Paediatrica Indonesiana 29 : 121 - 132 May - June 1989

SPECIAL ARTICLE

New Perspectives in the Nutrition of Premature and Low Birth Weight Infants

by

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Introduction

Everybody in this audience is well aware of the fact that in about the last two decades great advances have been made in fetal and neonatal medicine. Due to the recently gained knowledge in fetal biology as well as in neonatal biochemistry, physiology and pathophysiology a much better understanding of special dietary needs in prematurity and infancy has been achieved. Based on sound scientific background completely new feeding regimens are used today, which have not even been thought of about 20 or 30 years ago and which in turn have considerably contributed to the development of so-called "foods for special dietary purposes."

The disorders for which modified or even highly modified diets are used successfully can be grouped as follows:

Diarrhoea

1. Acute diarrhoea of bacterial or viral origin.
   First stage: Rehydration.
   Second stage: Realimentation.
2. Chronic Diarrhoea of various origin.
   - 2.1. Maldigestion and malabsorption syndromes.
   - 2.2. Hereditary disorders of the GI tract, e.g. primary lactase deficiency, glucose-galactose-malabsorption.

Prematurity
Low birth weight
Hereditary metabolic disorders

- Amino acid metabolism disorders e.g. phenylketonuria and allied disorders.
- Carbohydrate metabolism disorders e.g. galactosemia, fructose intolerance.

In this presentation I will concentrate on the particular dietary needs of premature and low birth weight infants, since their number is worrying and in many countries a public health problem.

Presented at the Seventh National Congress of Paediatric, Jakarta, 1987.
Received September 15^{th}, 1987.

Key Issues in Perinatal Growth and Metabolic Peculiarities of Prematurity

Since many decades it is known that preterm infants have special nutritional requirements. However, despite intensive research nearly all investigators have recognized the considerable uncertainty that persist in this area-indeed, the multiplicity of feeding regimens currently employed for low birth weight infants is itself a measure of this. In 1977 the American Academy of Pediatrics crystallized a widespread philosophy of research in preterm nutrition in the statement that

"the optimal diet for the low birth weight infant may be defined as one that supports a rate of growth approximating that of the third trimester of intrauterine life, without imposing stress on the developing metabolic and excretory system".

Whils this statement appears reasonable at first sight, it is clearly only a working hypothesis, unsupported by any data on the ultimate clinical benefits of attempting to mimic fetal growth. An equally plausible hypothesis is to provide a diet that permits the infant to make the most rapid adjustment to extrauterine life.

Prematurity is an unphysiological state. Preterm infants are not fetuses. They rapidly acquire a pattern of growth as well as metabolic and nutrient handling skills which would not be seen at a corresponding post-conceptional age in utero. Premature and low birth weight infants therefore offer an unprecedented challenge in securing normal physical and mental development.

Comparatively little is known about the 40-week normal period of prenatal life. The 40 weeks of gestational age show a fertilized ovum becoming an infant of about 3 kg. Two thirds of the 40 weeks are needed for half of that weight to develop. Most of this increase in weight is related to protein buildup. The fat accretion accounts for about 50 g only.

The next 1.5 kg acquired in the final one-third of gestation contain about 400 to 500 g of fat representing an energy reserve at birth. There is, however, considerable evidence that at about 34 weeks of gestation the velocity of weight gain decreases and that fetal growth slows down since the number of cells undergoing multiplication is progressively decreasing.

Prematurity causes some digestive and metabolic peculiarities which in turn have implications on nutrition and which can be summarized very briefly as follows:

(1) Poor control of body temperature.
(2) Poor control of body water.
(3) Immature live function causing (a) low blood glucose levels due to poorly developed gluconeogenesis, (b) jaundice due to accumulation of bilirubin, (c) iron deficiency anemia due to low iron stores, (d) inefficient drug detoxication due to poorly developed detoxication mechanisms.
(4) Low pancreatic lipase activity and low bile salt concentrations lead to poor fat digestion.
(5) Low secretion of lactase causing poor lactose digestion.
(6) Premature kidneys do not conserve water and sodium well. In addition the capacity of producing the haemopoietic factor is reduced aggravating anemia.
(7) The stomach is small causing a need for frequent, small feeds.
(8) Poor sucking and swallowing since the reflexes do not develop properly until the 34th week of gestation.
(9) The final problem is regurgitation of feed.

