

## ORIGINAL ARTICLE

## Early amino-acid administration improves preterm infant weight

CJ Valentine<sup>1,2,3</sup>, S Fernandez<sup>4</sup>, LK Rogers<sup>3</sup>, P Gulati<sup>4</sup>, J Hayes<sup>3,5</sup>, P Lore<sup>2</sup>, T Puthoff<sup>1</sup>, M Dumm<sup>1,6</sup>, A Jones<sup>1</sup>, K Collins<sup>1</sup>, J Curtiss<sup>1</sup>, K Hutson<sup>1,6</sup>, K Clark<sup>1</sup> and SE Welty<sup>1,2,3</sup><sup>1</sup>Department of Pediatrics, Neonatal Nutrition Team, Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA;<sup>2</sup>Department of Pediatrics, Section of Neonatology, Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA;<sup>3</sup>Department of Pediatrics, The Research Institute, Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA; <sup>4</sup>Center for Biostatistics, Ohio State University, Columbus, OH, USA; <sup>5</sup>Department of Pediatrics, Ohio State University, Pacific University, Forest Grove, OR, USA and <sup>6</sup>Ohio Health, Ohio State University, Columbus, OH, USA

**Objective:** Premature infants, especially those born less than 1500 g, often exhibit slow overall growth after birth and lack of early nutritional support may be an important element. We tested the hypothesis that early administration of amino acids (within the first few hours of life) to infants born at less than 1500 g would be associated with fewer infants that were less than the 10th percentile at 36 weeks post-conceptual age than infants that received amino acids after the first 24 h of life.

**Study Design:** A prospective intervention of early amino-acid (EAA) supplementation, began before 24 h of life, in preterm infants, <1500 g, was compared to a retrospective cohort of preterm infants receiving late amino-acid (LAA) supplementation, began after 24 h of life. The primary outcome variable was the proportion of infants at less than the 10th percentile at 36 weeks post-conceptual age.

**Result:** Fewer infants fell below the 10th percentile ( $P < 0.001$ ) in the EAA group. Furthermore, infants in the EAA groups had significantly greater weight gains than did the LAA group ( $P < 0.003$ ) after adjusting for gestational age and time from birth to discharge. In addition, shorter duration of parenteral nutrition was associated with EAA supplementation ( $P < 0.001$ ).

**Conclusion:** A prospective strategy of EAA in preterm infants <1500 g was associated with an improved weight gain, suggesting that nutrition that included amino acids may be critical during the first 24 h of life.

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included amino acids may be essential due to limited glycogen and fat reserves.<sup>1</sup> Despite this information, significant nutrient deficiencies are observed in the neonatal intensive care unit (NICU)<sup>3</sup> and premature infants are frequently discharged at weights less than the 10th percentile.<sup>4</sup> Perhaps more concerning than low discharge weights is the association of poor growth in the early weeks of hospitalization with abnormal neurodevelopment and an increased prevalence of cerebral palsy.<sup>5</sup> The goal of early amino-acid (EAA) supplementation is to provide the preterm infant with intravenous substrate that promotes protein deposition and increased lean body mass that more closely approximates fetal energy production and growth.<sup>6</sup> Recently, it has become evident that protein delivery of  $3 \text{ g kg}^{-1}$  per day beginning on day 1 of life is safe and is associated with plasma amino-acid concentrations similar to those of second and third trimester fetuses.<sup>7</sup> Protein deliveries as minimal as  $1.5 \text{ g kg}^{-1}$  per day have resulted in a neutral/positive nitrogen balance in most infants<sup>8</sup> but maximizing protein to provide  $3 \text{ g kg}^{-1}$  per day beginning immediately after delivery may further enhance protein deposition that is essential for early growth.<sup>9</sup> The amount of energy required to support post-delivery growth rates in premature infants has been demonstrated to be approximately  $3 \text{ g kg}^{-1}$  per day of protein and  $90 \text{ kcal kg}^{-1}$  per day.<sup>10,11</sup> In the present study, we tested the hypothesis that early administration (<24 h of life) of parenteral nutrition with EAA supplementation would be associated with better growth in preterm infants than in infants in which amino-acid supplementation was delayed (>24 h of life) (late amino acids, LAA).

