EDITORIAL

Optimizing protein intake in preterm infants

Journal of Perinatology (2009) 29, 465–466; doi:10.1038/jp.2009.53

One of the most consistent observations in preterm infants is their increase in protein synthesis and protein balance when fed more protein, either as enteral protein or intravenous amino acids.¹ Amino-acid oxidation also increases directly with amino-acid supply.² These two fundamental observations indicate that preterm infants cannot grow without more protein and are more reliant on other energy forms (carbohydrate and lipid) to promote positive protein and energy balance when amino-acid and protein supplies are low. Because most preterm infants are not fed as much protein as they would have received *in utero* by active placental transport of amino acids, it is not surprising that nearly all preterm infants end up growth restricted at term gestation, whether determined by fetal growth curves or postnatal cross-sectional growth curves.³ Of more concern is the equally consistent observation that such slower than normal growth is associated with later life neurodevelopmental delays and cognitive deficits.⁴

In this issue of the *Journal of Perinatology*, Arslanoglu *et al.*⁵ document that assumed protein intake in a group of preterm infants fed supplemented own mother's milk or banked milk was greater than what these infants actually received, because the estimate of milk protein content, with and without supplement, was less than the measured protein content, leading to protein intakes that were as much as 0.6 to 0.8 g kg⁻¹ per day less than what had been estimated. This striking observation is important for at least three main reasons. First, repeated observations have documented not only less than adequate growth of preterm infants⁶ as noted above, but also growth of lean body components, particularly organs such as the brain, is dependent on protein intake. Second, recent magnetic resonance imaging studies have shown strikingly deficient growth of the brain of as much as 40% of total brain volume in preterm infants,^{7,8} even into adolescence.⁹ Such relatively gross measurements fail to show reduced development of neuronal length and dendritic connections, but these have been known for many years to occur in animal models of fetal under nutrition.¹⁰ Such adverse patterns of growth are even more specific in regions of the brain, such as the caudate nucleus, that directly impact cognition. Because a large proportion of preterm infants have some cognitive deficits, it is not surprising that there is a direct relationship between the degree of undernutrition and the slower rate of growth, including poorer cognitive function. Third, very preterm infants do have the remarkable capacity for improved growth, particularly of the brain and its essential regions related to

cognitive outcomes, when fed more protein and energy. Lucas's group⁹ followed their experimental cohort of preterm infants, first reported in the late 1980s, into adolescence and were able to correlate directly the amount of nutrition provided to these infants with their adolescent body stature, brain and caudate nucleus size, and cognitive function, even at such an advanced age and stage of development. The article by Arslanoglu *et al.*,⁵ therefore, defines how assumptions about improved nutrition with milk supplements are quite far off the mark and actually limit essential nutrition that would in turn limit growth and development of the body, the brain and critical regions of the brain that regulate intellectual development.

Would an additional 1 g kg⁻¹ per day be too much for those infants whose mothers had good milk protein content? Not likely. Many measurements of human milk protein content, including those in this study, consistently have shown that concentrations above 2.0 g per 100 ml are relatively rare.^{11,12} Adding 1 g kg⁻¹ per day of protein to such milk would produce 3 g per 100 ml and an intake of 4.5 g kg⁻¹ per day at 150 ml kg⁻¹ per day, higher than most such infants ordinarily receive, but still within the range calculated to produce normal rates of fetal growth. Further, the higher milk protein concentrations from mothers providing milk to preterm infants decreases significantly over the first 1 to 3 weeks after delivery when maximal enteral feeding rates seldom are achieved, making it even less likely that excessive amounts of protein would be provided. Nevertheless, the authors appropriately recommend further clinical trials to address potential toxicity. Limited clinical trials with small numbers of infants might be available in 2 to 3 years if this approach is followed. It is unlikely, though, that significantly adverse effects will be observed and in the interim, many infants will continue to receive inadequate protein intakes. This study provides reasonable evidence to indicate that this may be one of those situations where enough evidence already is present.

Providing more protein requires a simple, well-tolerated, high-quality protein supplement. Unfortunately, this has been a major deficiency in the US milk formula industry. The authors used Pro-Mix from Corpak MedSystems (Wheeling, IL, USA). There is little literature to document the attributes of this product and even less information about how much of this product the company could provide should neonatologists try to order it. Prolacta (Prolacta Bioscience, Monrovia, CA, USA) provides human milk protein derived from lactating women, a theoretically promising approach to a high-quality protein supplement. Their products contain lipid

in amounts that increase with the protein concentration; they also (currently) carry a higher price that many neonatal intensive care units can afford. There is great need, therefore, for new product development to produce enough protein supplements of high digestibility, tolerance and quality to meet the demands of the thousands of preterm infants on a daily basis. Perhaps this article will encourage entrepreneurial development of such products as well as the practice of increasing protein intake with fortifier by 1 g kg^{-1} per day as suggested by the authors.

Will the addition of 1 g of protein per 100 ml of milk promote growth? Very few studies actually have addressed whether protein supplements *per se* do promote growth in preterm infants. The NICHD Neonatal Research Network¹³ and the Pediatrix organization¹⁴ attempted to address this issue by comparing growth in infants fed more protein a few days earlier in one group vs another group. Neither organization's studies demonstrated a greater gain of weight, length, head circumference or lean body mass in the groups fed more protein earlier. These results are not surprising, because the differences in protein intake between the two groups occurred during the first 7 to 10 postnatal days, a period when total protein and energy intakes are insufficient to produce normal fetal rates of growth and when water balance is the primary determinant of weight and weight change. The number of days that the protein intakes were different also was relatively small, thus asking for a large benefit, growth, from a relatively small difference in protein intake over a short period of a few days. Despite these studies, it must be understood by all that growth of lean body mass—muscle, bone, brain and organ mass—cannot increase without more protein, because these structures are built on a protein matrix.

The study and article by Arslanoglu *et al.*⁵ in this issue of the *Journal of Perinatology* is important, therefore, because it provides a rational basis for simply adding more protein (or fortifier) to milk in those infants whose enteral diet comes from milk, especially over long periods after birth when maternal milk or banked milk have very low protein contents. This practice might not produce more rapid early weight gain, or even protein balance if energy intake also is limited and the protein is used for oxidative metabolism, but without the extra protein, such infants have no chance for improved growth. The observations that improved nutrition in preterm infants enhances brain growth and cognitive function as late as adolescence provide even more justification for the approach suggested.

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