

# Enteral nutrition of the premature infant

Su Jin Cho, M.D., Ph.D.

Department of Pediatrics, Ewha Womans University School of Medicine

## = Abstract =

Early nutritional support for preterm infants is critical because such support influences long-term outcome. Minimal enteral feeding should be initiated as soon as possible if an infant is stable and if feeding advancement is recommended as relevant to the clinical course. Maternal milk is the gold standard for enteral feeding, but fortification may be needed to achieve optimal growth in a rapidly growing premature infant. Erythromycin may aid in promoting gastrointestinal motility in cases that exhibit feeding intolerance. Selected preterm infants need vitamins, mineral supplements, and calorie enhancers to meet their nutritional needs. Despite all that is known about this topic, additional research is needed to guide postdischarge nutrition of preterm infants in order to maintain optimal growth and neurodevelopment. (*Korean J Pediatr* 2010; 53:7-13)

**Key Words:** Enteral feeding, Preterm infant, Breast milk

## Introduction

Neonatal mortality rates for preterm infants have decreased steadily for the past 20 years<sup>1)</sup>. Neonatologists strive to improve the neurodevelopmental outcome of the surviving immature extremely low birth weight infants (ELBWI) and optimal nutrition is one of the main keys to achieving that goal. The goal for nutrition of the preterm infant should be to achieve a postnatal growth in anthropometric indices and body composition approximating that of the normal fetus of the same gestational age as recommended by the American Academy of Pediatrics<sup>2)</sup>. Nevertheless, underlying conditions make this goal difficult to achieve. Most preterm infants and especially those born with extremely low birth weight end up growth restricted during their hospital stay. Inadequate nutrition has long been suspected to be a cause of slow growth as well as impaired neurodevelopment of very low birth weight infants (VLBWI)<sup>3)</sup>. Such phenomenon was pointed out over 60 years ago and still remains a problem<sup>4)</sup>. This indicates that despite advances in neonatal care, nutritional strategies

has not been able to kept pace.

Many studies have demonstrated that specific nutritional deficits at critical stages of development limit fundamental components of growth that have long lasting effects. Undernutrition of rat fetuses reduced brain growth in neuronal number and synapses leading to reductions in brain size, cognitive capacity, and specific behaviors<sup>5)</sup>. Follow up studies of extremely low birth weight infants at 5.4 years of age has demonstrated that growth had affected the developmental outcome of these infants. Increasing weight and head circumference from birth to discharge were associated with a reduced risk for an abnormal neurologic examination. Catch-up growth of head circumference from birth to discharge was also associated with a reduced risk for impaired mobility. Weight at birth, an increase of weight from birth to discharge, and an increase of head circumference from discharge to follow-up had an effect on the mental processing composite score<sup>6)</sup>.

Hay pointed out that growth restricted infants end up later in life with a higher incidence of metabolic syndrome and at the other extreme of fetal growth, overgrown infants also have a higher incidence in later life of the metabolic syndrome. Therefore it is clear that just the right amount of the essential nutrients is required to produce optimal outcome of the preterm infant<sup>7)</sup>.

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Address for correspondence : Su Jin Cho M.D., Ph.D.  
Department of Pediatrics, Ewha Womans University School of Medicine  
911-1 Mok Dong, Yang Cheon Ku, Seoul 158-710, Republic of Korea  
Tel : +82.2-2650-2845, Fax : +82.2-2653-3718  
E-mail : suj-in-cho@ewha.ac.kr

### When to Start Feeding in the Preterm Infant

When Julius Hess established the unit for premature infants at Michael Reese Hospital, Chicago in 1922, the babies were not fed for the first two 12 hours of life for the fear of aspiration from feeble or absent sucking and swallowing<sup>8)</sup>. A change in attitude was evident from the 1960's. Victoria Smallpeice, the clinical director of the pediatric department at United Oxford Hospital felt that it made no sense to stop supplying nourishment abruptly at birth when it was afforded continuously via the placenta as a fetus and began feeding undiluted human breast milk within the first 24 hours via an indwelling nasogastric tube<sup>8)</sup>.