## Introduction

The preterm infant misses the last trimester of fetal nutrient accretion<sup>1,2</sup> and requirement for immediate nutrient delivery that

## Methods

The study was conducted in four NICUs contracted by Nationwide Children's Hospital in Columbus, OH after institutional review board approval (IRB no. 05-00411). Informed consent was not needed as the prospective intervention was a quality improvement process in the nursery. All data were collected by the same individual as a part of the Vermont Oxford NIC/Q (Neonatal

Correspondence: Dr CJ Valentine, Neonatal Nutrition and the Lactation Program, Section of Neonatology, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA. E-mail: Christina.Valentine@nationwidechildrens.org

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Intensive Care Unit Collaborative for Quality Improvement) and it incorporated a PDSA (plan-do-study-act) to implement the change. These types of cycles to implement changes have been described by Horbar<sup>12</sup> and in each individual cycle, specific plans are developed (Plan), the plans are conducted (Do), the results are evaluated (Study) and actions are taken based on what has been learned (Act). In this cycle the plan was to devise a strategy to initiate parenteral nutrition including amino acids on admission to the NICUs. The Do was to implement the intervention after education of all staff and pharmacy, which began in 2005, previously infants were begun on glucose on day 1 of life and parenteral nutrition including amino acids was usually started on day 2 of life, at the discretion of the neonatal team. The study component was to determine the effect of the intervention, which is encompassed in the data presented herein. The act component was to adopt the EAA approach on all infants born less than 1500 g at birth.

### Subjects

All preterm infants born during 2004 to 2006 and weighed <1500 g at birth, were appropriate for gestational age and survived the first 2 weeks after delivery were included in the study.

### Intervention

EAA and LAA supplementation had identical composition that consisted of TrophAmine (B. Braun, Bethlehem, PA, USA) with dextrose. The primary variable was the time of administration. Infants receiving EAA were given 3 g kg<sup>-1</sup> per day of amino acids in glucose administered at 6 to 8 mg kg<sup>-1</sup> per min in the NICU immediately after delivery. Within 24 h, glucose load was increased and lipid emulsion was added to provide 90 kcal kg<sup>-1</sup> per day. All clinical staff and faculty were instructed on the new standard of care and the goal to start the EAA as the first fluids immediately after delivery. Computer order entry was available for 'starter TPN' which was the notation used for EAA, and pharmacy links were instrumental in expediting the process. Monthly audits revealing failure to order EAA resulted in updated staff training and improvement in compliance. No abnormal elevations in blood urea

nitrogen or complications were associated with the new practice. No infants were withdrawn for intolerance.

### Statistical analyses

Descriptive analyses (two group comparisons) were performed for all the potential covariates and outcome measures and results are provided in Table 1. A generalized linear model was used to compare the mean weight gain between LAA (birth year 2004) and EAA (birth years 2005 and 2006) groups. Weight gain was computed as the difference between the weight at discharge and birth weight. Because greater weight gains could be a consequence of longer hospitalization, gestational age and time from birth to discharge were included in the model as a covariates and the weight gain was adjusted accordingly. Gestational age was included in the final model to control for differences in gestational ages at birth even though the variable 'time from birth to discharge' was included in the final model. High positive correlations were anticipated between age at discharge and weight gain. A sensitivity analysis using the number of infants in the 10th percentile of the infant growth chart by age and amino-acid supplementation data was performed.  $\chi^2$ -Tests and one-way analysis of variance were used for these sensitivity analyses.

### Results

In the years 2005 and 2006, 151 and 157 infants received EAA, respectively. These 308 infants were compared to 132 preterm infants from 2004 that did not receive the EAA supplementation. Table 1 shows the descriptive statistics, *P*-values and confidence intervals (CIs) for the unadjusted means of several variables, including the outcome measures. The unadjusted means for birth weight were marginally significantly different between the two groups (*P* = 0.059; Table 1), with lower birth weight infants in the EAA group. Incidences of intraventricular hemorrhage (IVH), bacteremia, necrotizing enterocolitis (NEC) were not significantly different among all groups studied (Table 2). A marginally greater

