Nutritional Needs of the Micropreterm Infant

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We have used an expansive definition of a micropreterm infant as <30 weeks' gestation to provide a global perspective to a "high risk" group of preterm infants for which there are little published data to guide nutritional management. Consensus nutritional guidelines for preterm infants have been developed for infants >1000 g birth weight and >28 weeks' gestational age. Micropreterm infants have greater nutritional deficits at birth than more mature preterm infants and accumulate greater postnatal deficits. Nutritional guidelines based on the needs of preterm infants born >28 weeks' gestation are unlikely, on a theoretical basis, to meet nutritional requirements of micropreterm infants. Unfortunately, very few good quality studies have addressed the nutritional requirements of this group specifically; this makes it difficult to formulate solid, evidence-based nutritional recommendations for these neonates. Nutritional management of micropreterm infants is based on recommendations established for preterm infants, which are adjusted after considering an infant's gestational age, birth weight, and clinical status. Minimal enteral feeding should commence on the first or second day of life, with incremental advancement and fortification of human milk when 100 mL/kg is tolerated. Early use of parenteral nutrition is recommended, ideally initiated within the first hours of life and enteral feeds are being established; this will help prevent the accumulation of nutritional deficits and incidence of growth failure. Fortified human milk should be given in order to meet nutritional requirements. When human milk is not available in sufficient quantity, a preterm formula should be given. *(J Pediatr 2013;162:S72-80)*.

Although the more commonly accepted classifications of preterm infants are extremely low birth weight (ELBW) and extremely preterm (<28 weeks' gestation), we defined micropreterm as <30 weeks' gestation. A subset of this population is small for gestational age (GA); these infants weigh <10th percentile at birth at <30 weeks' gestation. This expanded definition was selected to gain a global perspective of a "high risk" group of preterm infants. We were unable to locate substantial information about this population. This discussion addresses the current state of knowledge and clinical practice on the nutritional requirements of the micropreterm infant.

Developmental Physiology and Biology

The composition of weight gained by the fetus changes with GA. The difference in body composition between a micropreterm and a more mature infant impact decisions about nutritional management. For example, body water as a percentage of body weight decreases rapidly during the last trimester. Water comprises about 80% of weight gained between 24 and 28 weeks of gestation but only 60% of weight gained between 36 and 40 weeks. The proportion of weight gained as fat increases markedly from 8% at 24-28 weeks to nearly 20% near term.[1]

The fetal intestine is capable of digesting and absorbing milk feeds by 25 weeks' gestation, but not as well as that of a more mature infant. Gastrointestinal motor activity develops later and may limit tolerance to enteral feeds. Motility is described as being "disorganized" between 25 and 30 weeks of gestation. This can cause nutrients to remain in the intestine, especially if digestion is suboptimal, and may increase the risk of necrotizing enterocolitis (NEC).[2] Antenatal steroids accelerate the maturation of the gut and reduce the incidence of NEC (relative risk: 0.46; 95% CI 0.29-0.74).[3]

Swallowing activity begins to develop during the second trimester, and enteral ingestion of amniotic fluid contributes to fetal nutrition and development of the gastrointestinal tract. Postnatally, ingestion of colostrum and milk plays an important role in stimulating gut maturation. Accompanying the development of the gastrointestinal tract, there is also progressive development of different enzymes throughout fetal life.[4] Gastric pepsin and brush-border enzymes, including sucrase, aminopeptidase, and lactase, develop in parallel and are present in low concentrations in infants born prematurely. Lactase activity remains low throughout fetal life but increases markedly with the first enteral feed, regardless of age. Shulman et al[5] initiated feeds on

BW	Birth weight
DBM	Donor breast milk
ELBW	Extremely low birth weight
GA	Gestational age
NEC	Necrotizing enterocolitis
P:E	Protein:energy
PDF	Post-discharge formula
PTF	Preterm formula

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Table I. Summary of theoretical concerns and available data from micropreterm infants for specific enteral nutrients