The most common reason for the delay in enteral feeding is the concerns for increasing the risk of necrotizing enterocolitis (NEC) but the very withholding of feeding may indeed be the greatest risk factor of NEC<sup>9)</sup>. The absence of food in the gastrointestinal tract produces mucosal and villous atrophy and reduction of enzymes necessary for digestion and substrate absorption. Decreased mucosal Ig A from Peyer's patches and increased production of adhesion molecules and polymorphonuclear cell attraction increase the incidence of systemic inflammatory response syndrome<sup>10)</sup>. Not providing enteral nutrition to VLBWI is nonphysiologic when one considers that the fetus swallows about 150 mL/kg/day of amniotic fluid during the last trimester of fetal development and this occurs without the occurrence of NEC in utero<sup>8)</sup>.

The anatomically and functionally immature intestine can undergo maturation in a relatively short time if the necessary stimulation in the form of feeding is provided<sup>11)</sup>. Minimal enteral nutrition is subnutritional quantities of milk feeds provided to prime the gut by stimulating many aspects of gut function. Small amounts of feeds is given to supplement parenteral nutrition as early as the first day of life in infants <1,500 g at birth if the infant is stable. This method has been accepted because of benefits such as prevention of gastrointestinal atrophy, facilitation of gastrointestinal mucosal maturation, stimulation of the motor activity of the muscular layer of the gut, decreased cholestasis, and enhancement of the postprandial response<sup>12)</sup>. Other benefits include reduction of nosocomial infections, metabolic bone disease, and decreased duration of hospital stay<sup>13)</sup>.

Orogastic feeding is preferred since nasogastric tubes may increase airway resistance. Maternal breast milk

(colostrum) is the preferred feeding however, positive results have been reported with donor milk and formula feeding as well. Starting volume have varied from 5–25 mL/kg/day. The rate of advancement should not exceed 20 mL/kg/day. Feeding volumes are kept low regardless of the size of gastric residuals or are gradually increased as gastric emptying improves<sup>11)</sup>. Minimal enteral nutrition should be used with caution in any situation associated with gut hypoxia or associated decreased intestinal blood flow such as asphyxia, hypoxemia, hypotension, and marked diastolic steal secondary to a patent ductus arteriosus. Continuing feeds during indomethacin treatment is still a controversial issue and clinical practice differs between hospitals<sup>1)</sup>.

Lavoie et al<sup>14)</sup> reported that a reduction of incidence of bacteremia only in more mature VLBWI greater than 28 weeks of gestation who received full enteral feeding before the second week of life. More clinical studies are required to make a general statement concerning early enteral feeding and infection in the more immature preterm infants. However, Early trophic feeding during the first week of life did not affect feeding tolerance or growth rates in a systematic review of 754 VLBWI<sup>15)</sup>.

### How to Provide Enteral Feeding in the Preterm Infant

Most premature infants less than 1,500 g are fed by tube from their inability to suck, swallow, and breathe effectively in the beginning. Milk feeds are typically given over 10–20 minutes every 2–3 hours. Infants on continuous feeds took longer to reach full feeds without difference in growth or admission duration. Current trends support slow bolus feeding to continuous feeds but much controversy exists on this and the practice is institution dependent<sup>16)</sup>. Tube placement via the oral route is preferred despite findings that it is more prone to displacement and vagal stimulation because nasal placement may compromise respiration in the smaller infants<sup>1)</sup>.

At the gestational age of 32–34 weeks, the infant begins to demonstrate coordination of suck–swallow–breathe. Respiratory rates between 20–50 breaths per minute without retraction is required for nutritive feeding. The infant should handle feeding into the stomach and handling without excessive signs of stress<sup>17)</sup>.

Controversy regarding advancement of feeds is a much debated topic. A prospective randomized study conducted in Germany of 1,430 VLBWI from 13 tertiary NICU's allo-

cated the infants into rapid advancement to full feeding of less than or equal to 12.5 days and slow advancement of more than 12.5 days. Infants in the slow advancement group had a significantly higher rate of sepsis and longer duration of central venous lines and antibiotics treatment<sup>18)</sup>.

Feeding in response to hunger and satiation cues rather than on schedule was thought to aid the establishment of oral feeding but the rate of weight gain was lower in the ad libitum fed infants. Another study reported an earlier discharge in the ad libitum fed infants but no long term follow up data was available<sup>19)</sup>.

### What to Feed the Preterm Infant

Human milk is preferred for feeding term, preterm, and sick infants. In the absence of maternal breast milk, donor breast milk may be used in VLBWI after parenteral consent to initiate feeds. The mother of the preterm infant should be encouraged to start pumping immediately after delivery. Breast milk consumption results in the release of endocrine and metabolic factors such as gastrin, enteroglucagon, motilin, neurotensin, gastroinhibiting peptide, and pancreatic polypeptide. Breast milk results in better absorption and motility along with stimulation of the growth of Bifidobacteriae and Lactobacillus strains. Maternal breast milk may lack some nutrients for the optimal growth of the VLBWI than preterm formula milk but confers important non-nutrient advantages for the preterm infant<sup>20)</sup>.

