Nutrition of the Low-Birth-Weight Infant

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There are three major considerations affecting the quantity and quality of protein to be given to a low-birth-weight baby. These are (a) requirements for normal growth and body composition, (b) development of protein and amino acid metabolism, and (c) renal function.

A number of different techniques have been used to estimate the requirements in adults, for example, nitrogen balance, body composition, amino acid turnover, fractional nitrogen excretion, and calorimetry. The application of these methods to the problem of determining the protein requirement of the small preterm infant is very difficult, because the optimal rate at which preterm infants ex utero should accumulate protein has yet to be determined.

The classical factorial method has been used to estimate protein requirements. The results suggest that the amount of protein in human milk and in many formulas designed for normal babies is inadequate (33). The calculations assume that the in utero growth rate remains optimal ex utero and that the body composition of the developing fetus is adequately known. Also, many empirical studies have shown that babies fed expressed human milk gain weight at a slower rate than those receiving a cow's milk-based formula (5,8,20,32). But the question remains, does this difference in weight gain have any advantage? Is the difference in weight gain due to a difference in protein intake or to other factors, for example, a lower energy content or a lower sodium content in human milk compared with cow's milk-based formulas.

In any case, it is not sufficient merely to estimate protein requirements on the basis of theoretical calculations from in utero accumulation rates or to administer large quantities of protein in order to attain intrauterine growth rates in the immediate extraterine environment. The biochemical immaturity of the human preterm infant makes him nutritionally very vulnerable, and the margin between an adequate protein intake and protein undernutrition or overnutrition with possible adverse effects is small. There is an incomplete development of several amino acid metabolic pathways in the newborn infant, especially in the small preterm infant (22). Thus, many of the amino acids previously thought to be nonessential, for example, cysteine, taurine, may be essential, at least for the immature organism, and must be supplied in the diet. Also, amino acid catabolism is incomplete, and an administration of protein in quantities which exceed the needs for synthesis stress the infants metabolic
machinery for disposing of excess nitrogen and results in hyperaminoacidemia, metabolic acidosis, and hyperammonemia. Recent reviews have been published (19-22). Few of the classic studies (5,8,17,20,32) which showed that preterm infants gained weight better with high-protein formulas than with human milk measured metabolic effects.

The proteins of human milk have been reviewed recently (4,7,12,16). The protein content of human milk is about 1.2 g/dl (1.8 g/100 kcal) when expressed as total nitrogen × 6.38 and 0.9 g/dl (1.3 g/100 kcal) when expressed as amino acid nitrogen × 6.38. Transitional human milk (6 to 10 days postpartum) contains 1.6 g/dl and colostrum (first 5 days postpartum) 2.3 g/dl. The milk of women delivering prematurely contains approximately 20% more nitrogen for the first 14 days of lactation than milk of mothers delivering at term (3,10,28), but not all studies show this (2,27). The whey proteins represent more than 70% of the total proteins in human milk, but less than 20% in cow’s milk (12,16). β-Lactoglobulin is the main whey protein in cow’s milk but is absent from human milk, which is rich in α-lactalbumin, lactoferrin, and immunoglobulins. The whey proteins used in some formulas are thus very different in composition from the whey proteins in human milk. Human milk from milk banks can be enriched with components of human milk such as fat or protein, etc. (human milk engineering), but further careful clinical evaluation is needed (11,18).

Most commercial formulas used for feeding healthy term infants have a caloric density of 67 kcal/dl and a protein content of 1.5 to 2.0 g/dl, thus containing 2.2 to 3.0 g protein/100 kcal. The major part of the protein is whey (whey/casein 60:40), but there are a number of “unadapted” cow’s milk-based formulas available with a whey/casein ratio of 18:82.

Formulas specifically designed for low-birth-weight infants have a higher caloric density, usually from 75 to 81 kcal/dl, but also a somewhat higher protein content, from 1.8 to 2.4 g/dl, than the formulas generally used for term infants. These formulas thus contain about 2.2 to 3.2 g protein/100 kcal.

