Enteral Nutrient Supply for Preterm Infants: Commentary From the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition

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ABSTRACT

The number of surviving children born prematurely has increased substantially during the last 2 decades. The major goal of enteral nutrient supply to these infants is to achieve growth similar to foetal growth coupled with satisfactory functional development. The accumulation of knowledge since the previous guideline on nutrition of preterm infants from the Committee on Nutrition of the European Society of Paediatric Gastroenterology and Nutrition in 1987 has made a new guideline necessary. Thus, an ad hoc expert panel was convened by the Committee on Nutrition of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition in 2007 to make appropriate recommendations. The present guideline, of which the major recommendations are summarised here (for the full report, see *http://links.lww.com/A1480*), is consistent with, but not identical to, recent guidelines from the Life Sciences Research Office of the American Society for Nutritional Sciences published in 2002 and recommendations from the

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handbook *Nutrition of the Preterm Infant. Scientific Basis and Practical Guidelines*, 2nd ed, edited by Tsang et al, and published in 2005. The preferred food for premature infants is fortified human milk from the infant's own mother, or, alternatively, formula designed for premature infants. This guideline aims to provide proposed advisable ranges for nutrient intakes for stable-growing preterm infants up to a weight of approximately 1800 g, because most data are available for these infants. These recommendations are based on a considered review of available scientific reports on the subject, and on expert consensus for which the available scientific data are considered inadequate.

Key Words: child development, embryonic and foetal development, nutritional requirements, Premature infant feeding

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In 1987 the European Society of Paediatric Gastroenterology (ESPGAN), and Nutrition published recommendations on nutrition and feeding of preterm infants (1). Even though extensive reviews on the topic have recently been published (2,3), the ESPGHAN Committee on Nutrition considered it necessary to review the recommendations on nutrient needs of preterm infants.

An expert group reviewed the existing evidence and prepared draft manuscripts on advisable intakes of macro- and micronutrients for preterm infants. These proposals were reviewed and discussed in detail at a scientific workshop organised by the charitable Child Health Foundation (*www.kindergesundheit.de*) in March 2007. This meeting was attended by observing experts in infant formula design and manufacturing (Observers from the dietetic industry at the scientific workshop held to discuss the draft recommendations with invited expert guests (in alphabetical order): H. Böckler, G. Boehm, C. Garcia, F. Haschke, J. Wallingford), who were asked to provide advice on the feasibility of producing food products based on the recommendations made.

The aim of this commentary is to provide guidance on quantity and quality of nutrients needed for preterm infants, so as to achieve growth similar to foetal growth coupled with satisfactory functional development. The recommendations relate to ranges of enteral intakes for stable-growing preterm infants up to a weight of approximately 1800 g, because most data are available for these infants. No specific recommendations are provided for infants with a weight below 1000 g because data are lacking for this infant group for most nutrients, except for protein needs. The needs of infants with specific diseases (eg, bronchopulmonary dysplasia, congenital heart disease, short bowel syndrome) and those receiving parenteral nutrition have been reviewed recently (4) and are not specifically addressed in this commentary.

The Committee advocates the use of human milk for preterm infants as standard practice, provided it is fortified with added nutrients where necessary to meet requirements. Parents and health care providers should be aware that human milk composition may vary for the duration of lactation, within the day, and even during 1 expression. Also, the treatment following expression (eg, storage, pasteurisation) may influence composition. As an alternative to human milk, preterm formula may be used. This commentary focuses on providing guidance on appropriate nutrient intakes with fortified human milk or formula.

Recent extensive reports on this topic (2,3) and recommendations on nutrient supply for term infants (5) have been taken into account in preparing this commentary. A MEDLINE search was performed for publications on preterm nutrition. For several nutrients, however, there is insufficient evidence on which to base definitions of lower and upper intake levels. When sufficient data were not available, intakes provided with human milk feeding, available human milk fortifiers, and with preterm infant formulae were considered.

Ranges of advisable nutrient intakes are expressed both per kilogram body weight per day and per 100 kcal (Table 1). Calculation of the latter values was based on the minimum energy intake of 110 $kcal \cdot kg^{-1} \cdot day^{-1}$ that we chose to recommend. Thereby, the ranges of nutrient intakes per 100 kcal will ensure that the infant receives the minimum or maximum of each specific nutrient at an intake of 110 $kcal \cdot kg^{-1} \cdot day^{-1}$. One should be aware that at higher energy intakes, the individual nutrient should not exceed an acceptable maximum level of intake.