The predominance of whey protein and the mixture of amino acids in breast milk are compatible with the metabolic needs of the preterm infant. Digestion and adsorption is improved compared to formula and breast milk also provided immunologic protection<sup>20)</sup>. The lower renal solute load facilitates better tolerance and a decreased risk of NEC and a significantly higher intelligence quotient at 8 years of age is another major advantage. Breast milk contains omega 3 fatty acids that is alpha-linoleic acid from which other essential long chain polyunsaturated fatty acids (LCPUFAs), docosahexaenoic acids (DHAs), and arachidonic acid (AA) are produced. These play an important role in retinal and neurologic development<sup>21)</sup>. At 30 months, increased ingestion of breast milk was associated with higher Bayley Mental Developmental Index scores, higher Bayley behavior score percentiles for emotional regulation, and fewer re-hospitalizations between discharge and 30 months. There were no differences in growth parameters or incidence of

cerebral palsy. For every 10 mL/kg per day increase in breast milk, the Mental Developmental Index increased by 0.59 points, the Psychomotor Developmental Index by 0.56 points, and the total behavior percentile score by 0.99 points<sup>22)</sup>.

When sufficient maternal breast milk is not available, the alternative source are donor milk and preterm formula. Extraordinary efforts should be made to use mother's own milk because the advantages of non-nutrient components in human milk are significantly diminished by storage and heat processing of the donor milk. Future studies should investigate the processing of donor milk by alternative techniques to preserve the non-nutritive advantages while preventing disease transmission. Preterm maternal milk and banked milk provide insufficient amounts of energy, protein, sodium, calcium and phosphorus as well as other nutrients needed for rapid growth and normal development of the preterm infant. Human milk fortifier is indicated in preterm infants less than 31 gestational weeks and/or birth weight less than 1,500 g. Fortification is commenced at volume of feeding at 100 mL/kg/day.

Preterm formula is available to preterm infants whose mothers are unable to express sufficient breast milk. In general these formulas contain added whey protein, glucose polymers, and medium chain triglycerides, calcium, phosphorus, electrolytes, folate, and fat soluble vitamins compared to term formula<sup>23)</sup>. Preterm formulas may be used to supplement human milk feedings if the supply is inadequate. The composition of preterm formulas available in Korea is shown in table 1. Formula derived from soy protein rather than animal casein and whey are unsuitable for premature infants<sup>24)</sup>.

Meta-analysis of eight clinical trials concluded that in preterm and low birth weight infants, feeding with formula milk resulted in a higher rate of short term growth but also a higher incidence of NEC. However, this was prior to the use of fortification of human milk and cannot be applied directly to current clinical practice but demonstrates the superiority and safety of breast milk for the preterm infants<sup>25)</sup>.

### Nutritional Supplements for the Preterm Infant

Supplements are added to the enteral feeding of the preterm infant for a variety of reasons. Recent studies have been investigating the possible beneficial effects of adding

**Table 1.** Composition of Preterm Formulas in Korea (Reprinted with permission of the various manufacturers)

Manufacturing Brands	Calorie (kcal/dL)	Protein (g/dL)	Carbo-hydrate (g/dL)	Fat (g/dL)	Mineral (g/dL)	Sodium (mg/dL)	Potassium (mg/dL)	Calcium (mg/dL)	Phosphorus (mg/dL)	Iron (mg/dL)
Nam-Yang	76.7	2.3	7.8	4.1	0.5	30.0	75.0	108.0	58.5	0.23
Maeil	70.0	2.1	7.4	3.6	0.4	30.1	81.2	112.0	56.0	0.29
Ildong	71.0	2.1	7.1	3.8	0.3	30.0	70.0	100.8	54.6	0.20

immunoregulatory substances to the nutrition of infants and particularly nucleotides, prebiotics, and probiotics. A beneficial effect of supplementing milk with bifidobacter and other probiotics by decreasing intestinal permeability, improving growth, and improved feeding tolerance has been reported<sup>26)</sup>. A recent systematic review showed a significant decrease in NEC after the introduction of different strains and dosages of probiotics. the authors however, recommended more studies with regard to type of strain, dosage, and duration of treatment. Mechanisms by which probiotics could prevent NEC include increase in favorable type microflora with reduced colonization by pathogens, increased intestinal barrier to translocation of bacteria into the bloodstream, modification of the host response to microbial products by sensitization and immunization, and enhanced tolerance and advancement of enteral nutrition<sup>27)</sup>. Immuno-nutrition is thought to modulate the onset of infections and allergy in later life. Nevertheless, routine supplementation is as yet not an established practice and larger clinical trials are under way and caution is suggested until appropriately regulated products are available for use in the high risk population<sup>28)</sup>.