Despite its limitations, the factorial method of assessment provides a means to estimate these protein requirements. As discussed above, it provides no information on whether the amount provided by the diet can be absorbed or utilized after absorption. Intakes of 4.0 g/kg (3.1/100 kcal) for growth from 800 to 1200 g and 3.5 g/kg (2.7/100 kcal) for growth from 1200 to 1800 g have been suggested (33), but experimental evidence that they can be utilized is lacking.

Even if the protein content of breast milk is accepted as 1.2 g/dl (i.e., total nitrogen × 6.38), these advisable protein intakes could be achieved only with intakes of mature human milk around 300 ml/kg/day. Although such high intakes have been recorded (30), they are not common. The minimum intake of 2.25 g/kg/day recommended by the American Academy of Pediatrics’ Committee on Nutrition (1) could, however, be achieved by feeding about 185 ml/kg/day. Intakes of 185 to 200 ml/kg/day are common practice, and there is
new evidence showing that moderately-low-birth-weight babies (>1.5 kg) thrive and achieve an intrauterine rate of weight gain without signs of metabolic stress (6,14) on 185 ml of human milk/kg.

Two reports suggest that very-low-birth-weight babies (<1.5 kg) may benefit in terms of weight gain from preterm milk—presumably because of its somewhat higher protein content (9,21). This interesting finding requires confirmation and further evaluation. In the meantime, during the early weeks of life, when survival may be in doubt and when the "protective factors" in human milk may be of great value, clinical experience in some centers suggests that it is reasonable to accept the theoretically suboptimal protein content of breast milk. For this reason, it is acceptable to provide mature milk or, better, the mothers own preterm milk fed at 185 ml/kg/day or more when full volume intake can be accepted clinically. Perhaps any deficiencies of growth or body composition might be repaired after this critical period for survival is over (23,29). Recent studies have also shown better fat absorption and higher intraluminal bile acid concentration in preterm infants fed human milk as compared with formula-fed infants (13,15,31).

Formulas specially designed for low-birth-weight babies require thorough study and evaluation before routine use is justified, but the following guidelines may be helpful. There is today documented experience of feeding low-birth-weight babies (<1500 g) with formulas containing 1.5 g protein/dl (1.8 g/100 kcal) (30), and thus there is at present little justification for designing a formula for low-birth-weight babies which contains less protein than this. Since many low-birth-weight babies thrive on such formulas, it is suggested that the lower limit for protein content be set at 1.5 g/dl or 1.8 g/100 kcal; when fed at the level of 130 kcal/kg/day, it will provide 2.3 g/kg/day. If the upper estimate reached by the factorial method (33) of 4 g/kg/day is accepted, then at the level of 130 kcal/kg/day it implies a protein:energy ratio of 3.1 g/100 kcal. A number of formulas are available with such a protein:energy ratio, but detailed documented experience, particularly data on metabolic tolerance (e.g., plasma concentration of ammonia, amino acids, urea, hydrogen ion, urinary concentration) is very limited. One study found that an intake of 3.0 g/100 kcal compared with an intake of 2.3 g/100 kcal, (fed at 117 kcal/kg, i.e., 2.5-3.2 g/kg) did not lead to faster growth, but a quarter of the babies developed late metabolic acidosis (29). Formulas containing 3.0 g of protein/100 kcal (>2 g/dl) should be used with caution, particularly during the first week or so of life, until additional systematically recorded experience becomes available.

Formulas with protein content greater than this, for example, 3.8 g/100 kcal (3 g/dl/78 kcal, fed at 150 ml/kg, i.e., 117 kcal and 4.5 g protein/kg/day) are associated with high plasma concentrations of aromatic amino acid, ammonia and hydrogen ion, particularly if the protein is mainly casein (24,25). Although it is not established conclusively that such metabolic abnormalities are harmful, neither can it be said that they are safe. Formulas with a higher whey/casein ratio are associated with lower plasma aromatic amino acid concentration (26).
Formulas for low-birth-weight babies should contain predominantly whey protein. This will ensure an intake of cysteine at least equal to that of the breastfed baby. Babies who receive dietary taurine, for example, in breast milk or added to a formula, excrete taurine in the urine (25) and have a higher taurine to glycine ratio in their bile acids (14). Until there is evidence of definite clinical benefits, however, we have at present no justification for urging that formulas for low-birth-weight babies contain taurine. This is an area of active investigation which needs close observation.