Although the recommended ranges of nutrient intakes are considered reasonable, a high degree of uncertainty remains and hence the provision of nutrient intakes outside of the specified ranges is not discouraged if justified by good reasons. Nevertheless, it must be noted that using levels found in available commercial products without apparent problems as the basis for providing guidelines is less than satisfactory, because subtle adverse affects may not be detected without conducting adequate randomised controlled trials. Such trials can also be aimed at obtaining data on suitability and safety of intakes that are outside the specified ranges.

A detailed report is available electronically (*http://links.lww.com/A1480*), whereas this commentary focuses on the major changes that some of the specific recommendations underwent. A table is provided with specific recommendations for all nutrients, including nutrients that are not discussed separately in this commentary.

FLUID

Randomised controlled trials on enteral fluid intake of preterm infants are lacking as are studies comparing different fluid volumes providing identical nutrient intakes. From data of combined parenteral/enteral regimens, and assuming full enteral absorption, it follows that fluid volumes between 96 and 200 $mL \cdot kg^{-1} \cdot day^{-1}$ are tolerated, and that these values may serve as lower and upper limits (6), and that postnatal intakes at the lower range is likely to minimise risk of long-term morbidity such as bronchopulmonary dysplasia and patent ductus arteriosus. It is important to note that fluid volumes needed for enteral nutrition are influenced by osmolarity and renal solute load and are not synonymous with actual water needs.

We regard 135 $mL \cdot kg^{-1} \cdot day^{-1}$ as the minimum fluid volume and 200 $mL \cdot kg^{-1} \cdot day^{-1}$ as a reasonable upper limit. For routine feeding, rates of 150 to 180 $mL \cdot kg^{-1} \cdot day^{-1}$ nutrient intake when standard formula or fortified breast milk is used are likely to achieve meeting nutrient requirements. Some infants may need higher volumes to meet requirements of substrates other than fluid.

ENERGY

Recommendations for energy intake are based on the assumption that growth and nutrient retention similar to intrauterine references are appropriate. Yet we must make allowances for extrauterine environment and differences in nutrient supply and metabolism (eg, the foetus receives only a small proportion of energy as fat). Using intrauterine growth as a standard should involve not only achieving similar weight gain but also body composition, even though a higher extrauterine fat deposition may be needed to provide thermal and mechanical protection.

Studies in the 2 decades since the ESPGAN recommendations (1) have provided data on longer-term outcomes, and there are indications that rapid infant weight gain in term infants may be associated with adverse outcomes (7), adding to the uncertainty

TABLE 1. Recommended intakes for macro- and micronutrients expressed per $mg \cdot kg^{-1} \cdot day^{-1}$ and per 100 kcal unless otherwise denoted

Min–max	Per $kg^{-1} \cdot day^{-1}$	Per 100 kcal
Fluid, mL	135–200	
Energy, kcal	110–135	
Protein, g <1 kg body weight	4.0–4.5	3.6–4.1
Protein, g 1–1.8 kg body weight	3.5–4.0	3.2–3.6
Lipids, g (of which MCT <40%)	4.8–6.6	4.4–6.0
Linolenic acid, mg*	385–1540	350–1400
α-linolenic acid, mg	>55 (0.9% of fatty acids)	>50
DHA, mg	12–30	11–27
AA, mg†	18–42	16–39
Carbohydrate, g	11.6–13.2	10.5–12
Sodium, mg	69–115	63–105
Potassium, mg	66–132	60–120
Chloride, mg	105–177	95–161
Calcium salt, mg	120–140	110–130
Phosphate, mg	60–90	55–80
Magnesium, mg	8–15	7.5–13.6
Iron, mg	2–3	1.8–2.7
Zinc, mg‡	1.1–2.0	1.0–1.8
Copper, μg	100–132	90–120
Selenium, μg	5–10	4.5–9
Manganese, μg	≤27.5	6.3–25
Fluoride, μg	1.5–60	1.4–55
Iodine, μg	11–55	10–50
Chromium, ng	30–1230	27–1120
Molybdenum, μg	0.3–5	0.27–4.5
Thiamin, μg	140–300	125–275
Riboflavin, μg	200–400	180–365
Niacin, μg	380–5500	345–5000
Pantothenic acid, mg	0.33–2.1	0.3–1.9
Pyridoxine, μg	45–300	41–273
Cobalamin, μg	0.1–0.77	0.08–0.7
Folic acid, μg	35–100	32–90
L-ascorbic acid, mg	11–46	10–42
Biotin, μg	1.7–16.5	1.5–15
Vitamin A, μg RE, 1 μg ~ 3.33 IU	400–1000	360–740
Vitamin D, IU/day	800–1000	
Vitamin E, mg (α-tocopherol equivalents)	2.2–11	2–10
Vitamin K_1, μg	4.4–28	4–25
Nucleotides, mg		≤5
Choline, mg	8–55	7–50
Inositol, mg	4.4–53	4–48