Additional energy supplies with no concomitant increase in fluid volume is possible and supplementation results in an increase in short term weight gain, linear growth, and head growth. Glucose polymers consist of polymers of glucose of various chain length and they have been used as nutritional supplements for infants because they have lower osmolarity per kilocalorie than glucose. In the newborn, the polymers are hydrolyzed by salivary, pancreatic, and intestinal amylases and maltases to free glucose<sup>29)</sup>. Reduction or eliminations of lactose and replacement with the more readily digestible carbohydrate such as glucose polymers have been reported to improve feeding tolerance, weight gain, and calcium absorption. There are insufficient data to evaluate the effects of carbohydrate or fat supplementation on long term growth and development in preterm infants<sup>30)</sup>.

Iron is present in a porphyrin-heme complex and plays a prominent role in oxygen transport. Cytochrome a, b, and c are also iron proteins and these enzymes are essential

for electron transport and have a central role in cellular energetics. The high bioavailability of iron in breast milk is of limited significance because of the low iron concentrations. Early postnatal anemia is more pronounced in preterm than in term infants since erythropoiesis abruptly decreases after birth and the hemoglobin concentration declines rapidly at a rate of approximately 1 g/dL/week. If adequate iron is not given postnatally, late anemia of prematurity will begin to develop after 2 months of life<sup>31)</sup>. The long term cognitive sequelae and shorter term motor sequelae of iron deficiency is notable. Free iron is needed for the multiplication of all bacteria and excess iron is thought to enhance gram negative septicemia but on the other hand, iron is necessary for the normal development and functional integrity of the immune system. Insufficient amount and high rate of postnatal growth calls for a higher iron requirement in VLBWI. Premature infants weighing 1,000–2,000 g require 2–3 mg supplemental Fe/kg/day for 12–15 months. Recent recommendations for preterm infant formulas are a minimum of 1.7 to a maximum of 3.0 Fe/L. and the American Academy of Pediatrics recommends 2–4 mg/kg/day of enteral iron daily depending on the degree of prematurity between 2 weeks and 2 months<sup>23)</sup>.

Water soluble vitamins are cofactors for enzyme reactions in intermediary metabolism and as such required amounts are related to energy and protein supply as well as the infant's growth and energy utilization. In the absence of valid data on the minimal requirements for the enterally fed preterm infant, minimum supplies are based on the upper ranges of supplies with human milk<sup>23)</sup>. Preterm infants show evidence of fat soluble vitamin deficiency from limited tissue storage at birth, intestinal malabsorption, and rapid growth rates that increase requirements. Multivitamins should be started when full enteral feeding is established and continued until after discharge as needed.

### Feeding Intolerance

Functional or non obstructive gastrointestinal dysmotility associated with milk intolerance is referred to as feeding

intolerance. It may manifest as increased gastric residuals, intermittent vomiting, abdominal distension, occult blood in stool, apnea and bradycardia and signs of infection. However, abdomen decompression and intolerance is stopped by withholding feeds. A complete physical examination should be performed in all cases to rule out NEC<sup>32)</sup>. Antegrade peristalsis is not established before 32 weeks and in the absence of other clinical symptoms or signs, bile colored aspirate per se should not be a contraindication for feedings in VLBWI<sup>33)</sup>. Increasing feeding volume or continuing feeding may actually be helpful in improving tolerance. Aspirate volume of less than 20% of the feeds should not limit feeding in the absence of other signs and symptoms. Nevertheless, bloody residuals seem to be the best predictor for NEC and should not be ignored if clinically suspected<sup>34)</sup>. With a normal physical exam, feeding may be reduced in volume or spaced apart. With an abnormal physical exam, the radiologic findings should guide additional workup<sup>17)</sup>.