Nutrient	Theoretical concerns	Published data for micropreterm infants?	Current recommendations	New recommendations
Fluid	• Increased requirements due to immature skin • Vulnerable to fluid overload with worsening cardiovascular disease, patent ductus arteriosus	• No • Intakes of 150-180 mL/kg/d tolerated in enteral studies	• Range 135-200 mL/kg/d[12,13]	
Energy	• Low energy stores. Intake often inadequate due to concomitant illness restricting supply • Concern regarding NEC	• EE of 60-75 kcal/kg/d by indirect calorimetry and by doubly labeled water in stable ELBW infants[30,31] • Higher levels of EE of 88-96 kcal/kg/d by doubly labeled water method in infants with sepsis[31] and chronic lung disease[32]	• 130-150 kcal/kg/d[12]	• 120-140 kcal/kg/d
Protein	• Increased requirement for growth, especially if deficits accumulate • Greater risk of overload, metabolic acidosis, increased BUN and urea • Some amino acids conditionally essential	• ELBW infants (generally >750 g) included as subjects along with VLBW infants in enteral feeding studies defining protein requirements. • Factorial method[33] • ELBW infants randomized and treated for 7 days with IV amino acids starting at 0.5 g/kg/d and increased by 0.5-3.0 or starting 2 g/kg/d and increased by 1.0-4.0 daily; infants receiving higher amino acids in first week had lower NDI at 18 mo [not 2 y] and lower z-scores for weight, length, and head circumference at 2 y[34]	• Factorial approach[31]: 3.5-4.0 g/kg/d • Tsang et al[12]: 3.8-4.4 g/kg/d (26-30 wk PCA) • ESPGHAN[13]: 4.0-4.5 g/kg/d ELBW 3.8-4.4 g/kg/d VLBW	• 3.6-4.5 g/kg/d • Larger trials than Blanco, et al.[34] necessary to assess best IV amino acid advancement and dosage
P:E		• P:E 3.6 g/100 kcal with protein intake 4.6 g/kg/d tolerated for 1 wk[35] • P:E 3.6 g/100 kcal with protein intake 4.3 g/kg/d for longer periods reported some evidence of protein overload[36]	• Tsang et al[12]: 3.3-3.4 g/100 kcal • ESPGHAN[13]: 3.6-4.1 g/100 kcal	• 3.0-3.6 g/100 kcal
Carbohydrate	• Provides 40%-50% of calories • PTF has 23%-50% glucose polymers and some have Gos and Fos oligosaccharides as prebiotics	• 24-31 weeks GA infants (n=20): Formula supplementation with oligosaccharides reduced stool viscosity and accelerated GI transit[37]	• Tsang et al[12]: 9-20 g/kg/d for enteral feeding of growing ELBW infant	• 10.5-14 g/kg/d
Lipids	• May have increased requirements due to high energy needs and restricted fluid intake • Absorption may be reduced with resultant steatorrhoea • Provides 50% energy in human milk	• No	• Tsang et al[12]: 6.2-8.4 g/kg/d for enteral feeding of growing ELBW infant, or 4.1-6.5 g fat/100 kcal	• 5-7 g/kg/d for enteral feeding of growing micropreterm, or 4.4-6.0 g fat/100 kcal
LCPUFA	• Greater deficit at birth. LCPUFA oxidized if energy supply insufficient	• In a multicenter trial of infants <33 weeks maternal diet high in DHA and infant DHA dose of 1% total fatty acids increased MDI of females <1250 g[38] • For infants <1250 g, supplementation was associated with higher MDI in unadjusted, but not in adjusted, analyses • For males overall, and for all infants with bodyweight <1250 g the risk of BPD was lower in supplemented infants[39]	• DHA: 20-62 mg/kg/d • ARA: 30-36 mg/kg/d • EPA: ≤23 mg/kg/d	• Some evidence to suggest higher intake of DHA (1% of total fatty acids) might have particular benefits to micropreterm infants
Sodium	• High fractional excretion of sodium in first 10-14 d	• No		• 4-5 mmol/kg/d in first 10-14 d and • 2.5-3.0 mmol/kg/d thereafter
Calcium and phosphorus	• Greater mineral deficit at birth (majority of mineral accretion occurs in last trimester). Greater risk of metabolic bone disease. • Calcium absorption rate 50%-65%, phosphate absorption 90%	• No	• Tsang et al[12]: • Calcium 100-220 mg/kg/d • Phosphorus 60-140 mg/kg/d	• Calcium intake of 120-180 mg/kg/d • Phosphorus intake of 60-90 mg/kg/d; (maintain phosphorus levels ≥1.8 mmol/L)

(*continued*)