AA = arachidonic acid; DHA = docosahexaenoic acid; IU = international unit; MCT = medium-chain triacylglycerols.

Calculation of the range of nutrients expressed per 100 kcal is based on a minimum energy intake of 110 kcal/kg.

* The linoleic acid to α-linolenic acid ratio is in the range of 5 to 15:1 (wt/wt).

† The ratio of AA to DHA should be in the range of 1.0–2.0 to 1 (wt/wt), and eicosapentaenoic acid (20:5n-3) supply should not exceed 30% of DHA supply.

‡ The zinc to copper molar ratio in infant formulae should not exceed 20.

regarding optimal energy provision for preterm infants. Energy requirements for otherwise healthy preterm infants will depend on the postconceptional age (higher per kilogram body weight at 24 weeks than at 36 weeks postconceptional age), accumulated nutrient deficits (both pre- and postnatal growth restriction), alterations in body composition, and differences in resting energy expenditure. Synthesis of new tissue is energy intensive and strongly affected by the intake of protein and other nutrients; thus, achieving an adequate energy to protein ratio is as important as providing adequate energy intake (8).

Clinical studies suggest that energy intakes less than or equal to $100\,kcal \cdot kg^{-1} \cdot day^{-1}$ will not meet the needs of some preterm infants before discharge. Where protein to energy ratios are adequate (>3–3.6 g/100 kcal) in a formula providing well-absorbed nutrients, an energy intake $>100\,kcal \cdot kg^{-1} \cdot day^{-1}$ is generally appropriate (9) and may result in a fat mass (FM) percentage closer to both intrauterine references and normal term infants. Small-for-gestational age infants may need a higher energy intake than appropriate-for-gestational age infants (9); however, a focus on achieving an optimal lean mass accretion rather than FM may be more appropriate. Although higher intakes ($140–150\,kcal \cdot kg^{-1} \cdot day^{-1}$) appear generally safe in the short term, there is limited evidence of improved linear growth (as a proxy for lean mass accretion), but FM deposition appears excessive (9–12).

A reasonable range of energy intake for healthy growing preterm infants with adequate protein intake is 110 to $135\,kcal \cdot kg^{-1} \cdot day^{-1}$. Increasing energy intake may not be appropriate for infants whose growth appears inadequate (without evidence of fat malabsorption) because it is more likely that other nutrients (eg, protein) are rate limiting.

PROTEIN

There is a lack of data on long-term outcome effects of different protein intakes from randomised controlled trials, but there are some indications that a suboptimal intake of protein, energy, and other nutrients may lead to lower cognitive achievements (13).

Compositional analysis of foetal tissues has been a valuable data source for our understanding of the nutrient needs of the foetus, and by analogy, those of the growing preterm infant. Protein accretion has been estimated at approximately $1.7\,g \cdot kg^{-1} \cdot day^{-1}$ for foetuses throughout the second half of gestation but is lower at the end of gestation (14). Obligatory protein losses are at least $0.7\,g \cdot kg^{-1} \cdot day^{-1}$ but may be higher if nitrogen losses from skin and breath could be measured. Nevertheless, this value is close to that found necessary to reach a nitrogen equilibrium (15). Clinical practice, however, regularly shows deficits in protein supply relative to estimated requirements in the first few weeks of life, particularly in more immature preterm infants, depending on feeding policy, tolerance, and illness (16).

The quality of the provided protein may interfere with the recommended intake because the infant does not require proteins but requires specific amino acids. Little is known about optimal intakes of specific amino acids. A different composition of the proteins administered may change the quantity of proteins required.