Erythromycin is widely used to promote gastrointestinal motility via the motilin pathway, increasing proximal gut tone, enhancing the strength of intestinal contraction, and reducing pyloric outlet resistance. Meta-analysis reported that using erythromycin at higher treatment doses of 40–50 mg/kg/day or in infants of gestational age greater than 32 weeks had more positive effects in improving feeding tolerance and future research would determine the precise dose range and patient groups<sup>35)</sup>. Adverse effects to erythromycin such as infantile hypertrophic pyloric stenosis, potential emergence of multi-drug resistant organisms and alteration of pattern of stool microflora are possible<sup>36)</sup>.

Contrary to the recent Cochrane review which recommended against transpyloric feeding due to the increase in gastrointestinal disturbances<sup>37)</sup>, Malcolm et al<sup>38)</sup> recruited 72 VLBWI with a median birth weight of 870 g and gestational age of 26 weeks and initiated transpyloric feeding for a median duration of 18 days when they were of a median birth weight of 1,297 g. Their hypothesis was that gastroesophageal reflux may impede with feeding by causing significant apnea and bradycardia. After the initiation of transpyloric feedings, a statistically significant reduction in apnea and bradycardia was observed when comparing the total number of episodes for the 3 days before and after treatment. 7% developed NEC but none were on breast milk. However, further prospective studies are needed to determine the biological impact of bypassing the stomach

before modifying the current safety concerns regarding transpyloric feeding in this population.

### Nutritional assessment and follow-up

Serial measurements of weight, length, and head circumference allow the evaluation of growth in the premature infant. During the first week of life, weight loss of 10–20% of birth weight is expected because of changes in body water composition. Preterm infants generally begin to gain weight in by the second week of life and an average weight gain is 10–20 g/kg/day<sup>17)</sup>.

Two kinds of growth charts exists for very low birth weight infants; those based on intrauterine growth or those based on postnatal growth. Assessment of postnatal growth failure is better reflected on postnatal growth charts. Web based growth charts and growth curves are available on the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network homepage and may be valuable in tracking their growth long term.

Laboratory tests during enteral nutrition is required in the initial phase in the VLBWI with serial parameters of acid and base status, glucose, electrolyte, hematologic and blood chemistry tests. If the infant is in the stable phase and is achieving adequate growth, routine laboratory monitoring is indicated every 2–3 weeks<sup>39)</sup>.

Preterm birth puts the infant in a significant nutritional deficiency state and extrauterine growth failure is seen in as much as 20% at discharge. Recent data from the NICHD Neonatal Research Network show that even at 30 months chronological age, 32% infants with a birth weight of less than 1000 g are less than the 10th percentile for weight, 24% for length, and 21% for head circumference on the national growth curve<sup>40)</sup>. Therefore post discharge nutrition of the preterm infants became an area of growing interest. The use of a special nutrient enriched post-discharge formula has a significant positive effect on bone growth and mineralization during a period of rapid skeletal development<sup>41)</sup>.

Two special formulas with nutrient concentration in between standard term formula and preterm formula is available in the US but not currently in Korea. Breastmilk-fed preterm infants are at risk for calcium and phosphorus deficiency after discharge since fortification is provided up until the time of discharge. Controversial results have been reported on the long term growth of these infants and

close follow up of growth is required<sup>42, 43</sup>. Replacement of one third of calorie intake with a preterm formula or restricted fortification with HMF may be needed to enhance nutrient intake. However, no data is available whether this has any long term benefits<sup>44</sup>.

### Conclusion

The goal of nutrition of preterm infants is to achieve a postnatal growth that approximates the in utero growth of a normal fetus at the same postconceptional age. Current evidence supports that preterm infants' own mother's breast milk is the gold standard not only for nutritional value but for a better neurodevelopmental outcome. However, fortification with human milk fortifier is necessary to ensure optimal growth.

Minimal enteral feeding has many advantages and should begin as soon as possible. Bolus intermittent intragastric feeding via an orogastric feeding tube with slow increment of feeding is known to prevent NEC. Non nutritive sucking may be beneficial without side effects. In patients with feeding intolerance, erythromycin has been used to promote motility but the optimal dosage and duration of treatment is under debate. Supplementation with multivitamin should begin once full enteral feeding is established and iron should begin when the doubling of birth weight occurs.

Not only is it important not to underfeed these preterm infants but also not to overfeed them for excessive growth leads predominantly to fat deposition and is associated with later life complications of obesity, insulin resistance, diabetes, and cardiovascular disease.

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