**Table 1** Demographics and weight data analyzed by LAA vs EAA

|                                      | LAA, mean (s.e.),<br>N = 132 | EAA, mean (s.e.),<br>N = 308 | Difference<br>(EAA-LAA) | P-value            | 95% CI          |
|--------------------------------------|------------------------------|------------------------------|-------------------------|--------------------|-----------------|
| Birth weight (g)                     | 1202.2 (20.1)                | 1157.9 (13.0)                | -45.30                  | 0.059              | (-92.40, 1.73)  |
| Gestational age (weeks)              | 29.4 (0.19)                  | 29.06 (0.13)                 | -0.38                   | 0.106              | (-0.85, 0.08)   |
| Discharge weight (g)                 | 2242.8 (33.4)                | 2342.8 (24.3)                | 100.04                  | 0.016 <sup>a</sup> | (18.69, 181.39) |
| Gestational age at discharge (weeks) | 36.48 (0.17)                 | 36.73 (0.13)                 | 0.25                    | 0.241              | (-0.17, 0.68)   |
| Net time (weeks)                     | 7.04 (0.23)                  | 7.68 (0.16)                  | 0.64                    | 0.025 <sup>a</sup> | (0.08, 1.19)    |
| Weight gain                          | 1040.6 (38.8)                | 1186.0 (26.8)                | 145.379                 | 0.003 <sup>a</sup> | (50.76, 239.99) |
| Birth weight <1000 g (%)             | 20.45                        | 26.62                        | 6.17                    | 0.153              | (-0.02, 0.15)   |

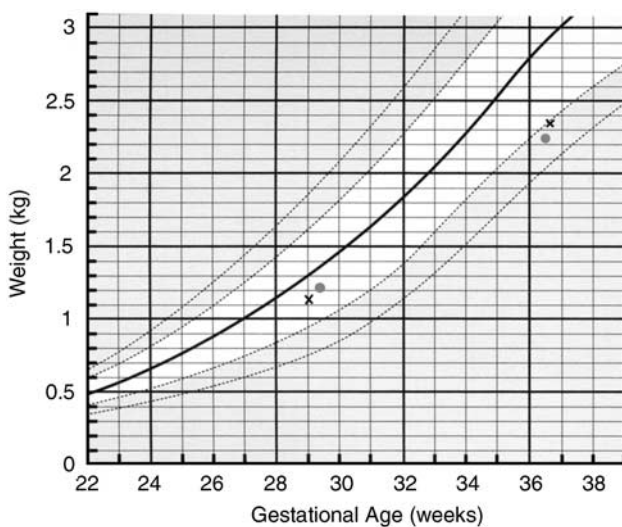
Abbreviations: EAA, early amino acid; LAA, late amino acid.

<sup>a</sup>For statistical analyses see Methods, *P* < 0.027 was needed for significance.

**Table 2** Morbidities between the LAA and EAA groups

| Counts (%) | LAA, mean (s.e.),<br>N = 132 | EAA, mean (s.e.),<br>N = 308 | Difference<br>(EAA–LAA) | P-value | 95% CI         |
|------------|------------------------------|------------------------------|-------------------------|---------|----------------|
| Bacteremia | 15 (11.4%)                   | 23 (7.5%)                    | –3.9%                   | 0.215   | (–10.0, 2.3)   |
| NEC        | 7 (5.30%)                    | 22 (7.14%)                   | 1.83%                   | 0.451   | (–2.9, 6.6)    |
| IVH        | 32 (24.2%)                   | 65 (21.1%)                   | –3.1%                   | 0.475   | (–11.75, 5.45) |
| PDA        | 36 (27.27%)                  | 100 (32.47%)                 | 5.2%                    | 0.270   | (–4.02, 14.41) |
| BPD        | 25 (18.93%)                  | 84 (27.27%)                  | 8.3%                    | 0.050   | (0.00, 16.67)  |

Abbreviations: BPD, bronchopulmonary dysplasia; EAA, early amino acid; IVH, intraventricular hemorrhage; LAA, late amino acid; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.