Based on the protein needs and nitrogen utilisation, the protein intake should be at least $3.0\,g \cdot kg^{-1} \cdot day^{-1}$. Empirical data show that weight gain approximating that in utero can be achieved at approximately $3\,g \cdot kg^{-1} \cdot day^{-1}$ protein intake (3,15,17,18) and that weight gain rates are linearly related to protein intakes up to $4.5\,g \cdot kg^{-1} \cdot day^{-1}$. Intrauterine weight gain can be matched at protein intakes <3 to $3.5\,g \cdot kg^{-1} \cdot day^{-1}$ accompanied by a high energy intake, but body fat percentage will then be much higher than observed in the foetus.

Protein supply needs to compensate for the accumulated protein deficit observed in almost all small preterm infants, and can be increased to a maximum of 4.5 $g \cdot kg^{-1} \cdot day^{-1}$, depending on the magnitude of the accumulated protein deficit. Intakes in the range of 3 to 4.5 $g \cdot kg^{-1} \cdot day^{-1}$ will achieve acceptable plasma albumin and transthyretin concentrations (19). Some excess of protein intake over requirements was not shown to cause detrimental effects in preterms, but a small deficit will impair growth. We therefore recommend aiming at 4.0 to 4.5 $g \cdot kg^{-1} \cdot day^{-1}$ protein intake for infants up to 1000 g, and 3.5 to 4.0 g for infants from 1000 to 1800 g that will meet the needs of most preterm infants. Protein intake can be reduced towards discharge if the infant's growth pattern allows for this. The recommended range of protein intake is therefore 3.5 to 4.5 $g \cdot kg^{-1} \cdot day^{-1}$ or 3.2 to 4.1 g/100 kcal.

LIPIDS

Dietary lipids provide the preterm infant with much of its energy needs, essential polyunsaturated fatty acids, and lipid-soluble vitamins (3). Amount and composition of dietary lipids affect both growth pattern and body composition. The availability and metabolism of long-chain polyunsaturated fatty acids have direct implications for cell membrane functions and the formation of bioactive eicosanoids. Brain grey matter and the retina are particularly rich in long-chain polyunsaturated fatty acids, and complex neural functions are related to energy supply and the composition of dietary fatty acids.

Assuming a daily intrauterine fat deposition of 3 g/kg (3), 10% to 40% loss from fat malabsorption, and 15% loss from unavoidable oxidation, and conversion of absorbed triglyceride to deposited triglyceride in tissue, the minimum fat intake to meet is estimated at 3.8 to 4.8 $g \cdot kg^{-1} \cdot day^{-1}$. On this basis, a minimal dietary fat intake of 4.8 $g \cdot kg^{-1} \cdot day^{-1}$ is suggested.

The ESPGHAN Committee on Nutrition (20) and the expert committee convened by the US Life Science Research Office (2) recommended fat intake upper limits of 6.0 g/100 kcal (54% of energy; E%) (20) and of 5.7 g/100 kcal (51 E%) (2), that are similar to the upper end of the range usually observed in human milk samples. Although some infants with restricted fluid and feed intakes may need high fat intakes to meet energy needs, for most preterm infants a reasonable range of fat intake is 4.8 to 6.6 $g \cdot kg^{-1} \cdot day^{-1}$ or 4.4 to 6.0 g/100 kcal (40–55 E%). The medium-chain triglyceride content in preterm formulae, if added, should be in the range of up to 40% of the total fat content.

Essential Fatty Acids

There is no evidence of linoleic acid deficiency or of adverse effects from high intakes in infants fed the present preterm formulae. Linoleic acid intakes of 385 to 1540 $mg \cdot kg^{-1} \cdot day^{-1}$ or 350 to 1400 mg/100 kcal (3.2–12.6 E%) are considered acceptable.

Present understanding suggests that the essential fatty acid, α-linolenic acid, plays an essential role as a precursor for synthesis of eicosapentaenoic acid and docosahexaenoic acid (DHA). A reasonable minimum intake of α-linolenic acid for preterm infants of 55 $mg \cdot kg^{-1} \cdot day^{-1}$, or 50 mg/100 kcal (0.45 E%) has been suggested to be equivalent to about 0.9% of total fatty acids (3).