Low birth weight infants have higher needs for almost all nutrients as well as energy compared to full-term infants with subsequent implications on the composition of the feed.

Let us now examine desirable goals to be aimed for in the nutrition of the low birth weight infant in relation to its genetic potential for growth, development and body composition.

Energy

The evaluation of the energy requirement of the growing orally fed low birth weight infant is based on the energy balance equation:

Energy intake = energy stored + energy expended + energy excreted

The difinitions are as follows:

(1) Energy intake is the energy provided by food.
(2) Energy stored is the energy laid down as protein and fat and other components in newly formed tissue.
(3) Energy expended comprises (a) resting energy expenditure or resting metabolic rate, (b) intermittent activity, (c) thermoregulation, (d) synthesis of new tissues.
(4) Energy is excreted mainly via the feces and only to a small extent in the urine.
(5) Energy cost of growth includes energy utilised for synthesis of new tissues and the energy stored in those tissues.
(6) Energy for maintenance is defined as the minimal energy expenditure within a thermoneutral environment, when no growth occurs.

The estimation of energy stored by orally fed low birth weight infants is based on the assumption (1) that adequate growth should imitate intrauterine growth quantitatively and (2) that for the same weight gain, quality of this gain is identical both in utero and in extrauterine life. However, weight gain composition in the two situations is quite different, with more fat and less water being deposited during extrauterine life.

Since thermoregulation is an important part of neonatal intensive care special attention should be paid to heat loss due to radiation and convection. Occasionally also evaporation may become important, for example if an infant is ventilated without adequate humidity. Energy excretion occurs due to nitrogen and fat losses, the major factor being the well-known fat malabsorption of the low birth weight infant.

Guidelines regarding the energy intake may be summarized as follows:

(1) Under normal circumstances an intake of 130 kcal/kg b.w./day (with a range of 110 to 150 kcal/kg b.w./day) meets the energy requirements of the low birth weight infant.
(2) This mean energy intake may be provided by supplemented breast milk or by a formula with a caloric density of about 70 kcal/100 ml in a volume of 150–200 ml/kg b.w./day.
(3) If a higher density is required a concentration of 85 kcal/100 ml should not be exceeded.

Main Nutrients

Protein

Most of the studies done so far focused on the quantity and quality of ingested proteins and on rates of weight gain in order to define optimal protein requirements for premature and low birth weight infants. From the point of view of growth protein gain plays the central role over the whole range from molecular biology to clinicians 'everyday's concern.

Protein requirements of premature infants have therefore been the center of considerable interest for a long time. Since the first experimental work in this field by Gordon in 1947, four decades have passed. Despite the voluminous literature available the most appropriate goal for protein supply in low birth weight infants is still not definitively known.

But nowadays the protein requirement is probably better understood than requirements for most other nutrients. The precise definition of protein requirements is of considerable interest:

(1) Excessive protein intake is poorly tolerated by small preterm infants and may have late adverse effects, e.g. late metabolic acidosis.
(2) Protein deficiency leads to slowed growth. Chronic severe deficiency will cause irreversible neurologic damage.

The recommendations given so far do not differentiate between (a) so-called apparently healthy low birth weight infants appropriate for gestational age, (b) sick, non-growing low or very low birth weight infants, and (c) small for gestational infants.

Using new techniques Micheli and Schutz have approached this question in a new way taking into consideration the different characteristics of postnatal growth and protein metabolism in healthy or sick infants.

