Growth and Post Discharge Nutrition of Preterm Infants

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Summary

A high proportion of preterm infants, especially VLBW, are growth retarded at hospital discharge. This deficit remains high into infancy and childhood. Several randomised studies have shown that growth deficit, particularly in boys, is greater in preterm infants fed standard term formula than in_those fed nutrient-enriched diets (preterm formula or post discharge formula). This is not surprising since standard formula is designed to meet the needs of the term infant. After hospital discharge, preterm infants fed unfortified human milk versus nutrient-enriched formulas have slower growth rates and lower bone mass during infancy. These findings suggest that the post-discharge period may be a critical time for influencing the important phase of catch-up growth that is characterised by an increase in the speed of growth in order to reach normal growth trajectory levels. Further studies and more in-depth studies are needed to establish whether differences persist or have long-term consequences, and to clarify which formulas are most suitable to fill the needs of the former preterm infants during the first years of life.

Introduction

Over the past two decades the clinical management of preterm infants has improved considerably, and survival rates have increased, especially for very low birth weight (VLBW, birth weight <1,500g) and extremely low birth weight (ELBW, birth weight <1,000 g) newborns (1-8).

The greater survival of VLBW newborns has led to new problems involving nutritional aspects, morbidity, and growth restriction, both during hospitalisation and after discharge.

Table 1

	Body weight, g					
	500–700	700–900	900–1,200	1,200–1,500	1,500–1,800	1,800–2,200
Fetal weight gain, g/day	13	16	20	24	26	29
g/kg/day	21	20	19	18	16	14
Protein, g						
Inevitable loss	1.0	1.0	1.0	1.0	1.0	1.0
Growth (accretion)	2.5	2.5	2.5	2.4	2.2	2.0
Required intake						
Parenteral	3.5	3.5	3.5	3.4	3.2	3.0
Enteral	4.0	4.0	4.0	3.9	3.6	3.4
Energy, kcal						
Loss	60	60	65	70	70	70
Resting expenditure	45	45	50	50	50	50
Miscellaneous expenditure	15	15	15	20	20	20
Growth (accretion)	29	32	36	38	39	41
Required intake						
Parenteral	89	92	101	108	109	111
Enteral	105	108	119	127	128	131
Protein/energy, g/100kcal						
Parenteral	3.9	4.1	3.5	3.1	2.9	2.7
Enteral	3.8	3.7	3.4	3.1	2.8	2.6

Modified from Ziegler, Thureen, Carlson: Clin Perinatol 2002;29:225.

Over the last few years, it has become quite clear that one of the most important aspects involved in the care of VLBW newborns is the adequate intake of the nutrients that are needed to fulfill the complex nutritional requirements of these patients.

The American Academy of Pediatrics (AAP) recommendations state that preterm infants must be ensured the nutrition that will provide them with the qualitative and quantitative growth similar to that of a fetus of the same postmenstrual age, and that will maintain normal concentrations of blood and tissue nutrients (9).

Ziegler et al (10) calculated the nutrient intake that is needed at various gestational ages to achieve the same weight gain as the fetus (Table 1).

However, it is actually quite difficult to reach the objectives recommended by the AAP due to a number of reasons, including ; the difficulty in assuring the appropriate protein and energy requirements as of birth, the need to avoid the morbidity that is associated with prematurity, and the use of the most suitable formulas to meet the needs of the various categories of VLBW infants.

Several studies have examined the postnatal growth of preterm infants and have demonstrated that a high proportion of preterm infants, especially VLBW, are growth retarded at hospital discharge. The percentage of ELBW infants who are below the 10^{th} percentile for weight, length and head circumference at discharge is close to 80% (11).

This deficit remains high into infancy and childhood (12,13,14).

Lemons et al (2) reported that growth failure, defined as weight less than the 10th percentile at 36 weeks post-menstrual age, was present in 97% of all preterm infants whose birth weight was <1,500 g, and in 99% of infants whose birth weight was <1,000g.

