. (2005). Continuous feeding promotes gastrointestinal tolerance and growth in very low birth weight infants. *Journal of Paediatrics and Child Health, 147*, 43-49.

Ehrenkranz, R.A., Dusick, A.M., Vohr, B.R., Wright, L.L., Wrage, L.A., & Poole, W.K. (2006). Growth in the neonatal intensive care unit influences neurodevelopmental

and growth outcomes of extremely low birth weight infants. *Pediatrics, 117* (4), 1253-1261.

Eleni-dit-Trolli, S., Kermorvant-Duchemin, E., Huon, C., Mokthari, M., Husseini, K., Brunet, M.L., . . . Lapillonne, A. (2009). Early individualised parenteral nutrition for preterm infants. *Archives of Disease in Childhood-Fetal and Neonatal Edition, 94*, 152-153.

Embleton, N.E., Pang, N., & Cooke, R.J. (2001). Postnatal Malnutrition and Growth Retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics, 107* (2), 270-2273.

Erasmus, H.D., Ludwig-Auser, H.M., Paterson, P.G., Sun, D., & Sankaran, K. (2002). Enhanced weight gain in preterm infants receiving lactase-treated feeds: a randomized, double-blind, controlled trial. *Journal of Pediatrics, 141*, 532-537.

Ernst, K.D., Radmacher, P.G., Rafail, S.T., & Adamkin, D.H. (2003). Postnatal malnutrition of extremely low birth-weight infants with catch-up growth postdischarge. *Journal of Perinatology, 23* (6), 477-482.

Fanaroff, A.A., Stoll, B.J., Wright, L.L., Carlo, W.A., Ehrenkranz, R.A., Stark, A.R., . . . NICHD Neonatal Research Network. (2007). Trends in neonatal morbidity and mortality for very low birthweight infants. *American Journal of Obstetrics and Gynecology, 196* (2), 147.

Fewtrell, M.S., Morley, R., Abbott, R.A., Singhal, A., Isaacs, E.B., Stephenson, T., . . . Lucas, A. (2002). Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. *Pediatrics, 110* (1), 73-82.

Geary, C.A., Fonseca, R.A., Caskey, M.A., & Malloy, M.H. (2008). Improved growth and decreased morbidities in <1000 g neonates after early management changes. *Journal of Perinatology, 28*, 347-353.

Grover, A., Khashu, M., Mukherjee, A., & Kairamkonda, V. (2008). Iatrogenic malnutrition in neonatal intensive care units: urgent need to modify practice. *Journal of parenteral and enteral nutrition, 32* (2), 140-144.

Guzmán, J.M., Jaraba, M.P., De La Torre, M.J., Ruiz-González, M.D., Huertas, M.D., Alvarez, R., & Zapatero, M. (2001). Parenteral nutrition and immature neonates: comparative study of neonates weighting under 1000 and 1000-1250 g at birth. *Early Human Development, 65*, S133-S144.

Hans, D.M., Pylipow, M, Long, J.D., Thureen, P.J., & Georgieff, M.K. (2009). Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. *Pediatrics, 123*, 51-57.

Ho, M., Yen, Y., Hsieh, M., Chen, H., Chien, S., & Hus-Lee, S. (2003). Early versus late nutrition support in premature neonates with respiratory distress syndrome. *Nutrition, 19*, 257-260.

Kotsopoulos, K., Benadiba-Torch, A., Cuddy, A., & Shah, P.S. (2006). Safety and efficacy of early amino acids in preterm <28 weeks gestation: prospective observational comparison. *Journal of Perinatology, 26*, 749-754.

Kuschel, C.A., Evans, N., Askie, L., Bredemeyer, S., Nash, J., & Polverino, J. (2000). A randomized trial of enteral feeding volumes in infants born before 30 weeks' gestation. *Journal of Paediatrics and Child Health, 36* (6), 581-586.

Lenclen, R., Crauste-Manciet, S., Narcy, P., Boukhouna, S., Geffray, A., Guerrault, M., . . . Brossard, D. (2006). Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants. *European Journal of Pediatrics, 165*, 512-518.

Martin, C.R., Brown, Y.F., Ehrenkranz, R.A., O'Shea, M., Allred, E.N., Belfort, M.B., . . . Extremely Low Gestational Age Newborns Study Investigators. (2009). Nutritional practices and growth velocity in the first month of life in extremely premature infants. *Pediatrics, 124* (2), 649-657.

O'Connor, D.L., Hall, R., Adamkins, D., Auestad, N., Castillo, M., Connor, W.E., . . . Zemon, V. (2001). Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. *Pediatrics, 108* (2), 359-371.