Clinical trials in preterm infants fed formulae containing both arachidonic acid (AA) and DHA have shown beneficial effects on the developing visual system and measures of cognitive development during the first year of life, and on immune phenotypes (3,21–23). There was no evidence of adverse effects including growth among infants fed formulae containing up to 0.5% DHA and up to 0.7% AA of the total formula fatty acids. Eicosapentaenoic acid competes with AA, and eicosapentaenoic acid levels are low in human milk. These considerations led to the conclusion that both AA and DHA should be included in preterm formulae, and that oils containing significant amounts of eicosapentaenoic acid should be avoided. Recommended intakes are for DHA (22:6n-3) 12 to 30 $mg \cdot kg^{-1} \cdot day^{-1}$ or 11 to 27 mg/100 kcal and for AA (20:4n-6) 18 to 42 $mg \cdot kg^{-1} \cdot day^{-1}$ or 16 to 39 mg/100 kcal. The ratio of AA to DHA should be in the range of 1.0–2.0 to 1 (wt/wt), and eicosapentaenoic acid (20:5n-3) supply should not exceed 30% of DHA supply.

CARBOHYDRATES

Carbohydrates are a major source of energy. Glucose is the principal circulating carbohydrate and the primary source of energy for the brain. It is an important carbon source for de novo synthesis of fatty acids and several nonessential amino acids. The upper limit of carbohydrate intake has been calculated as the glucose equivalent of the total energy expenditure minus the energies from the minimum requirements for protein and fat. A maximum carbohydrate content of preterm infant formula (glucose or nutritionally equivalent di-, oligo-, and polysaccharides) of 12.0 g/100 kcal is recommended. The lower limit for carbohydrate intake has been defined based on energy requirements of the brain and other glucose-dependent organs, minimising the irreversible loss of protein and nitrogen by limiting gluconeogenesis, and preventing ketosis. A minimum content of 10.5 g carbohydrate/100 kcal (glucose or nutritionally equivalent di-, oligo-, or polysaccharides) in preterm infant formulae is recommended.

CALCIUM

A number of mineral balance studies have been performed in premature infants fed human or formula milk (24). Collectively, these studies showed that calcium absorption depends on calcium and vitamin D intakes, and that calcium retention is additionally related to absorbed phosphorus. They suggest that calcium retention ranging between 60 to 90 $mg \cdot kg^{-1} \cdot day^{-1}$ decreases the risk of fractures, diminishes the clinical symptoms of osteopenia, and ensures appropriate mineralisation in very-low-birth-weight (VLBW) infants. Thus, a calcium absorption rate of 50% to 65% will lead to a calcium retention of 60 to 90 $mg \cdot kg^{-1} \cdot day^{-1}$ at an intake of 120 to 140 $mg \cdot kg^{-1} \cdot day^{-1}$.

PHOSPHORUS AND CALCIUM TO PHOSPHORUS RATIO

The calcium to phosphorus ratio may be an important determinant of calcium absorption and retention (25). In human milk, the calcium to phosphorus ratio is approximately 2 in terms of mass and 1.5 as molar ratio. In premature infants, phosphorus accumulation is related to calcium and nitrogen retention but with a lower proportion for bone compared with that in the foetus. Phosphorus absorption is efficient (±90%) in infants fed human milk or formula. Nevertheless, the use of poorly absorbable calcium salt, such as calcium triphosphate, is associated with significant reduction in phosphorus absorption (25). The present recommendation for preterm formula is a calcium to phosphorus ratio close to 2:1, but ideally this should be adapted taking into account nitrogen retention as well as bioavailability of the calcium salt. Considering a nitrogen retention ranging from 350 to 450 $mg \cdot kg^{-1} \cdot day^{-1}$ and calcium retention from 60 to 90 $mg \cdot kg^{-1} \cdot day^{-1}$, the adequate phosphorus intake represents 65 to 90 $mg \cdot kg^{-1} \cdot day^{-1}$ of a highly absorbable phosphate source (90%) with a calcium to phosphorus ratio between 1.5 and 2.0. Newly acquired understanding of bone physiology (26) makes it advisable to review the present

recommendations of mineral content for preterm formula, thereby promoting the use of calcium sources with better fractional absorption rate as well as mechanical stimulation of the skeleton during the neonatal period. Considering that a calcium retention level ranging from 60 to 90 $mg \cdot kg^{-1} \cdot day^{-1}$ ensures appropriate mineralisation and decreases the risk of fracture, an intake from 120 to 140 $mg \cdot kg^{-1} \cdot day^{-1}$ (110–130 mg/100 kcal) of highly bioavailable calcium salts and 60 to 90 $mg \cdot kg^{-1} \cdot day^{-1}$ (55–80 mg/100 kcal) of phosphate is recommended. Individual needs can be determined by measuring spot urinary calcium and phosphate excretion aiming at a low excretion rate.