REFERENCES

DISCUSSION

Dr. Koldovsky: When you increase the volume from 170 ml to 185 ml, which is about 10%, the weight gain increases from 12.8 g to 15.1 g, so that by giving 10% more you actually get a 20% better weight gain. What could be the explanation?

Dr. Raihá: We are increasing the intake of electrolytes, the caloric intake, and the protein intake, so I cannot really answer your question. There is, however, a definite difference in the rate of weight gain, and with the high volumes, the weight gain is close to, if not identical with, the IU weight gain.

Dr. Rey: The maintenance energy requirement of a human or of an animal is the energy expenditure without growth. If you increase the energy intake above the maintenance requirement, you increase the weight proportionately to the energy available for growth, so there is nothing surprising at all in finding that a 10% increase in energy intake results in 20% or 30% or more weight increase.

Dr. Hagelberg: As you pointed out at the beginning, the preterm milk contains more protein than term milk, and that seems good because the preterm infants need more protein. However, it might be interesting to know what kind of protein is increased in the preterm milk, because if it is secretory IgA, for example, it is not very interesting from a nutritional point of view, since it is not absorbed in the gut.

Dr. Raihá: There is good evidence that it is partly secretory IgA. In fact, the difference in the protein concentration lasts a very short time—only 2 to 3 weeks—and I don’t think it has much nutritional importance on a long-term basis.
Dr. Hagelberg: It has been postulated that the preterm milk is a sort of prolonged colostrum, and it seems, therefore, logical to assume that IgA is increased. Did you see any adverse effects of increasing the volume up to 200 ml/kg?

Dr. Raihà: Yes, I am aware of the work by Oh and others who experienced clinical problems with high volumes. The volume of 200 ml/kg/day is, of course, high, but we did not see any adverse effects in our infants.

Dr. Gamarra: What do you recommend to give to very-low-birth-weight premature infants, less than 32 weeks old, for whom the intake of water must be limited because of respiratory distress?

Dr. Raihà: All the cases that we have studied were preterm infants that we were able to feed enterally. On the basis of our results, I cannot answer your question. I would think, however, that in a case of severe respiratory distress when the baby weighs, say, 1,200 g and is on a respirator, we would keep the baby on a very-low-volume intake during the first few days. We give the baby fresh breast milk in very small volumes—1 to 5 ml/hr—and then supplement it with intravenous feeding: glucose, sometimes amino acids if the intravenous feeding has to be prolonged for more than 5 or 6 days. We hardly ever use Intralipid®, and we don't worry too much about the caloric intake during those first days when the infant is very sick. We try to increase the volume of breast milk, and in our experience, it is not impossible to maintain some breast milk intake even in babies who are on the respirator. This may be due to the fact that the emptying of the stomach is much faster with human milk than with formula, for instance. I don't think we should push those babies, nor should we try to give them optimal caloric and amino acid amounts, because this is also a source of metabolic stress. The albumin always goes down in preterm infants on human milk. We let it go down, and it will eventually rise within some weeks. This is the usual trend. Of course, there is a possibility that lower serum albumin levels may even be beneficial for the kidney function and glomerular filtration rate.

Dr. Eeckels: I just wanted to ask you how low the lowest safe figure is for albumin in the premature infant?

Dr. Raihà: We have seen some preterm infants at around the 4th to 6th week, with serum albumin as low as 30 g/liter. Very few of those infants show edema or any clinical signs of being ill. We just follow them, and then they begin to improve. This was shown by Crosse many years ago and may be of physiological significance. I think we are getting back to the fact that the preterm infant is a special biological entity. We don't really know what is normal and what is abnormal, and I don't think we should try to bring them up to IU standards of weight gain or even of amino acid levels.