Olsen, I.E., Richardson, D.K., Schmid, C.H., Ausman, L.M., & Dwyer, J.T. (2002). Intersite differences in weight growth velocity of extremely premature infants. *Pediatrics, 110* (6), 1125-1132.

Radmacher, P.G., Lewis, S.L., & Adamkin, D.H. (2009). Early amino acids and the metabolic response of ELBW infants (\< 1000g) in three time periods. *Journal of Perinatology, 29*, 433-437.

Rodriguez, A., Raederstorff, D., Sarda, P., Lauret, C., Mendy, F., & Descomps, B. (2003). Preterm infant formula supplementation with x linolenic acid and docosahexaenoic acid. *European Journal of Clinical Nutrition, 57*, 727-734.

Steward, D.K., & Pridham, K.F. (2002). Growth patterns of extremely-low-birth-weight hospitalized preterm infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 31* (1), 57-65.

Tan, M.J., & Cooke, R.W. (2008). Improving head growth in very preterm infants: a randomised controlled trial I: neonatal outcomes. *Archives of Disease in Childhood-Fetal and Neonatal Edition, 93*, 337-341.

Thureen, P.J. (2007). The neonatologist's dilemma: catch-up growth or beneficial undernutrition in very low birth weight infants- what are optimal growth rates? *Journal of pediatric gastroenterology and nutrition, 48*, 121-122.

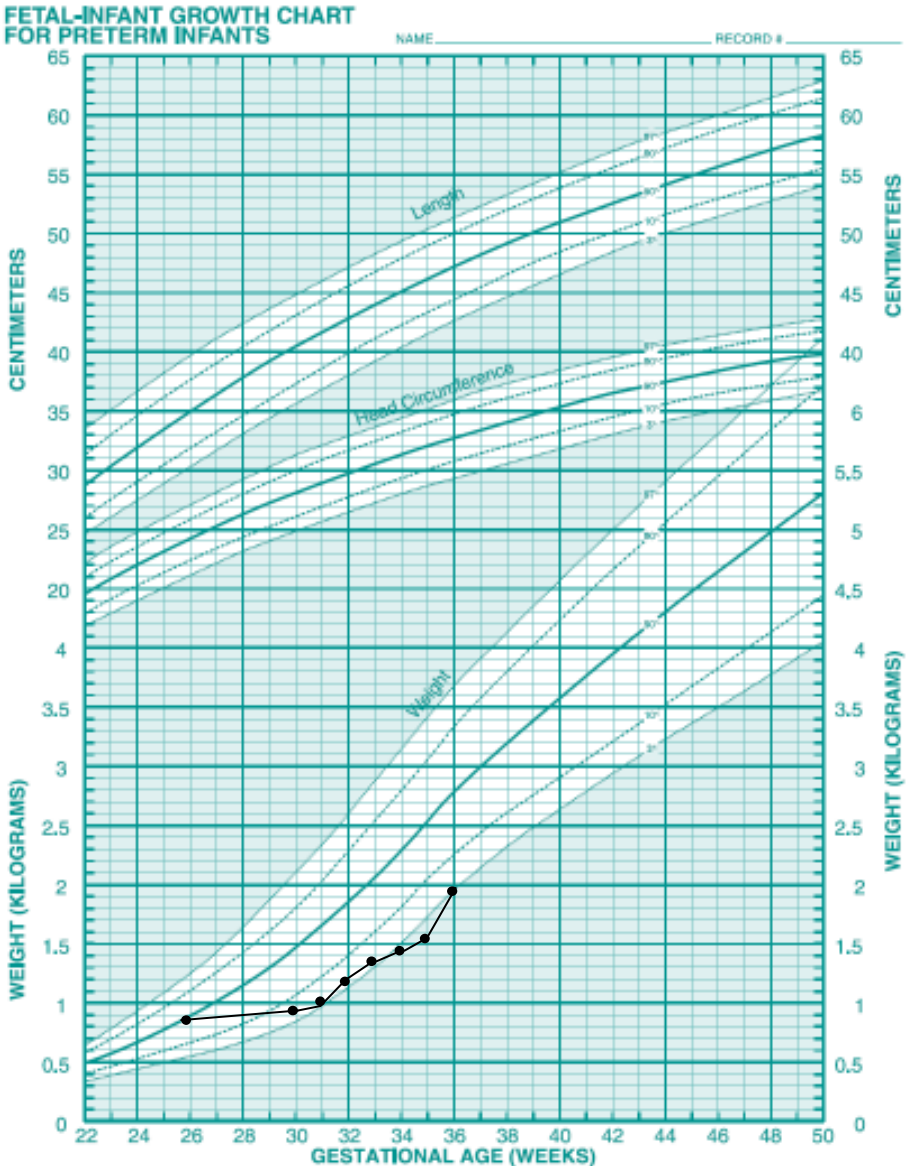
Uhing, M.R., & Das, U.G. (2009). Optimizing growth in the preterm infant. *Clinical Perinatology, 36* (1), 165-176.