Their studies result in estimates for protein requirements as follows:

(1) When the *average "healthy" premature* with a birth weight less than 1.5 kg is fed with about 3.5 g protein/kg b.w./day and aboutt 120 kcal/kg b.w./day weight gain and long term statural growth will be close to optimality.
(2) *Critically ill prematures* need a different approach to cover their protein requirements. A pragmatic approach based more on speculation than on experimental data states that 0.5 - 1.5 g protein/kg b.w./day would be a defensible estimate. An intake of this order may be expected to maintain the infant at zero protein gain as long as it is severely ill.
(3) Since *small for gestational age infants* are more mature in a number of physiological and biochemical systems they may be able to tolerate higher protein intakes without adverse effects.
(4) For the *infant born after 30 weeks of gestation with a birth weight of 1.5 kg or more,* who experiences minimal difficulties in adjusting to extrauterine life, 2.9 to 3.5 g protein/kg b.w./day are recommended according to ESPGAN, 1987.

It should, however, be kept in mind that gain in weight per se does not provide any information on its composition. To assess the composition of weight gain more sophisticated methods are needed, e.g. metabolic balance studies and indirect calorimetry.

The question arises whether simple methods are available for the determination of protein needs of low birth weight infants. To monitor the adequacy of protein intake Senterre had developed a simple scheme by measuring the blood urea nitrogen level, which reflects urinary excretion of nitrogen quite well. This scheme also considers the energy intake in conjunction with protein intake. There are, of course, also more specific indicators of protein intake's adequacy available, e.g. concentrations of albumin, total protein, prealbumin, retinol binding protein and amino acid pattern in serum which, however, are sometimes difficult to assess.

Another point of view which has to be taken into consideration and which clearly needs further investigation is the quality of protein. The amino acid profile of human milk with a whey protein: casein ratio of 60:40 seems to be most suitable. Higher proportions of casein cannot be handled with the same efficiency as evidenced by metabolic acidosis and higher tyrosine and phenylalanine levels.

Taurine has to be considered as an essential amino acid for the premature infant. It has been shown that human milk contains ten times more taurine than cow's milk. During lactation taurine is the second most abundant free amino acid in human milk. The concentration remains constant during the different stages of lactation. Taurine is normally synthesized from methionine via cystathionine and cysteine as metabolites. The conversion from cysteine to taurine is regulated by cysteine-sulfinic acid decarboxylase. It has been shown, however, that in the premature infant the activity of this enzyme is not yet fully developed. Therefore a certain amount of taurine must be supplied with the feed.

Fat

Fats are vital for normal growth and development because they provide fatty acids necessary for brain development, are an integral part of all cell membranes, and are the sole vehicle for fat soluble vitamins and hormones in milk. Furthermore these energy rich lipids can be stored in the body in large amounts contrary to the limited storage capacity for carbohydrates and proteins.

The fetal requirement for fatty acids is supplied mainly as free fatty acids from the maternal circulation. After birth, fat is supplied directly in the form of triglycerides from human milk or formula. Mature human milk and formulas have a fat content of about 3.5 to 4.5% corresponding to a supply of 40 to 50% of the energy intake as fat.

The studies done so far comparing the absorption of different fats in low birth weight infants have shown that the medium and long-chaln triglycerides are equally well absorbed. This might be related to the appearance of lingual and gastric lipases before 26 weeks of gestation and their high activity levels at birth. There is, however, only limited knowledge available of the enzymes and cofactors active in the lipid clearing process following absorption.

The final step in the catabolism of long-chain fatty acids depends on the presence of carnitine since this compound is an essential cofactor for their β-oxidation at the mitochondrial level. In addition experimental findings suggest that carnitine could favour protein synthesis and be involved in the metabolism of branched chain amino acids. Recent studies show that the newborn including the low birth weight infant has a critical need for carnitine. Adequate amounts of carnitine are supplied by human milk as well as by cow's milk based formulas. However, total parenteral nutrition and most soy based formulas do not contain this compound. Additional studies are needed to clarify whether it is useful to supplement TPN, soy-based and semi-elemental formulas with carnitine.

Medium chain triglycerides (MCT) provide a readily available source of energy that can be absorbed rapidly. Digestion and absorption of MCT are not dependent on duodenal intraluminal bile salt levels. Furthermore they enhance calcium absorption and improve nitrogen retention. For these reasons MCTs are frequently used in the nutrition of low birth weight infants.