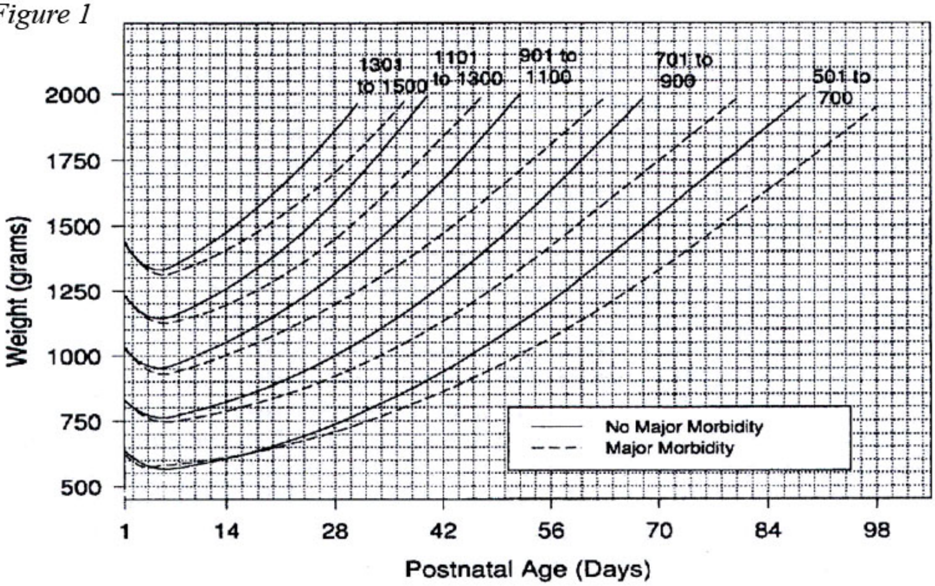
The reasons for delayed growth at the time of hospital discharge are mainly due to the anatomical and functional immaturity of low birth weight (LBW) infants and to their pathological conditions. In fact, the greater the morbidity, the higher the degree of postnatal growth delay at hospital discharge.

Fig 1 shows the growth curves of infants with greater or lesser morbidity. VLBW newborns with lower weight and greater morbidity require more time for their catch-up growth (an increased velocity of growth observed after a temporary arrest of growth) (15).

The greater need for intensive and subintensive care in VLBW and especially in ELBW infants involves a longer period of catch-up growth, and, as a consequence, a greater growth deficit. This problem is also related to the reduced intake of nutrients as compared to the nutritional and growth needs of the child. In fact, after birth, feeding should begin with small amounts of milk, which must then be gradually increased in order to minimise the risks of feeding-related complications and to avoid intolerance to nutrients or metabolic instability. Moreover, feeding is often discontinued due to the worsening clinical situation or because of the need to perform invasive procedures.

A study by Embleton et al (16) quantified the nutritional deficit in hospitalised preterm infants whose birth weight was 1,750 g or less, and who were

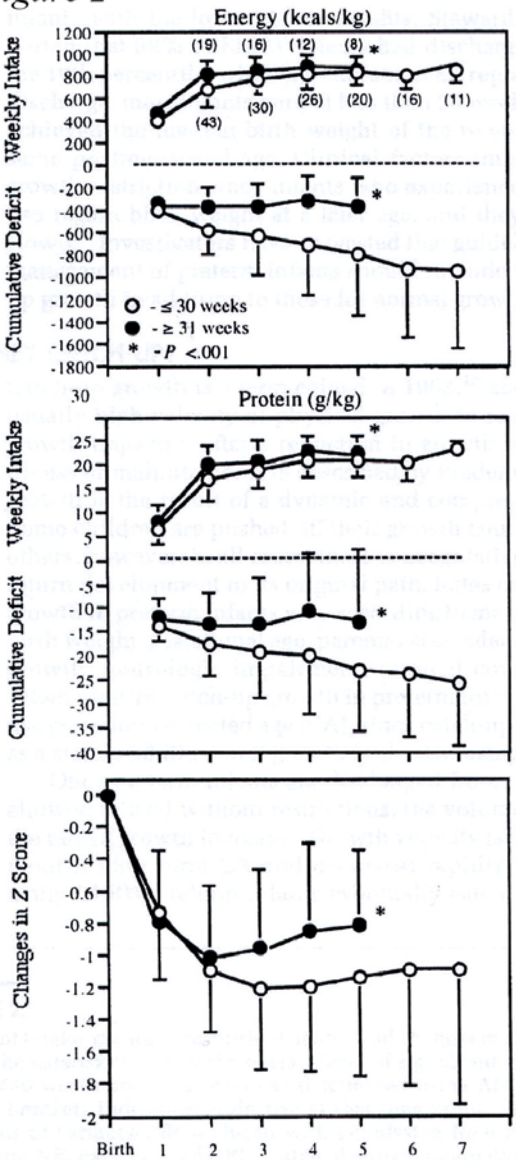
Figure 1



Ehrenkranz RA et al: Pediatrics 104:280-289,1999.

fed according to a standard protocol (Fig. 2). The cumulative energy deficit in infants whose gestational age (GA) was 30 weeks or less was 406 Kcal/Kg ± 92 Kcal and 813 Kcal/Kg ± 542 Kcal by the end of the first and fifth weeks of life, respectively. Protein deficits at these ages were 14 ± 3 g/Kg and 23 ± 12 g/Kg, respectively. Infants whose GA was 31 weeks or more also had high, though less significant, deficits (Fig 2).