**Figure 1** Percentiles of mean weight at birth and discharge for the late amino acid (LAA, red dot) and early amino acid (EAA, 'x') were plotted. Discharge weight was significantly greater in the EAA group ( $P = 0.03$ ). The infants in the EAA groups had significantly less growth failure at discharge as defined by number <10th percentile. The  $z$ -scores<sup>15</sup> at 36 weeks were  $-1.27$  in the LAA and  $-1.03$  in the EAA, respectively, and the decrement in  $z$ -score was  $0.62$  in the EAA group and  $1.01$  in the LAA group from birth to discharge. Figure reprinted with permission from Tanis Fenton.<sup>18</sup>

incidence of bronchopulmonary dysplasia (BPD), defined as moderate BPD (supplemental oxygen at 36 weeks gestation), was observed in the EAA group ( $P = 0.05$ ). The infants in the EAA groups achieved full enteral feeding sooner ( $>100$  ml  $\text{kg}^{-1}$  per day of enteral feeds, no parenteral nutrition) with a mean 7.7 days in 2005 and 8.3 days in 2006 compared to 9.9 days in 2004 ( $P < 0.039$ ), despite similar incidences of morbidities.

Time from birth to discharge was positively associated with weight gain ( $P < 0.001$ ). Although gestational age was not a significant predictor ( $P = 0.309$ ), group (EAA or LAA) was a significant predictor of weight gain ( $P = 0.034$ ). The difference in the adjusted mean weight gain between the EAA and the LAA groups was 51.28 g (95% CI 3.76, 98.81) resulting in adjusted

weight gains of 1158 vs 1106 g. Weights at birth and discharge were plotted on the Fenton growth chart (Figure 1). Sensitivity analyses of weights at 36 weeks corrected gestational age (CGA) indicated fewer infants falling below the 10th percentile in the EAA groups (23.7%) than in the LAA group (41.7%) ( $P < 0.0001$ ; 95% CI  $-27.6, -8.30$ ; Figure 1).

$z$ -score calculations were evaluated for both groups. The decrement in falling away from the curve was less in EAA than in the LAA group; the  $z$ -scores at birth were  $-0.41$  (34th percentile) and  $-0.26$  (40th percentile) and progressed to  $-1.03$  (15th percentile) and  $-1.27$  (10th percentile) at 36 weeks CGA, respectively.<sup>15</sup> Most interesting was the result that parenteral nutrition duration was affected by how early the PN was started. PN start times of  $<24$  h, 24 to 48 h or  $>48$  h were associated with durations of 13, 18 and 23 days, respectively ( $P < 0.001$ ).

## Discussion

Early administration of amino acids has been shown to be safe and promotes nitrogen balance and glucose tolerance in preterm infants.<sup>7,8,14</sup> Our hypothesis was that this nutritional intervention would be associated with better weight gain and decrease growth failure (defined by being less than the 10th percentile at discharge) traditionally seen in NICU graduates.

Better weight gain is a bit difficult to interpret because longer hospitalizations should be associated with higher weight gains than shorter hospitalizations and because the duration of hospitalization is not necessarily included in the analysis. However, we adjusted for this statistically and the data adjusted for length of hospitalization remained significant. Furthermore, the  $z$ -scores, which are a measure of the difference from the mean, had a statistically larger decrement in the LAA group than in the EAA group, resulting in fewer infants that were less than the 10th percentile at 36 weeks PCA in the EAA group than in the LAA group. Interestingly, a greater incidence of BPD was observed in the EAA group that, because BPD is associated with slower weight gains, should have blunted the weight gains in our EAA group.

Previous studies have examined the relationship of amino-acid delivery with weight gain. The first study was initially powered for examination of glutamine supplementation and therefore weight gain was a secondary analysis of their data.<sup>15</sup> They did find that early provision of  $3 \text{ g kg}^{-1}$  per day of amino acids within 5 days of birth improved weight at 36 weeks compared to preterm infants that received  $3 \text{ g kg}^{-1}$  per day after 5 days. However, the groups remained in low weight percentiles with 82 and 95% less than the 10th percentile, respectively, according to the Alexander *et al.* chart.<sup>16</sup> These data are consistent with our data but the cutoff of 5 days was far more conservative than the intervention used in this study. The second study was designed to evaluate preterm infant weight gains at 28 days after amino-acid supplementation and infants were randomly assigned at 3.5 and  $2.5 \text{ g kg}^{-1}$  per day, respectively.<sup>17</sup> The inclusion criteria were preterm infants 23 to 29 weeks and 6 days gestation in a multicenter ( $n = 11$ ), randomized controlled trial to begin amino-acid support with  $1 \text{ g kg}^{-1}$  per day and advanced by  $0.5$  to  $1 \text{ g kg}^{-1}$  per day to final intake of 3.5 and  $2.5 \text{ g kg}^{-1}$  per day protein, respectively.<sup>17</sup> Filter paper spots (whole blood) were obtained to measure amino-acid levels. The higher intake of protein resulted in greater blood amino-acid levels but no difference was observed in weight gain at 28 days (12.9 vs  $11.4 \text{ g}$ , respectively).<sup>17</sup> In our study,  $3 \text{ g kg}^{-1}$  per day of amino acids were administered as soon as possible after delivery (mean of 7.5 h by 2006), which may explain our difference in final weight outcome.