Table I. Continued

Nutrient	Theoretical concerns	Published data for micropreterm infants?	Current recommendations	New recommendations
Vitamins	• Born with lower body stores, especially of fat-soluble vitamins. May have reduced absorptive capacity for some vitamins. May benefit from pharmacological doses of some vitamins. • Insufficient vitamin A in preterm breast milk • Insufficient vitamin D in breast milk	• Folate: 64 infants (BW 801-1300 g) on EPO randomized to B12 + folate 100 μg/kg/d versus folate 60 μg/d had enhanced erythropoiesis and lower fall in hemoglobin[40] • Folate, iron, B12: ELBW infants (BW <800 g) randomized to EPO, B12, iron, and folate had significantly lower transfusion requirement than controls[40] • ELBW infants: meta-analysis reported supplementation associated with reduction in death or oxygen requirement at 36 wk gestation[41]	• Tsang et al[12]: 25-50 μg/kg/d • Tsang et al[12]: 700-1500 IU/kg/d • Tsang et al[12]: 150-400 IU/kg/d	• At least 100 μg/d • 1330-3330 IU/kg/d • 800-1000 IU/d
Iron	• Deficient stores at birth, sufficient to synthesize 18 g of hemoglobin in 1 kg infant • Human milk low in iron	• No	• 2-3 mg/kg/d from 2-4 wk of age adjusted for transfusions and EPO	• 2-4 mg/kg/d from 2-4 wk of age adjusted for transfusions and EPO
Trace elements	• Zinc: greater deficit at birth; transitional breast milk has sufficient zinc but not mature milk • Copper: deficiency is a potential problem during rapid growth	• No	• Tsang et al[12]: 1000-3000 μg/kg/d	• 2.0-2.25 mg/kg/d • 190-230 μg/kg/d
Probiotics	• Gut rapidly colonizes with bacteria after birth • Formula-fed infants colonize with Gram negative bacilli	• ELBW infants: observational study (101/226 in time period 1 and 220/338 in time period 2) reported significant reduction in NEC, sepsis, and death after introducing probiotics mixed in breast milk or formula[42]		• Only "off label" products available outside of RCT

ARA, arachidonic acid; *BPD*, bronchopulmonary dysplasia; *BUN*, blood urea nitrogen; *DHA*, docosahexaenoic acid; *EE*, energy expenditure; *EPA*, eicosopentaeoic acid; *EPO*, erythropoietin; *ESPGHAN*, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; *Fos*, fructo-oligosaccaride; *GI*, gastrointestinal; *Gos*, galacto-oligosaccharide; *IV*, intravenous; *LCPUFA*, long chain polyunsaturated fatty acids; *MDI*, Mental Development Index; *NDI*, neurodevelopmental index; *PCA*, postconceptual age; *RCT*, randomized controlled trial; *VLBW*, very low birth weight.

day 4 or day 15 in 135 infants at 26-30 weeks' gestation and found that early feeding was associated with increased lactase activity. Macronutrient transporters are present by the third trimester.[2] Certain enzymes of amino acid metabolism develop late in gestation, including those involved in: (1) the synthesis of cysteine from methionine, taurine from cysteine, and tyrosine from phenylalanine; (2) the degradation of tyrosine; and (3) the production of urea.[6] Based on these observations, micropreterm infants might be expected to require certain amino acids (eg, cysteine and taurine), which are not essential later in life, and may be at risk for accumulating excessive amounts of others (eg, phenylalanine, tyrosine, and methionine). Enzymes used in gluconeogenesis such as phosphoenolpyruvate carboxykinase may not develop until just before or just after term delivery. This is not surprising because the fetal liver stores glucose as glycogen, and there is a steady flow of glucose to the fetal circulation via the placenta. Immediately after birth, glycogen phosphorylase and glucose 6-phosphatase act to release glucose from liver glycogen. Gluconeogenesis is not necessary to maintain blood glucose concentrations until 24-48 hours after birth. The micropreterm neonate is born with low stores of liver glycogen,[7] a reduced gluconeogenic ability, and is, thus, at particular risk for developing hypoglycemia.

Current Practice

Perhaps reflecting the lack of specific data and nutritional recommendations, the nutritional management of micropreterm infants varies markedly among neonatal units and countries. In 2006, neonatal practitioners were surveyed and reported that they provided parenteral and enteral nutrition sooner and in larger volumes than they had previously, indicating improved nutritional management as a result of increased knowledge.[8] Regardless, postnatal growth failure is virtually inevitable in micropreterm infants. It is important to act promptly to secure an adequate nutrient supply because early growth failure is associated with adverse neurodevelopmental outcomes. In a review from the National Institute of Child Health and Human Development that evaluated ELBW infants, 89% of infants weighed <10th percentile for GA at 36 weeks post-menstrual age, and 40% of infants had weight, length, and head circumference <10th percentile at 18-22 months corrected age.[9] The many causes of growth failure include complications of extreme prematurity; extended time to meet recommended dietary intakes; and failure to provide adequate nutrients for recovery or "catch-up" growth.[10]

Evidence Base for Defining Nutritional and Feeding Practices for Micropreterm Infants

Nutrient Requirements

Very few studies have examined the nutrient requirements of micropreterm infants, and most published studies do not stratify by birth weight (BW) or GA or include subgroup analyses. The available data for specific nutrients are summarized in Table I.