The increasing survival of very low birth weight infants (birth weight below 1.5 kg) has recently led to the study of the developmental accretion of long-chain polyenoic fatty acids during the last trimester of fetal development through the early weeks of life. It could be shown that these fatty acids accumulate rapidly in the fetal brain and that they are essential for brain development. Recent evidence suggests that low birth weight infants might depend on external sources for the supply of long chain polyenoic fatty acids.

Carbohydrate

During the first days of life low birth weight infants have relatively low intestinal mucosal lactase activity, resulting in lactose malabsorption. The undigested lactose underlies bacterial fermentation in the lower intestine causing intestinal distension by its osmotic effect.

However, glucosidases hydrolizing glucose polymers are active even in the small premature infant. Carbohydrates can therefore be provided as a mixture of lactose and glucose polymers. In addition the oligosaccharides have the advantage that they do not contribute to the osmolarity of the feed.

Composition of Weight Gain

As has already been mentioned there is an agreement that the growth rate of a premature should be similar to the intrauterine one, namely about 15 g/kg b.w./day.

However, the weight gain composition of a healthy fetus in utero in the last trimester of pregnancy differs considerably from a preterm infant. A preterm infant growing to an extrauterine pattern stores about two times as much fat as his fetal counterpart (about 800 g versus 400 g of fat). Whether or not this might have any consequence later in life is completely unknown. Quality of gain in weight has therefore become a central issue in neonatal nutrition. However, only in the recent past various studies with prematures have been performed the results of which permit some conclusions with regard to weight gain composition and its quality. It turned out that mainly energy and protein intake play a key role in the quality of weight gain: A higher protein intake is correlated with increased protein accretion and higher energy expenditure which in turn decrease the amount of energy available for storage. The high fat accretion seen in premature infants might therefore be the expression of an inadapted nutrient intake.

Minerals

Sodium and Potassium

Due to the immature renal concentration capacity, low birth weight infants excrete high amounts of sodium during the first two weeks of life. In prematures fed on human milk or on adapted infant formulas which usually have a low sodium content hyponatremia has often been observed. For premature formulas a comparatively high sodium content is therefore proposed in order to meet the higher needs. The potassium requirement of low birth weight infants is estimated to be similar to that of term infants.

Calcium and Phosphorus

Probably the most controversial recommendations concern the calcium and phosphorus intake of low birth weight infants. The recommendations are based on a factorial approach taking into account the fetal urinary and dermal losses as well as the accretion rate in utero.

It is for sure that the low calcium and phosphorus content of human milk and so-called ''adapted'' infant formulas does not meet the requirements of low birth weight infants for these two minerals. However, neonatologists in the European countries do not favour the high calcium content of formulas used in the United States for various reasons:

(1) High calcium intakes may interfere with fat absorption.
(2) The rate of calcium absorption varies from one infant to the other whereas phosphorus is always well absorbed leading to the risk of a phosphorus overload.
(3) The ratio of calcium to phosphorus has to be taken into consideration: (a) High levels of calcium in a formula require an increase of the phosphorus content, (b) Contrarywise, the lower the calcium content of the feed the lower the calcium: phosphorus ratio should be.

Because of the lack of evidence that high calcium concentrations are beneficial, formulas for low birth weight infants manufactured in Europe do not contain more than 140 mg calcium/100 kcal.

Trace Elements

The knowledge on trace element requirements of premature infants is very limited. Mainly the content of human milk is considered as reference. Most of the experimental work done so far was carried out on zinc, copper and manganese.

Zinc

Negative zinc balances have been observed in the first weeks of life of premature infants, however, no clinical signs of zinc deficiency. Even when human milk is fed a postnatal decline in serum zinc and negative zinc balances occur. There is some evidence of limited intestinal absorption capacity of zinc as well as of highly correlated absorption with fat and nitrogen.

Copper

Copper balances are also negative in the first weeks, becoming only positive at about 5 weeks. Since a deficiency can occur with low oral intake a supplementation of copper is recommended.

Iron

The low birth weight infant has much smaller iron stores than the full term infant and is therefore very susceptible to the development of anemia. However, iron supplementation failed to prevent from early physiologic anemia due to the interference with vitamin E metabolism. The premature infant requires iron supplementation once it reaches about 2 kg in weight or is discharged from hospital.