The Fenton curve was recently adopted by the Vermont Oxford Quality Improvement Collaborative on Nutrition to be the growth chart appropriate for use in the preterm infant population (Figure 1). Our data demonstrated fewer infants falling below the 10th percentile for weight from the Fenton curves<sup>18</sup> compared to the previous publication by Poindexter *et al.*<sup>15</sup> A recent study reported by the NICHD indicated that 90% of infants  $<1000 \text{ g}$  fell below fetal growth curve estimates<sup>19</sup> at 36 weeks CGA. The mean weight cutoff for the 10th percentile used by this groups was a fetal weight curve by Alexander *et al.*<sup>16</sup> which has a 10th percentile mean of  $2354 \text{ g}$  for 36 weeks whereas the Fenton curve that we used in our study has the mean weight cutoff for the 10th percentile at  $2237 \text{ g}$ . Had we used the Alexander reference growth data, only 64, 40 and 30% of our infants would fall below that 10th percentile mean in 2004, 2005 and 2006, respectively, all of which are improvements from previous observations reported in the literature.

Another interesting observation was that the infants in the EAA groups had shorter durations of TPN administration and achieved full enteral feeding earlier despite being smaller and younger. Milk initiation, method, advancement and type can influence feeding tolerance.<sup>20–22</sup> Our written neonatal nutrition guidelines emphasizing early (by day 4 of life), trophic ( $<20 \text{ ml kg}^{-1}$  per day) and bolus feeding were followed throughout the study time period. Our institution uses tolerated feeds of  $120 \text{ ml kg}^{-1}$  per day as the criteria for ceasing parenteral nutrition such that duration

of parenteral nutrition is inversely related to the time for tolerance of enteral nutrition. Human milk and formula feeding were similar throughout all years. Because the composition of the parenteral amino-acid mixture and the enteral feeding protocols were identical during the time frame included in these studies, these findings raise the provocative question whether EAA improves gastrointestinal motility and reduces feeding intolerance. We postulate that EAA may result in earlier attainment of enteral feeds by improving gastrointestinal motility perhaps through neural or humeral responses. The earlier transition may have had an overall effect on growth by providing enteral stimulation and thus earlier protein synthesis. However, this study was not designed or powered to address this question.

On the basis of the  $z$ -scores calculated from the Fenton curve, the growth rates of the infants in this study given EAA were not abnormally accelerated whereas the group receiving LAA actually had a higher incidence of growth retardation. Slower weight gain as defined by velocities has been correlated to lower developmental index scores and increased risk of cerebral palsy<sup>5</sup> and emphasizes the importance of early interventions to promote growth. In contrast, excessive weight gain as defined by velocities exceeding growth parallel to percentile lines can be a concern for the development of later metabolic diseases.<sup>23</sup> The biological effect of the small difference observed in weight gain between the EAA and LAA groups is unknown, but may be important because of the association between weight gain velocities and neurodevelopmental outcomes.

Despite less extrauterine growth failure in the EAA groups, all groups had fallen off their own intrauterine trajectory and weighed less at discharge than they would have had they stayed in their intrauterine environment. This fall off of growth, in spite of our interventions, may mean that our preterm infants were still protein limited even with the provision of  $3 \text{ g kg}^{-1}$  per day of amino acids. One study evaluating daily enteral intakes approximating  $3.2$  to  $3.5 \text{ g kg}^{-1}$  per day protein ( $500$  to  $550 \text{ mg kg}^{-1}$  per day nitrogen) was able to more closely mimic intrauterine estimations for nitrogen retention.<sup>24</sup> With more immature infants surviving and the established relationship between amino-acid supplementation and extrauterine growth, future studies evaluating greater supplementation levels immediately after delivery such as  $3.5$  to  $4 \text{ g kg}^{-1}$  are appropriate.