Table II. Preterm nutrient recommendations (per 100 kcal) by expert group

Nutrient	Unit	ESPGHAN, 2010[13]	Tsang et al, 2005[12] <1000 g BW	Tsang et al, 2005[12] >1000 g BW	LSRO, 2002[11] (preterm)	WHO >1000 g BW (Birth to 7 d)*	WHO >1000 g BW (stabilization to term)*	WHO >1000 g BW (term to 1 y)*
Protein	g	3.2-4.1†	2.5-3.4	2.6-3.8	2.5-3.6	[1.3-4.0]	[2.5-3.0]	[2.0]
Fat	g	4.4-6.0	4.1-6.5	4.1-6.5	4.4-5.7	[0.7-4.8]	[3.8-5.7]	[4.0-6.6]
Linoleic	mg	350-1400	467-1292	462-1309	[350-1425]‡	NS	NS	NS
α-Linolenic	mg	>50	NS	NS	[77-228]§	NS	NS	NS
LA:ALA		5-15	5-15	5-15	6-16	NS	NS	NS
ARA	mg	16-39	≥22	≥22	[0-34]¶	NS	NS	NS
DHA	mg	11-27	≥16	≥16	[0-20]‖	NS	NS	NS
Carbohydrate	g	10.5-12	6.0-15.4	5.4-15.5	9.6-12.5	[6.7-26.7]	[6.3-12.9]	[6.8-14.1]
Vitamin A	IU	[1199-2464]	467-1154	538-1364	[680-1270]	[933-2000]	[583-1250]	[545-1273]
	μg RE	360-740	[140-347]	[162-410]	204-380	[280-601]	[175-375]	[164-382]
Vitamin D	IU	800-1000**	100-308	115-364	75-270	[40-260]**	[400-800]**	[400]**
Vitamin E	IU	[3.0-14.9]	4.0-9.2	4.6-10.9	[3.0-11.9]	[8.0-16.0]	[5.0-10.0]	[5.5-10.9]
	mg α-TE	2-10	[2.7-6.2]	[3.1-7.3]	2-8††	[5.4-10.7]	[3.4-6.7]	[3.7-7.3]
Vitamin K	μg	4-25	5.3-7.7	6.2-9.1	4-25	[10.7-13.3]	[6.7-8.3]	[7.3-9.1]
Thiamin	μg	125-275	120-185	138-218	30-250	[53-67]	[33-42]	[45]
Riboflavin	μg	180-365	167-277	192-327	80-620	[480-613]	[300-383]	[45]
Vitamin B6	μg	41-273	100-162	115-191	30-250	[15]‡‡	[15]‡‡	[15]‡‡
Vitamin B12	μg	0.08-0.7	0.20-0.23	0.23-0.27	0.08-0.7	[0.15]**	[0.15]**	[0.15]**
Niacin	μg	345-5000	2400-3700	2800-4400	550-5000	[720]	[720]	[720]
Folic acid	μg	32-90	17-38	19-45	30-45	[50]**	[50]**	[25]**
Pantothenic acid	μg	300-1900	800-1300	900-1500	300-1900	[1067-1733]	[667-1083]	[727-1182]
Biotin	μg	1.5-15	2.4-4.6	2.8-5.5	1.0-37	[2.0]	[1.3]	[1.4]
Vitamin C	mg	10-42	12-18.5	13.8-21.8	8.3-37	[8-13]	[5-8]	[18]
Choline	mg	7-50	9.6-21.5	11.1-25.5	7-23	NS	NS	NS
Inositol	mg	4-48	21-62	25-74	4-44	NS	NS	NS
Taurine	mg	NS	3.0-6.9	3.5-8.2	5-12	NS	NS	NS
Carnitine	mg	NS	1.9-2.2	2.2-2.6	2-5.9	NS	NS	NS
Calcium	mg	110-130	67-169	77-200	123-185	[80-107]	[134-200]	[253]§§
Phosphorus	mg	55-80	40-108	46-127	82-109	[41-62]	[65-98]	[105]§§
Ca:P	mg:mg	NS	NS	NS	1.7-2.0:1	NS	NS	NS
Magnesium	mg	7.5-13.6	5.3-11.5	6.1-13.6	6.8-17	[6.5-8.1]	[4.1-8.1]	[4.4-13.3]
Iron	mg	1.8-2.7	1.333-3.077	1.538-3.636	1.7-3.0	0.0	[1.7-2.5]	[1.8-2.7]
Zinc	mg	1.0-1.8	0.667-2.308	0.769-2.727	1.1-1.5	[0.57]	[0.42-0.67]	[0.89]
Manganese	μg	6.3-25	0.5-5.8	0.5-6.8	6.3-25	[0.7-1.5]	[0.5-0.9]	[0.5-1.0]
Copper	μg	90-120	80-115	92-136	100-250	[93-161]	[58-101]	[64-110]
Iodine	μg	10-50	6.7-46.2	7.7-54.5	6-35	[34]	[26-53]	[29-58]
Selenium	μg	4.5-9	0.9-3.5	1.0-4.1	1.8-5.0	[4.2-6.3]	[2.6-3.9]	[2.9-4.3]
Sodium	mg	63-105	46-88	53-105	39-63	[31-92]	[48-77]	[42-63]
Potassium	mg	60-120	52-90	60-106	60-160	[130-182]	[81-114]	[89-124]
Chloride	mg	95-161	71-192	82-226	60-160	[47-142]	[74-118]	[64-97]
Chromium	μg	0.027-1.12	0.07-1.73	0.08-2.05	NS	[0.07-0.13]	[0.04-0.08]	[0.05-0.09]
Molybdenum	μg	0.27-4.5	0.20-0.23	0.23-0.27	NS	[0.26-0.51]	[0.16-0.32]	[0.17-0.35]
Fluoride	μg	1.4-55	NS	NS	0-25	NS	NS	NS
Total Nucleotides	mg	≤5	NS	NS	NS	NS	NS	NS
AMP	mg	NS	0.23-0.62	0.27-0.73	NS	NS	NS	NS
CMP	mg	NS	1.4-3.2	1.6-3.7	NS	NS	NS	NS