Vitamins

Vitamins are essential in small amounts for specific metabolic functions. Since they cannot be synthesized in the body, since their accretion in fetal tissues is going on during the whole of pregnancy and since blood concentrations and possibly body stores are lower at birth in preterm than in term infants the supplementation of vitamins is recommended. If breast milk is fed it should be supplemented with a multivitamin preparation whereas preterm formulas are fortified with all vitamins.

The exact requirements of premature infants for the various vitamins are still not known. In the recent past three vitamins have received particular attention in premature nutrition: Riboflavin (Vitamin B2), Cholecalciferol (Vitamin D) and α-Tocopherol (Vitamin E).

Vitamin B2

Few studies have explored the importance of riboflavin deficiency in premature infants. Infants receiving human milk during the first two weeks become biochemically riboflavin-deficient, partly through photodegradation of riboflavin during the banking and delivery of human milk. However, such biochemical deficiency in preterm infants is of unknown significance. It seems prudent to supplement them with vitamin B2 (300 ug/kg b.w./day).

Vitamin D

In recent years, several studies have focused on the interaction between mineral homeostasis and vitamin D metabolism in prematures in whom during the first days of life a transient decrease of serum calcium frequently occurs. Whether this represents the adaptation to extrauterine life or the expression of mineral homeostasis imbalance as a consequence of the interruption of calcium and phosphorus transfer across the placenta, has yet to be established.

Hypocalcemia occurs during the first days of life in about 75% of preterm infants being practically the rule with a birth weight below 2000 g. It is usually of short duration and may not express itself clinically. The hypocalcemic episode cannot be explained on the basis of a defective vitamin D activation or functional hypoparathyroidism. However, the pathogenesis of hypomineralization of bones is most often multifactorial, insufficient intake of calcium and phosphorus and/or poor calcium absorption in case of vitamin D deficiency being the main causes.

The requirements of vitamin D can briefly be summarized as follows:

(1) Preterm infants with a poor vitamin D status a birth have a daily requirement of 1.200 - 1.500 IU.
(2) To prevent phosphorus deficiency in breastfed preterms human milk should be supplemented with phosphorus (0.6 ml of a molar solution of neutral potassium phosphate).
(3) Human milk should also be supplemented with calcium resulting in a calcium : phosphorus ratio not higher than 2 : 1.
(4) Feeding preterm formulas providing an intake of 100 to 140 mg calcium/kg b.w./day and a calcium : phosphorus ratio not higher than 2 : 1 leads in most cases to satisfactory mineralization of the skeletonprovided the vitamin D supply is sufficient.
(5) There is no evidence for routine use of vitamin D metabolites in preterm infants.

Vitamin E

Vitamin E supplementation for premature infants has for many years been a matter of considerable controversy. There is only an almost general agreement that correction of the low plasma vitamin E levels up to adult levels prevents hemolytic anemia of prematurity.

Four diseases of the premature infant have to be discussed in the context of vitamin E supplementation: (a) Anemia of prematurity, (b) Retinopathy, (c) Bronchopulmonary dysplasia, and (d) Intraventricular and periventricular hemorrhage.

There is, however, still controversy whether the pharmacological doses (20 – 100 mg/kg b.w./day) recommended to prevent those disorders are really beneficial. Only very recent studies have shown that 25 mg of vitamin E acetate administered i.m. an days 1 and 3 seem to yield plasma consentrations of vitamin E which could be protective for the premature and at the same time avoid side effects.

Feeding Regimens

As has been highlighted in the introduction of this presentation the uncertainties about ''adequacy'' of low birth weight infant nutrition lead to a multiplicity of feeding regimens in neonatal intensive care units - or would it be better to say a multiplicity of ''dogmas''?

If one is, however, looking for the types of feeds used for the oral nutrition of low birth weight infants their number reduces considerably. The types of feeds can be characterized as follows:

(1) Human milk: (a) milk of the infant's own mother; (b) pooled human milk; and (c) human milk with supplements.
(2) Adapted infant formulas.
(3) So-called ''Premature formulas''.