VITAMIN D

Vitamin D is important for supporting a large number of physiological processes such as neuromuscular function and bone mineralisation. The intestinal receptor-dependent actions of calcitriol [$1,25(OH)_2D$] are critical for optimal calcium absorption (27) and the pathways of vitamin D absorption and metabolism are fully operative in babies <28 weeks of gestation (28,29). Nevertheless, the requirements for optimal growth in VLBW and extremely-low-birth-weight infants are still matters for discussion. Studies in adults suggest a vitamin D dietary allowance of 1000 to 2000 international units (IU) per day and the target value of circulating 25(OH)D to at least 75 nmol (30 ng/mL) (30–32).

Several studies (33–40) evaluated the relation between vitamin D_3 intake and the mean circulating concentration of 25(OH)D. The findings led to the consensus that, in preterm infants of vitamin D–deficient mothers, a vitamin D intake of 800 to 1500 IU/day is necessary to reach a circulating 25(OH)D concentration above 75 nmol/L.

Bronner et al (41) showed that calcium absorption in low birth weight infants was directly proportional to the daily calcium intake in the range from 40 to 142 mg/kg, and was independent of daily vitamin D supplementation of up to 2000 IU. These studies led to the concept that most of the calcium absorption in preterm infants is probably because of a passive diffusion and that the vitamin D–regulated mechanisms are expressed during early infancy. However, that study was not initially designed to evaluate the influence of vitamin D on calcium absorption rate.

There is evidence that, as early as in the 20th week of gestation, the human foetal intestine possesses functional calcitriol receptors that regulate the expression of calcium-binding protein and calcidiol-24-hydroxylase (42,43). In contrast to Brenner's study (41), Senterre et al (44) have shown, by performing 3-day metabolic balances, that calcium net absorption increased from 50% to 71% by feeding appropriate-for-gestational age preterm infants weighing <1500 g banked human milk alone or supplemented with 30 μg of cholecalciferol/day (1200 IU) without calcium fortification. One year earlier, Senterre and Salle (45) had reported similar results in a study involving 28 preterm babies fed banked human milk. These 2 studies demonstrated that vitamin D indeed affected the calcium absorption rates.

There is a general consensus to increase the reference values and the threshold level of circulating vitamin D in infants as in adult with a target value for 25(OH)D of >80 nmol/L (32). Considering the prevalence of vitamin D deficiency in pregnant mothers, higher vitamin D supply in preterm infants could be necessary to rapidly correct the foetal low plasma level. A vitamin D intake of 800 to 1000 IU/day (and not per kilogram) during the first months of life is recommended. This implies that a formula should provide the basic needs to which a supplement must be given (eg, on the order of 100–350 IU/100 kcal), avoiding toxic intakes at high levels of formula consumption. An intake of 800 to 1000 IU/day would improve serum 25(OH)D concentrations and the plasma levels of $1,25(OH)_2D$ and subsequently the calcium absorption rate, allowing reduction of the high calcium content of some formulae. This statement holds for both premature infants fed mother's milk and those fed formula milk.

IRON

Iron is essential for brain development, and prevention of iron deficiency is important. Many observational studies have shown an association between iron deficiency anaemia and poor neurodevelopment in infants (46). In contrast to most other nutrients, however, there is no mechanism for regulated iron excretion from the human body. Excessive iron supplementation of infants may lead to increased risk of infection, poor growth, and disturbed absorption or metabolism of other minerals (47). Furthermore, iron is a potent prooxidant, and nonprotein-bound iron has been suggested to cause formation of free oxygen radicals and to increase the risk of retinopathy of prematurity, especially when given in high doses as a component of blood transfusions or as an adjunct to erythropoietin therapy (48–51). Thus, one must prevent not only iron deficiency but also iron overload.

Preterm infants with an average birth weight of 1.46 kg received an iron intake of 5.9 versus 3.0 $mg \cdot kg^{-1} \cdot day^{-1}$ at discharge and about 3 versus 2 $mg \cdot kg^{-1} \cdot day^{-1}$ at 3 to 9 months (52). There was no difference between the 2 groups in anaemia prevalence or neurodevelopment at 12 months, but the high-iron group had higher glutathione peroxidase concentrations (a marker of oxidative stress), lower plasma zinc and copper levels, and more respiratory tract infections, suggesting possible adverse effects from the higher intake. Recently, Franz et al (53) randomised 204 infants with an average birth weight of 0.87 kg into an early iron group receiving 2 to 4 $mg \cdot kg^{-1} \cdot day^{-1}$ of iron supplements from about 2 weeks and a late iron group that did not receive iron supplements until 2 months of age. There were no differences in serum ferritin and hematocrit at 2 months of age but infants in the late iron group had received more blood transfusions.