(*continued*)

Table II. Continued

Nutrient	Unit	ESPGHAN, 2010[13]	Tsang et al, 2005[12] <1000 g BW	Tsang et al, 2005[12] >1000 g BW	LSRO, 2002[11] (preterm)	WHO >1000 g BW (Birth to 7 d)*	WHO >1000 g BW (stabilization to term)*	WHO >1000 g BW (term to 1 y)*
GMP	mg	NS	0.03-0.54	0.04-0.64	NS	NS	NS	NS
UMP	mg	NS	0.6-0.9	0.7-1.1	NS	NS	NS	NS

ALA, alpha-linolenic acid; *AMP*, adenosine monophosphate; *Ca:P*, calcium to phosphorous ratio; *CMP*, cytosine monophosphate; *GMP*, guanosine monophosphate; *LA*, linoleic acid; *LSRO*, Life Sciences Research Office; *NS*, none specified; *PUFA*, polyunsaturated fatty acids; *RE*, retinol equivalents; *TE*, tocopherol equivalents; *UMP*, uridine monophosphate; *WHO*, World Health Organization.
Single values indicate a minimum recommendation. Values in brackets have been calculated.
*Calculated based on the average of the maximum and minimum energy recommendations for the indicated population; 75, 120, and 110 kcal/kg/d for birth to 7 days, stabilization to term, and term to 1 year, respectively.
†3.6-4.1 g/100 kCal for infants <1 kg body weight; 3.2-3.6 g/100 kCal for infants 1-1.8 kg body weight.
‡Minimum: 8% of total fatty acids. Maximum: 25% of total fatty acids.
§Minimum: 1.75% of total fatty acids with the further stipulation that the LA:ALA not exceed 16:1. Maximum: 4.0% of total fatty acids with the further stipulation that the LA:ALA not be less than 6:1.
¶A minimum recommendation for ARA was not established. Maximum: 0.6% of total fatty acids with the further stipulation that the ARA:DHA is within the range of 1.5-2.0:1.
‖A minimum recommendation for DHA was not established. Maximum: 0.35% of total fatty acids with the further stipulation that the ARA:DHA is within the range of 1.5-2.0:1.
**Recommendation given per day, independent of body weight and energy intake.
††The ratio of vitamin E to PUFA (mg of α-TE per g PUFA) should exceed 1.5 mg/g.
‡‡Recommendation per gram protein fed.
§§Recommendation in mg/d for breast fed infants. Formula fed infants should receive at least 377 mg/d of calcium and 273 mg/d of phosphorous.

Recently, several expert groups have reviewed the available scientific evidence and formulated consensus guidelines for the nutritional management of preterm infants. In 2002, the Life Sciences Research Office of the American Society for Nutritional Sciences made recommendations for the nutrient content of formulas for preterm-low BW infants based on current scientific knowledge and expert opinion. The examples and sample calculations were based on a 1000 g preterm infant and defined for different stages of postnatal life (transition, stable growing, and post-discharge stages). The Life Sciences Research Office pointed out that it was not known whether these recommendations would meet the needs of infants weighing less 750 g because so few data concerning their nutritional requirements were available.[11] Tsang et al[12] defined reasonable nutrient intakes for ELBW and VLBW infants and for different stages of postnatal life: day 0; transition (the period of metabolic and physiologic instability after birth); and the stable, growing period. The authors highlighted the vulnerability of ELBW infants, who are likely to have greater needs for many nutrients, be more susceptible to excess, and be a more heterogeneous population in terms of their clinical status than other infants. The authors noted that almost no data relate directly to this sub-group. In 2010, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition published updated guidelines on enteral nutrition supply for preterm infants.[13] No specific recommendations were provided for infants with BWs below 1000 g because only data for protein were available. Despite the lack of data for ELBW infants, all expert groups recognized the importance of supplying sufficient protein and energy to compensate for the accumulated deficits seen in almost all ELBW/micropreterm infants during the early postnatal period. Recommended intakes by the three expert groups are listed in **Table II**.