Figure 2



Embleton NE, et al .Pediatrics 107:270-273,2001

Energy and protein deficits at discharge are inevitable in preterm infants. In fact, the lower the birth weight of the newborn, the greater the degree of deficit (17).

Such deficits inevitably increase in infants who are fed term formula or unsupplemented breast milk after discharge. In addition, a specific nutrient deficiency in preterm infants involves a mineral deficiency that may have an impact on growth (18,19) since most body stores of minerals are accumulated during the last trimester of pregnancy.

During the first weeks after birth, it is difficult to ensure that newborns receive adequate dietary and mineral intake. In particular, calcium and phosphorus are especially important in the smallest and in the sickest low birth weight infants in order to minimise bone demineralisation and negative balance at the time of hospital discharge (20,21) since these conditions have been found to limit both linear growth and catch-up growth.

Children with biochemical evidence of metabolic bone disease during the neonatal period were significantly shorter at follow-up. (22)

Several studies carried out in the post-discharge period have shown that former preterm newborns have low bone mineral content, with the lowest values being found in infants who had received unsupplemented human milk (21,23,24).

At discharge, other minerals were found to be in negative balance in preterm infants. Ehrenkranz (25) quantified the total body content of zinc, copper and iron at discharge in apparently healthy, low birth weight infants. The mineral content they predicted was lower than what was expected in utero at 36 weeks' gestation, and mineral levels proved to be lower in newborns who had been fed preterm formula rather than fortified human milk.

Nutritional Options After Discharge

An important issue concerns whether the long term consequences of postnatal growth retardation in preterm infants can be improved by post-discharge nutritional intervention. At discharge, LBW infants have peculiar nutritional requirements since the majority are of 34-35 weeks of gestational age, weigh between 1,800-2,000 g and, as highlighted before, have delayed growth. After discharge from hospital, preterm newborns are fed without restrictions and, generally speaking, an increase in both milk intake and in growth are observed. In the first months after term correct age (CA), a more important phase of catch-up growth takes place that is characterised by an increase in the speed of growth in order to reach normal growth trajectory levels. Most catch-up growth is observed in the first 2 to 3 years of life and, in some cases, may continue until adolescence.

The velocity of postnatal catch-up growth in LBW infants depends on many factors including birth weight, gestational age, intrauterine growth, type of neonatal pathology, clinical course, constitutional characteristics of the child's parents, and nutritional intake.

Carver et al demonstrated (26-29) that preterm infants with accelerated catch-up growth have better outcomes.

The amount and quality of nutrition is one of the most important factors. In the past, following discharge from hospital, preterm infants were fed with either human milk (HM) or with term infant formula (TF). Both these types of feeding are formulated to assure the nutritional needs of the term infant rather than of preterm infants. Thus, this resulted in preterm infants being underfed during the first 6-12 months of life.

Over the last few years, the number of available options have increased in an effort to provide preterm infants with more suitable nutritional intake during hospitalisation and after discharge. This is done by delaying the switch from enriched formulas to TF.

Currently, four dietary options are available and they include; HM, TF, preterm formula (PTF), and nutrient-enriched, post-discharge formula (PDF) (Table 2). Preterm infants are discharged with one of these nutritional options. In Italy, most preterm infants receive PTF or breast milk or a combination of the two at discharge. Infants who are given PTF continue receiving this formula until their weight reaches 3,500 g.

Term Formula Versus Preterm Formula

PTF provides higher levels of nutrients as compared to TF. The main differences between PTF and TF formulas concern energy content (approximately 80 Kcal/100ml versus 67 Kcal/100ml) and protein content (2.4 g/100ml versus 1.4 g/100ml).

Other characteristics regard the addition of greater amounts of calcium, phosphorus, zinc, trace elements, and vitamins to PTF formula.

Most of the studies comparing PTF and TF administration after discharge were published in the 1990s. All the randomised trials reported that infants who were fed with PTF had increased catch-up growth.