Iron intakes of <2 $mg \cdot kg^{-1} \cdot day^{-1}$ are likely to result in iron deficiency in preterm infants, at least in those with birth weights <1800 g. Because high enteral iron intakes have been associated with possible adverse effects, an intake of 2 to 3 $mg \cdot kg^{-1} \cdot day^{-1}$, corresponding to 1.8 to 2.7 mg/100 kcal, is recommended. Prophylactic enteral iron supplementation (given as a separate iron supplement, in preterm formula or in fortified human milk) should be started at 2 to 6 weeks of age (2–4 weeks in extremely-low-birth-weight infants). Infants who receive erythropoietin treatment and infants who have had significant, uncompensated blood losses may initially need a higher dose, requiring a separate iron supplement in addition to preterm formula or fortified human milk. Enteral iron doses >5 $mg \cdot kg^{-1} \cdot day^{-1}$ should be avoided in preterm infants because of the possible risk of retinopathy of prematurity. Iron supplementation should be delayed in infants who have received multiple blood transfusions and have high serum ferritin concentrations (54). Iron supplementation should be continued after discharge, at least until 6 to 12 months of age depending on diet.

PRE- AND PROBIOTICS

Prebiotics

Human milk contains more then 130 different oligosaccharides that are fermented in part in the infant's colon. The concentration changes with the duration of lactation, being highest in the colostrum at 20 to 23 g/L, about 20 g/L on day 4 of lactation, and 9 g/L on day 120 of lactation (55). Preterm infants show some absorption of intact human milk oligosaccharides, but most resist

digestion in the small intestine and undergo fermentation in the colon (56).

The composition of oligosaccharides in human milk is genetically determined and thus large variability in oligosaccharide composition exists in the population. Therefore, it is difficult to define the exact oligosaccharide composition of human milk. In infant formula primarily 1 type of oligosaccharide mixture (GosFos) has been systematically studied in term and preterm infants (57–62). GosFos are not oligosaccharides present in human milk, but they represent short- and long-chain moieties of oligosaccharides: GosFos is a mixture of 90% short-chain galactooligosaccharides and 10% long-chain fructooligosaccharides. Only 2 randomised trials have been conducted in preterm infants in whom GosFos supplemented standard preterm formula, at concentrations of 8 g/L and 9 g/L, respectively. GosFos has been shown to increase faecal bifidobacteria counts, to reduce stool pH, to reduce stool viscosity, and to accelerate gastrointestinal transport (61,63). It has been hypothesized that GosFos may accelerate feeding advancement, reduce the incidence of gastrointestinal complications such as necrotizing enterocolitis, improve immunological functions, reduce the incidence of hospital-acquired infections, and improve long-term outcome, but there are no data available from preterm studies to support these assumptions. Further trials relating to the safety of GosFos should address nutrient bioavailability, intestinal gas production, intestinal water loss, intestinal flora, and possible interaction with other fermentable substances.

Probiotics

A recent systematic review showed a significant decrease in necrotizing enterocolitis after the introduction of different strains and dosages of probiotics (64). In addition, the time to full feeds was significantly shorter in the probiotic group. The most effective probiotic or combination of probiotics, dosage, and timing are unknown. In addition, the effect may depend on type of feeding. Although the available studies have not reported any adverse effects, we counsel caution in the introduction of any potentially infectious agent for immunologically immature VLBW infants. Whereas potential benefits must be weighed against potential harms, safety cannot be defined as an absolute risk-free condition (65). Future randomised probiotic trials should also address the risk of transformation of probiotics in vivo, infections by probiotics, transposition of antibiotic resistance, and lasting effects on gut microbiota. Each probiotic strain and potential combinations needs to be characterised separately.

In conclusion, there is not enough available evidence suggesting that the use of probiotics or prebiotics in preterm infants is safe. Efficacy and safety should be established for each product. We conclude that the presently available data do not permit recommending the routine use of prebiotics or probiotics as food supplements in preterm infants.

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