Use of Human Milk for Micropreterm Infants

Although human milk is accepted as the gold standard for feeding healthy term infants, it cannot be assumed that this is the case for micropreterm infants who have higher requirements for most nutrients. Hence, it is important to critically evaluate the nutritional adequacy and health effects of human milk for this specific population in order to make evidence-based recommendations for optimal nutrition. A detailed discussion of the use of human milk for preterm infants is provided elsewhere (see the discussion of human milk by Tudehope et al, in this supplement); the discussion here focuses specifically on data relevant to the use of human milk and infant formulas in the micropreterm infant.[14] Term infant formulas are not suitable for feeding preterm infants and are certainly inappropriate for micropreterm infants.

Unmodified human milk is unlikely to meet the nutritional requirements of micropreterm infants for several key nutrients, including protein and energy (especially when mature donor milk is used), sodium, calcium, phosphorus,

magnesium, trace elements, and certain vitamins. However, human milk does have theoretical advantages compared with formulas, including the composition and absorbability of its fats and the bioavailability of certain trace metals. Human milk also has a lower renal solute load than formulas designed to meet the needs of preterm infants and contains specific components that enhance mucosal maturation, provide protection from bacteria, and modulate gut inflammation and motility.

Health Effects of Human Milk in Micropreterm Infants

Few studies have examined the benefits to health provided by human milk in micropreterm infants. Many of the longer-term benefits reported with human milk in preterm infants, (eg, improved developmental outcome, cardiovascular health, and bone health) might be anticipated to be greater in micropreterm infants who have a greater risk for sub-optimal, long-term outcomes, but no specific data are available to confirm or refute this hypothesis.

Growth and Brain Development

A number of studies have reported slower growth, in both weight and length, in preterm infants <32 weeks' gestation who were fed unsupplemented breast milk before hospital discharge, compared with those who were fed formula.[15,16] An observational study reported that infants <30 weeks' GA who were fed fortified human milk had slower weight gain (22 vs 26 g/kg/d), smaller length increments, and lower discharge weights (2428 g vs 2998 g) than those fed preterm formula (PTF) but were discharged home earlier [22 vs 26 days].[15] However, ELBW infants who were fed human milk shortly after birth had higher mental development scores at 30 months than did infants who were not.[17] An observational trial compared outcomes for preterm infants <30 weeks' gestation who were fed mother's milk exclusively with those who received supplemental donor breast milk (DBM) or PTF as a supplement to maternal milk when volume was inadequate[15] Those who received only mother's milk had fewer episodes of late onset sepsis [23% vs 36%, OR 0.47 (0.25-0.7)] and total infection-related events; shorter durations of hospital stay (73 vs 88 days); fewer gram-negative organisms isolated from blood cultures; but the same incidence of NEC (6% vs 9%) compared with those who needed to be supplemented. The addition of DBM to mother's milk when volume was inadequate offered limited short-term advantages over PTF.[15]

Infection and NEC

A recent study compared a complete human milk-based diet with a diet of DBM fortified with bovine milk fortifier or PTF and found that infants with BWs of 500-1250 g who received a complete human milk-based diet had a significant reduction in NEC ($P < .02$) and, especially, NEC requiring surgical intervention. There were no differences among groups in growth or rates of late-onset sepsis.[18]

Use of DBM in the Micropreterm Infant

To make appropriate choices about the use of DBM in the micropreterm infant, it is important to consider the relative advantages and disadvantages. A recent Cochrane systematic review[19] compared outcomes in preterm infants fed DBM or formula. None of the 8 studies analyzed focused specifically on micropreterm infants, and most were 20-30 years old and from an era when DBM was fed without fortification or mineral supplements, often as the sole diet. Only 1 study compared the effects of nutrient-fortified DBM versus PTF as a supplement to mother's breast milk in micropreterm infants.[20] This study was unable to establish any short-term benefit for DBM over PTF.

Fortification of Human Milk for the Micropreterm Infant

A recent Cochrane review concluded that the use of multinutrient fortifiers in infants weighing <1500 g is associated with short-term improvements in weight gain, linear growth, head growth, nitrogen retention, and blood urea levels.[21] The review did not consider micropreterm infants separately. A small randomized controlled trial[22] showed that "adjustable" fortification of human milk (based on the infant's blood urea concentration) resulted in greater weight and head circumference gains, which were significantly correlated with protein intake compared with "standard" fortification.