One acknowledged limitation to our study was the retrospective component of the comparisons. The optimal approach to determine the effects of EAA intervention would be a randomized controlled approach, however, our institution felt that the evidence for the benefits of EAA supplementation was too compelling to conduct such a trial for LAA supplementation after 2004. A second limitation was the lack of assessments of protein kinetics or body composition. In the clinical setting these are often difficult and at the current time, weight can be used as a good measure of nutritional adequacy.<sup>25</sup> In addition, more sophisticated measures of

nitrogen balance, growth, hormonal stimulation and body composition are needed to define mechanisms of nutrient intake and growth in the preterm infant.

In summary, we found an association between EAA administration and less growth failure at term than in infants given amino acids later. Additional studies to determine the effects of EAA administration on protein kinetics and evaluation of even more aggressive nutritional interventions are warranted.

### Conflict of interest

The authors declare no conflict of interest.

### References

- Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. *Growth* 1976; **40**(4): 329–341.
- Widdowson EM, Dickerson JW. The effect of growth and function on the chemical composition of soft tissues. *Biochem J* 1960; **77**: 30–43.
- Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics* 2001; **107**(2): 270–273.
- Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? *Semin Perinatol* 2003; **27**(4): 302–310.
- Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage IA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006; **117**(4): 1253–1261.
- Thureen PJ, Anderson AH, Baron KA, Melara DL, Hay Jr WW, Fennessey PV. Protein balance in the first week of life in ventilated neonates receiving parenteral nutrition. *Am J Clin Nutr* 1998; **68**(5): 1128–1135.
- Thureen PJ, Melara D, Fennessey PV, Hay Jr WW. Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. *Pediatr Res* 2003; **53**(1): 24–32.
- Rivera Jr A, Bell EF, Bier DM. Effect of intravenous amino acids on protein metabolism of preterm infants during the first three days of life. *Pediatr Res* 1993; **33**(2): 106–111.
- Dupont C. Protein requirements during the first year of life. *Am J Clin Nutr* 2003; **77**(6): 1544S–1549S.
- Zlotkin SH. TrophAmine. *Pediatrics* 1988; **82**(3): 388–390.
- Thureen PJ, Hay Jr WW. Early aggressive nutrition in preterm infants. *Semin Neonatol* 2001; **6**(5): 403–415.
- Horbar J. The Vermont Oxford Network: evidence-based quality improvement for neonatology. *Pediatrics* 1999; **103**(1): 350–359.
- Fewtrell MS, Morley R, Abbott RA, Singhal A, Isaacs EB, Stephenson T *et al*. Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. *Pediatrics* 2002; **110**(1 Part 1): 73–82.
- Ibrahim HM, Jeroudi MA, Baier RJ, Dhanireddy R, Krouskop RW. Aggressive early total parental nutrition in low-birth-weight infants. *J Perinatol* 2004; **24**(8): 482–486.
- Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA. Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. *J Pediatr* 2006; **148**(3): 300–305.
- Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol* 1996; **87**(2): 163–168.
- Clark RH, Chace DH, Spitzer AR. 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* 2007; **120**(6): 1286–1296.
- Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. *BMC Pediatr* 2003; **3**: 13.
- Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR *et al*. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* 2007; **196**(2): 147 e141–148.
- Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics* 1999; **103**(6 Part 1): 1150–1157.
- Schanler RJ, Shulman RJ, Lau C, Smith EO, Heitkemper MM. Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. *Pediatrics* 1999; **103**(2): 434–439.
- Meetze WH, Valentine C, McGuigan JE, Conlon M, Sacks N, Neu J. Gastrointestinal priming prior to full enteral nutrition in very low birth weight infants. *J Pediatr Gastroenterol Nutr* 1992; **15**(2): 163–170.
- Godfrey KM, Barker DJ. Fetal nutrition and adult disease. *Am J Clin Nutr* 2000; **71**(5 Suppl): 1344S–1352S.
- Catzeflis C, Schutz Y, Micheli JL, Welsch C, Arnaud MJ, Jequier E. Whole body protein synthesis and energy expenditure in very low birth weight infants. *Pediatr Res* 1985; **19**(7): 679–687.
- Heird WC. Determination of nutritional requirements in preterm infants, with special reference to 'catch-up' growth. *Semin Neonatol* 2001; **6**(5): 365–375.



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