Valentine, C.J., Fernandez, S., Rogers, L.K., Gulati, P., Hayes, J., Lore, P., . . . Welty, S.E. (2009). Early amino-acid administration improves preterm infant weight. *Journal of Perinatology, 29*, 428-432.

Westerbeek, E.A.M., van Elburg, R.M., van den Berg, A., van den Berg, J., Twisk, J.R., Fetter, W.P.F., & Lafeber, H.N. (2008). Design of a randomised controlled trial on immune effects of acidic and neutral oligosaccharides in the nutrition of preterm infants: carrot study. *BMC Pediatrics, 8* (46), PAGE NUM?

Ziegler, E.E. (2007). Nutrient requirements of premature infants. *Nutrition support for infants and children at risk, 59*, 161-176.

Appendix A


FETAL-INFANT GROWTH CHART
FOR PRETERM INFANTS
NAME
RECORD #
CENTIMETERS
WEIGHT (KILOGRAMS)
Length
Head Circumference
Weight
GESTATIONAL AGE (WEEKS)
22 24 26 28 30 32 34 36 38 40 42 44 46 48 50

Appendix B

Author	Purpose	Population	Weight Indices of Growth	Other Anthropometric Indices	Inclusion of SGA & reference
Olsen	- To explain differences in weight growth velocity of extremely premature infants in 6 Level III NICUs	- 564 infants, stratified by GA - <30 weeks GA -In NICU at least 16 days	- g/kg/day - GV 3-28 days of life		- Included SGA - SGA deemed < 5th percentile - No growth reference identified
Westerbeek	- To determine the effect of enteral supplementation of acidic and neutral oligosaccharides on infectious morbidity, immune response to immunizations, feeding tolerance and short-term and long-term outcome in preterm infants	- 120 preterm infants - <32 weeks GA and/or BW <1500 g - Stratified by BW	- z-scores		- Included SGA - SGA deemed < 10th percentile - Growth reference identified
Arslanoglu	- To evaluate a new adjustable fortification regimen that would increase infants' protein intakes and improve weight gain compared to	- 32 infants - 26-34 weeks GA - 600-1750 g BW	- g/ day - g/kg/day	- length - HC	- Included SGA - No growth reference identified

	standard fortification regimens				
Clark	- To measure the effects of 2 distinct strategies for parenteral nutrition on neonatal growth and blood amino acid profiles	- 122 neonates - 23-29 and 6/7 weeks GA	- g/day - g/kg/day - attained weight - GV 0-28 days of life	- change in occipitofrontal HC (cm) - length - length change (cm)	- Included SGA - No growth reference identified
Cormack	- To compare nutritional intake and growth in babies on a specific unit with published data	- 34 infants - <30 weeks GA or <1200 g BW	- z-scores - g/day - g/kg/day - attained weight - GV ?- 30 days		- Included SGA - Growth reference identified
Donovan	- To evaluate the adherence to the nutrition guidelines and to compare pre- and post guideline outcomes	- 70 infants - </ 1250 g BW	- g - g/day		- ELBW defined as <1000g - No growth reference identified
Eleni-dit-Trolli	- To evaluate the effect of a computerized parenteral nutrition ordering process on improving early nutritional intake, reducing early nutritional deficit, and influencing early growth and neonatal	- </ 28 weeks GA	- z-scores		

	outcomes				
Kotsopoulos	- To assess the safety and efficacy of early amino acid administration in preterm neonates	- 32 infants - < 28 weeks GA	- g - g/kg/day - attained weight	- change in HC (mm/day) - length	- Growth reference identified
Kuschel	- To compare the effect of two volumes of enteral feeds on postnatal growth in infants born before 30 weeks gestation	- 54 infants - < 30 weeks GA	- g/kg/day - attained weight - g/kg/day start pt= unknown	- length - occipitofrontal HC - mid-arm circumference - static triceps skinfold thickness - arm area - arm muscle area - arm fat area	
Radmacher	- To evaluate early amino-acid administration in ELBW infants over three time periods	- </ 1000g BW	- % - attained weight	- change in occipitofrontal HC (cm)	- Included SGA defined as < 3rd percentile - No growth reference identified
Tan	- To examine the feasibility of providing macronutrients at amounts above current recommendations to improve nutrition and head growth in preterm infants	- 142 infants - < 29 weeks GA	- z-scores - attained weight - g/kg/d start pt= BW	- length - HC (z-scores) - lower leg growth rate - change in HC (mm/d) - length (z-scores) - mid arm circumference	- Included SGA - No growth reference identified