Consensus Position on Feeding Micropreterm Infants

What to Give: Nutrient Requirements

Because so few studies have focused specifically on the micropreterm infant, evidence-based guidelines cannot be formulated for the majority of nutrients for this group. Our consensus position is that the recommendations for preterm infants should be applied to micropreterm infants for most nutrients. Although the reasonable nutrient intakes provide an indication of nutrient requirements, they cannot and should not be followed rigidly. Each infant's nutrient requirements should be determined on an individual basis after considering GA, BW, presence or absence of growth restriction, and clinical factors. Absorption and bioavailability of nutrients from different types of milk vary widely and generally are higher when human milk is used rather than infant formula or other breast milk substitutes. Furthermore, nutrient requirements change over time; micropreterm infants, in particular, accumulate nutritional deficits during first few weeks of life. Thus, nutritional management of these infants should include requirements for catch-up growth.

Available Enteral Feedings

In practice, the main options for enteral feeds are human milk or PTF. There is strong and convincing evidence that

feeding human milk to preterm infants has beneficial effects for short-term (risk of infection and NEC, feed tolerance) and longer-term (neurodevelopmental outcome, cardiovascular risk, bone health) outcomes. Given the generally poorer outcomes for micropreterm infants, it is reasonable to hypothesize that this group may gain even greater benefits from human milk than other preterm infants. However, feeding unsupplemented human milk is associated with slower ponderal and linear growth, higher risk of metabolic bone disease, and deficiencies of micronutrients; these concerns are likely to be greater in micropreterm infants, who generally have higher nutrient requirements. Thus, although human milk is preferred over formula feeding, supplementation or fortification of human milk is required for this group of infants. When mother's breast milk is unavailable or in short supply, DBM or PTF can be used. The short-term use of breast milk substitutes for preterm babies has not been shown to have demonstrable adverse effects on risks of allergy, bowel microflora, duration of breastfeeding, or childhood or adult diseases. PTFs are designed to meet the estimated nutrient requirements for routine preterm infants but may not necessarily meet the requirements for micropreterm infants. For example, when volumes sufficient to provide an energy intake of 120 kcal/kg/d are fed, the available preterm infant formulas and fortified human milk diets provide protein intakes of approximately 3.2-3.6 g/kg/d, which are below the recommended higher protein intakes for micropreterm infants (especially ELBW infants). When higher energy intakes of 130-140 kcal/kg/d are provided, some PTFs will support the recommended protein intakes for these infants, but the higher energy intakes might result in increased fat deposition. The more immature the infant, the greater is the need for enteral feeding regimens with a higher protein:energy (P:E) to meet the goal of greater protein gain relative to fat. Supplementation of current PTF (P:E 2.7-3.0 g/100 kcal) with protein will increase the P:E and result in more lean mass and relatively less fat deposition. Recently PTFs with P:E of 3.3-3.6 g/100 kcal have become available in several countries. A PTF with relatively high P:E may be desirable for the micropreterm infant. However, at present, safety and efficacy of formulas with higher P:E (>3.6/100 kcal) for micropreterm infants are not known and need to be studied.

Feeding Schedules

The objectives of feeding right after birth are to stimulate gut maturation and hormone release and test gut motility. Trophic feeding or minimal enteral feeding, defined as <24 mL/kg/d, should commence on day 1 if possible or day 2 at the latest. Gastric residues should not be allowed to interfere with feeding. Feeding volumes of 1-2 mL/feed should be provided every 3-6 hours for infants <30 weeks' gestation on days 1-2. When these feeds are tolerated and the infant is well, volumes can be increased by about 20 mL/kg/d. However, this approach may not be reasonable for all infants. For example, infants who have no or reversed end diastolic blood flow before delivery may be more likely to develop NEC, especially when they are growth-restricted. These infants may have abnormalities in splanchnic blood flow before and after birth that may become less marked during the first week of life. In these infants, there may be justification for a delayed and careful introduction of enteral feeding, preferably with colostrum.

One of the goals of providing postnatal nutrition for micropreterm infants is to ensure that the transfer of nutrients to the fetus and neonate is maintained. Because immaturity of the gastrointestinal tract precludes provision of substantial nutritional support via the enteral route, nearly all micropreterm and very low BW infants receive parenteral nutrition. This liberal approach to parenteral nutrition, adopted over the last decade, has markedly improved nutritional intakes of ELBW infants. However, parenteral nutrition is associated with risks, mainly sepsis and metabolic complications, and the risk-benefit ratio must be considered. Parenteral nutrition must be started early to maintain a continuous nutrient supply during the transition from the fetus in utero to the preterm infant ex utero, preferably within the first 24 hours of life, for micropreterm infants. Many neonatal intensive care units now have the ability to place central lines and initiate total parenteral nutrition.