Chan et al (30,31) performed two randomised trials on healthy preterm infants who were fed TF, or special post-discharge formula, or PTF from the time of hospital discharge until 8 weeks of age. The energy supplied by each

Table 2 Composition of milk used for preterm infants after discharge (per 100 ml)

	Mature human milk	Preterm infant formula	Term Formula	Post-discharge formulas *
Energy (Kcal)	68-70	80	67	75
Proteins (g)	1.1-1.3	2.4	1.4	2
Carbohydrates (g)	67-70	7.7	7.3	7.4
Lipids (g)		4.4	3.6	4.1
Calcium (mg)	35	100	51	69
Phosphorus (mg)	15	53	29	36
Sodium (mg)	15	41	17	26
Zinc (mg)	0.3	0.7	0.49	0.71
Iron (mg)	0.076	0.9	0.7	1.2
Copper (µg)	39	80	44	62
Vitamin D (µg)	0.01	2.4	1.2	1.6
LCPUFA	+	+	+	+

* *Aptamil PDF*

of the three formulas was 20 Kcal/oz, while the protein content differed among the three. At 8 weeks of age, the anthropometric parameters were similar for all feeding groups.

Wheeler and Hall (32) fed preterm infants either TF or PTF containing a protein intake of 1.8 g/liter for 8 weeks after discharge. Both formulas contained 20 Kcal/oz. No differences were observed between the two groups with regards to weight, while the infants who were fed PTF had greater mean length and head circumference.

The largest study comparing the growth of infants fed with TF versus PTF formulas was carried out by Cooke et al (33). At hospital discharge, preterm infants (<1,750 g birth weight) were randomly assigned to be fed either a preterm formula (80 Kcal/100ml) or a term formula (68 Kcal/100ml) until 6 months' CA.

A third group of infants was fed with PTF until term, and then TF till 6 months.

Infants who were fed PTF took lower volumes of milk (180 ml/Kg) and had similar energy intake but they received greater protein intake (around 4 g Kg/day), as well as greater amounts of calcium and phosphorus than the other groups. Male infants who were fed PTF after discharge were significantly heavier and longer and had greater head circumference by 6 months' CA than those who were fed TF, with the greatest growth rates being observed between discharge and term CA.

At 18 months' CA, males fed PTF continued to be heavier (on average 1 kg), longer (on average 1 cm) and had larger head circumference (on average 1 cm) than male infants fed TF(34).

At 12 months' CA, males fed PTF also had the greatest lean body mass, fat mass and bone mineral mass as measured by dual x-ray absorptiometry (DXA).

Body composition measurements demonstrated that the increase in weight consisted_predominantly of lean body mass rather than fat mass.

Neurodevelopmental evaluation was carried out at 18 months' CA using the Bayley scales of infant development, and showed no differences among the 3 groups.

Agosti et al (35) published the results of the Italian GAMMA study regarding 121 randomised newborns whose birth weight was <1,500 g. Infants were divided into two groups, one (group A) was fed with PTF (80 Kcal/100 ml), the other one (group B) was fed with TF (70 Kcal/100 ml) from 40 weeks ' to 55 weeks' CA.

At one year of age, both weight and head circumference were greater in infants fed with PTF, and the difference was only significant at 55 weeks' and at 6 months' CA in male infants. The small for gestational age (SGA) newborns had a greater increase in length at one year of age, while head circumference growth caught up from week 40 to week 55. Evaluation by the Griffiths' Developmental scale at 6 and at 9 months showed that males who had been fed PTF had better scores.

Post-Discharge Formula Versus Term Formula

The amounts of nutrients that are provided by PDF range between the amounts provided by TF and PTF.

The energy provided by PDF is approximately 75 Kcal/100ml. The main difference between PDF and TF formulas concerns the protein content (1.9 g/100ml versus 1.4 g/100ml). Other differences regard the higher amounts of calcium, phosphorus, zinc, trace elements and vitamins that are found in PDF as compared to TF.

One of the first scientific studies was published by Lucas et al in 1992 (36,37), and it involved 31 preterm infants with birth weight <1,800 g and gestational age < 34 weeks, who were recruited randomly prior to discharge.

Fifteen newborns were fed with TF and 16 with PDF from the time of hospital discharge to 9 months' CA. At 9 months' CA, PDF-fed infants were heavier and longer than TF-fed infants. PDF-fed infants showed progressive catch-up towards the 50° percentile for weight and length, while the TF group remained closer to the 10° percentile. At 3 and 9 months' CA, bone mineral content was higher in the infants who had been fed with PDF.