Valentine	- To examine the hypothesis that the effect of early amino acid administration to infants with BW < 1500 g would result in fewer infants < 10^{th} percentile at 36 weeks postconceptual age than infants receiving amino acids after 24 hrs of life	- < 1500 g BW	- z-scores - g - weight gain= DC weight - BW - statistical adjustments made to weight		- Growth reference identified
Dsilna	- To compare the effects of continuous vs. intermittent feeding on GI tolerance and growth in VLBW infants	- 70 infants - < 1200 g BW and 24-29 weeks GA		- lower leg growth rate (mm/d)	- Included SGA - No growth reference identified - VLBW defined as < 1200 g BW
Lenclen	- To evaluate the relevance of the implementation of a standardized parenteral nutrition regimen on one unit	- 40 infants - < 32 weeks GA	- g - loss of BW (%)		- Included SGA
Guzman	- To examine and analyze parenteral and enteral nutrition and the differences in the evolution of the weight curve in immature infants	- 53 neonates - < 1250 g BW and 23-34 weeks GA	- g/kg/day - g/day - attained weight - g/kg/day start pt= unknown	- HC (cm)	- Included SGA - No growth reference identified

Ho	- To evaluate two different modes of nutrition supplementation in premature neonates with respiratory distress syndrome	- 108 neonates - 1100-2000 g BW and < 37 weeks GA	- g/kg/day		- Included SGA - No growth reference identified
Anchieta	- To assess the weight of preterm AGA newborns during 1st 12 weeks of life	- 260 preterm infants - < 2500 g BW - Stratified by BW (250 g intervals)	- g/day - g/kg/day - %		- Only included AGA - Growth reference identified
Rodriguez	- To investigate if supplementation of formula with a high DHA/EPA ratio with ALA was able to maintain plasma and red blood cell DHA levels similar to that of breast milk feeding w/o altering n-6 fatty acid status	- 38 preterm infants - < 34 weeks GA and BW > 10th percentile	- g/kg/day - attained weight - loss of BW (%)	- length - HC (cm)	- No growth reference identified
Erasmus	- To evaluate whether lactase-treated preterm feeds enhance weight gain and feeding tolerance in premature infants	- 130 infants - 26-34 weeks postconceptu-al age - stratified by GA	- g/day	- change in occipitofrontal HC (cm) - length	- Included SGA - No growth reference identified
Martin	- To describe nutritional practices	- 1187 newborns	- z-scores - g/kg/day		

	in 1st month of life for extremely low GA newborns and determine the impact of these practices on GV	- 23-27 6/7 weeks GA	- GV 7-28 days of life		
Embleton	- To prospectively document energy and protein intakes, compare the intakes with RDI, and to examine the relationship between the accumulated deficit and postnatal growth	- 105 infants - </ 1750 g BW and </ 34 weeks GA - stratified by GA	- z-scores - %		
Fewtrell	- To test the hypothesis that the balanced addition of n-3 and n-6 LCPUFA to a formula would result in improved subsequent neuro-developmental outcome at 9 and 18 months corrected age; to test safety and tolerance of the formula	- 195 infants - < 1750 g BW and < 37 weeks GA - stratified by BW	- z-score - g/kg/day - attained weight	- length - HC (mm/d)	- Included SGA - No growth reference identified
O'Connor	- To assess effects of supplementing premature infant	- 470 infants - 750-1800 g BW and < 33	- g - g/kg/day	- length (mm/wk) - HC (mm/wk)	- Included SGA - No growth reference identified

	formulas with oils containing the long-chain polyunsaturated fatty acids AA and DHA on growth, visual acuity, and multiple indices of development	weeks GA - stratified by BW			
Geary	- To investigate the hypothesis that changes in surfactant at delivery followed by immediate extubation to nasal CPAP, decreased oxygen exposure, and early parenteral amino acids would decrease the incidence of EUGR by 25%	- </ 1000 g BW	- attained weight - %		- Only included AGA - No growth reference identified - EUGR defined as growth < 10^{th} percentile for postmenstrual age
Trintis	- To evaluate the safety and efficacy of early amino acid administration in VLBW infants	- < 1500 g BW	-attained weight		-Included SGA -No growth reference identified