Post-Discharge Feeding

It is unlikely that unsupplemented breast milk meets the nutritional requirements of micropreterm infants after discharge. Although the proportion of these infants who are breastfed exclusively after discharge varies in different settings and is sometimes low, the majority of infants receive some breast milk for at least the first few weeks after discharge. There are various possible methods to increase nutrient (and particularly protein) intake of micropreterm infants who breastfeed after discharge, although none has been formally evaluated. Mothers can mix expressed breast milk with fortifiers for each feed, or a number of breast feeds can be replaced with a preterm or post-discharge formula (PDF). Both strategies are likely to increase nutrient intakes, but they may interfere to some degree with breastfeeding and increase the risk of infection. However, these risks must be weighed against the risks of malnutrition and poor growth. The timely introduction of foods rich in energy, protein, iron, and zinc should be encouraged in this group of infants.

Ideally, micropreterm infants who are fed formula after discharge should receive a nutritionally enriched PDF. These formulas are considered as stepping-stones between preterm and term formulas. They have an energy content of 71-74 kcal/100 mL and are enriched with more protein, minerals, vitamins, and trace minerals per 100 kcal than term formula. A 2012 Cochrane systematic review (including 10 randomized controlled trials of good methodological quality and 762 infants) was limited because the measured outcomes differed.[23] No subgroup analyses were conducted for micropreterm infants, and most studies enrolled preterm infants under 1850 g. Infants fed PDF consumed less formula, the same amount of energy, but more protein, calcium, and phosphorus than those fed term formula. A meta-analysis of 4 trials reported a significant difference in weight and

length but not head circumference at 9 months corrected age. In 2001, Lucas reported no difference in Bayley Mental Development Index and Psychomotor Development Index scores at 18 months in the two groups.[24] Four trials reported no difference in bone mineralization. The review concluded that available data did not provide strong evidence that feeding preterm infants with nutrient-enriched formula following hospital discharge affects growth rates or development up to 18 months post-term compared with standard term formula.[25] However, this conclusion was criticized for the "limited ability to combine the summary data available in the published manuscripts."[26] Cooke pointed out that in studies with adequate sample size and duration of 6-12 months, infants fed PTF or PDF (particularly males) had enhanced growth.

Monitoring of Nutritional Practices and Status

Growth

Growth monitoring is an integral part of the medical and nutritional assessment and management of micropreterm infants, who are at high risk for intrauterine and extrauterine growth restriction. The ideal postnatal growth rate for micropreterm infants is not known. Lean body mass gain (nitrogen retention) could be measured in addition to weight gain to derive better estimates of macronutrient requirements, but this approach is difficult to apply outside of research settings.[27] Without a universally-accepted growth standard for monitoring longitudinal growth of preterm infants in hospital, the goal is to replicate the fetal growth rate of at least 15-20 g/kg/d. The International Fetal and Newborn Growth Consortium [INTERGROWTH-21] study currently is monitoring longitudinal growth in a cohort of preterm infants 23-36 weeks' gestation to provide new growth standard curves.[28] The World Health Organization Multi-Center Growth Reference Group created sex-specific growth curves,[29] which should be used to plot longitudinal growth for micropreterm infants from the expected date of delivery.

Discussion

Future research should focus either on micropreterm/ELBW infants or stratify subjects by GA or BW to allow balanced sub-group analyses. Ideally, a standard definition should be used (based on GA or BW) so data across studies can be compared. It is important to define optimal protein and energy intakes and P:E, and measure lean mass, not just weight gain, as an outcome. The specific nutritional needs of micropreterm infants with postnatal growth restriction before and after discharge need to be defined.

Micropreterm infants have greater nutritional deficits at birth than more mature preterm infants and accumulate greater postnatal deficits. Recommendations for routine preterm infants are not likely on a theoretical basis to meet requirements for micropreterm infants. Only a few good-quality studies have addressed this group specifically, making it impossible to formulate evidence-based recommendations for most nutrients. Nutritional management of micropreterm infants should be based on existing recommended intakes for preterm infants, individualized according to an infant's GA, BW, and clinical status. Early use of parenteral nutrition is recommended while establishing enteral feeds to avoid the accumulation of nutrient deficits and growth failure. Human milk should be used when available but should be fortified to meet requirements, ideally based on measurement of milk composition. When human milk is not available in sufficient quantities, a PTF should be used. ■

Author Disclosures

Mary Fewtrell, MD, has received research funding and performed advisory or consultant work Philips Advent and Pfizer. Sudha Kashyap, MD, has served on an advisory board for Mead Johnson Nutrition. He has also, in the past, served on advisory boards as a consultant for Abbott and Baxter. Enrique Udaeta, MD, is a consultant for Nestle and Mead Johnson Nutrition and is an academic speaker for Mead Johnson Nutrition. All authors received an honorarium from Mead Johnson Nutrition for attendance, presentation, and manuscript preparation. D. T. wrote the first draft of this manuscript.

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