Increased knowledge and experience in the recent past have shown that human milk varies considerably mainly with regard to the energy content. Furthermore it does not cover the higher needs of prematures for protein and some minerals.

The too low content of energy and some nutrients can be overcome by supplementing the milk of the infant's own mother with easily digestable carbohydrate (glucose polymers) as a source of energy and with the deficient nutrients, mainly with protein, sodium, calcium and phosphorus. The vitamins B2, D and E have already been discussed and are recommended for supplementation too.

The main compositional criteria of adapted infant formulas are closely related to mature human milk. These formulas are mainly suitable for feeding the infant once it has reached a weight of about 2.5 kg and the mother is unable to breastfeed the baby herself.

However, since a fairly good understanding of the metabolic and nutritional needs of normal, stable low birth weight infants under controlled environmental conditions has been gained this knowledge could be made available to the development of so-called premature formulas. Even if the mutual balance and interactions of the major nutrients still present problems the scientific work done over the last decade has given a reasonable understanding to set up guidelines for the feeding of low birth weight infants. There have been numerous revues of the nutritional needs of low birth weight infants, however, only two national bodies have issued guidelines, namely the American Academy of Pediatrics in 1977 and 1985 and the Canadian Pediatric Society in 1981. The guidelines of the European Society of Pediatric

Gastroenterology and Nutrition (so-called ESPGAN) on "Nutrition and Feeding of Preterm Infants" have only recently been published and are the most comprehensive ones available at the time being.

Two members of the European Committee, Prof. Salle (Lyon/France) and Prof. Senterre (Liege/Belgium) have conducted a clinical trial with a premature formula which corresponded to the guidelines of the ESPGAN. The results of this study have clearly shown that gain in weight as the most important parameter of growth, furthermore intake of water, energy and main nutrients were within the limits expected by theoretical considerations. The trial also confirmed that guidelines are really needed and that they are a considerable help to define the term "adequate nutrition".

Does diet in Preterm Infants Influence the Clinical Outcome?

Since prematurity is an unphysiological state no normal standards are available which could be used to assess the short term responses to died observed postnatally in terms of outcome. This is specially true for the marked differences described in biochemical effects of died.

Interim data from a follow-up study at the time being conducted in Cambridge/U.K. confirm that clinical outcome cannot be predicted from findings in the neonatal period. However, the preliminary results of a long term observation suggest that the diet of preterm and low birth weight infants may have long term effects in development, growth and other outcome responses. If those findings are confirmed they will add weight to the view that it does indeed matter how premature babies are fed in terms of their future quality of life.

Summary

In summary the following can be stated:

(1) The comparable large number of premature and low birth weight infants leads in many countries to a public health problem.

(2) Prematurity is an unphysiological state which causes some peculiarities in digestive and metabolic functions which in turn have implications on nutrition.

(3) Under normal circumstances an intake of about 115–130 kcal/kg b.w./day meets the energy requirements.

(4) For the so-called healthy low birth weight infant with a birth weight of 1.5 kg or more 2.9 to g protein/kg b.w./day seem to be adequate. Small for gestational age infants tolerate higher, severely ill low or very low birth weight infants only much smaller amounts or protein.

(5) Quality of gain in weight has become a central issue in neonatal nutrition. Data available so far indicate the key role of energy and protein intake.

(6) Due to the high requirements for growth the premature and low birth weight infant has greater needs for almost all other nutrients compared to term infants.

(7) If human milk is fed - whether from the infant's own mother or pooled - it should at least be supplemented with protein, calcium, phosphorus and sodium as otherwise the high requirements could not be covered.

(8) The scientific work done over the last decade has made available so-called premature formulas.

(9) Only a very few bodies have issued guidelines on the nutrition of low birth weight infants, the most comprehensive one which has just been published by the ESPGAN.

(10) Clinical trials with a premature formula which was formulated according to those quidelines confirmed the theoretical considerations of ESPGAN.

(11) Final goals for nutrition of premature and low birth weight infants remain to be clarified by future scientific work. There is, however, considerable evidence that the diet fed to premature or low birth weight infants influences their future quality of life.

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