Afterwards, the same investigators conducted a larger, randomised trial (38) regarding 229 preterm infants with a mean birth weight of approximately 1,389 g and a mean gestational age of 30.9 weeks. Between discharge and 9 months' CA, 113 infants were fed with PDF and 116 with TF.

A reference group of 65 infants were breast-fed for at least 6 weeks after term CA. At 9 months' CA, PDF infants were significantly heavier and longer than TF infants and the difference in length persisted till 18 months' CA. The growth differences appeared greater in boys, who had a length advantage of 1.5 cm.

The mean weight of PDF-fed infants was still below the 50° centile. At 9 months' CA, breast-fed infants had lower growth rates than PDF-fed infants. No differences were detected between the treatment groups with regards to head circumference or developmental outcome at 9 and 18 months' CA.

The study by Carver et al. (39) involved preterm infants whose birth weight was 1,800 g or less, stratified according to birth weight (<1,250, >1,250 g), and randomised to be fed either PDF or TF between discharge and 12 months' CA. At 3 months' CA, infants who had been fed PDF were significantly heavier than those fed with TF. The PDF-fed infants whose birth-weight was below 1,250 g had greater head circumference at term and at 3, 6 and 12 months' CA. Males showed a greater increase in catch-up growth than females. Energy intake was similar in the two groups but protein intake was higher in preterm infants who were fed with PDF. Moreover, this latter group had lower milk intake.

De Curtis et al (40) randomised a group of preterm infants (<31 weeks' gestational age, birth weight < 1,750 g), including 16 who were fed PDF and 17 who were fed TF from hospital discharge (37 weeks' CA) till two months' CA. Energy and protein intakes were greater in PDF-fed infants, but there were no differences in milk intake. Anthropometric variables were evaluated longitudinally, and body composition using DXA was assessed twice, i.e., prior to discharge and at 2 months' CA. No differences where detected in growth or body composition between the two groups.

The Cochrane Neonatal Review Group method was used by Henderson et al (41) to review the evidence from randomised, controlled trials which had shown that, as compared to standard TF, feeding infants with calorie and protein-enriched formulas following hospital discharge improves the growth and development of preterm or low birth weight infants. They found six trials that were eligible for inclusion, and thus reviewed a total of 424 infants.

The analysis of data showed that several aspects of the studies differed, including the energy and protein contents of nutrient-enriched formulas, which varied from 72-80 Kcal/100ml and 1.8-2.2 g/100 ml ; the duration of nutritional intervention, that went from term to 12 months' CA ; cohort sizes, which ranged from 20 to 229 infants; the presence or absence of stratification for degree of immaturity and gender.

The first evaluation concerned the amount of growth during the trial period.

The results obtained by De Curtis(40) et al. highlighted that growth velocity changes rapidly from term to 2 months' CA, but that there are no significant differences between groups.

Meta-analysis of data from two trials (34,38) revealed a statistically significant effect on crown-heel length at 18 months' CA (weighted mean difference 9.7 millimeters), but not on weight or head circumference. Meta-analysis of data from the trials that assessed neurodevelopment at 18 months' CA revealed no statistically significant differences in either Bayley Mental Development Index or in the Psychomotor Development Index.

These authors concluded that the limited, available data do not provide strong evidence to claim that feeding preterm or low birth weight infants with calorie and protein enriched formula following hospital discharge affects growth rates or development up to 18 months' CA.

Recently, Koo and Hockman (42) published a randomised, double blind study on the_nutritional effects that were observed in two groups of preterm infants, 45 of whom were fed TF and 44 who received PDF after discharge. Birth weights of the infants ranged_from 630 to 1,620 g (median 1,250 g) and gestational ages went from 24 to 34 weeks (median 29 wks). The infants were discharged at day 43.2, and the two formulas were administered until 1 year after discharge. Weight, length, and head circumference were measured at enrollment into the study, and at 2, 4, 6, 9, and 12 months after discharge. Total body bone mass as bone mineral content (BMC) and fat and lean mass were measured by DXA at enrollment and at 2, 4, 6, and 12 months after discharge.

The authors concluded that the use of nutrient enriched formula for preterm infants after hospital discharge shows no advantages over TF with regards to growth, bone mineralisation, or body composition. Neither gender nor race had independent effects on bone, fat or lean mass. More studies are needed to determine the optimal post-discharge nutrition support for preterm infants.

More recently, Litmanovitz et al. (43) carried out a longitudinal pilot study comparing the effects of PDF to those of TF on very low birth weight infants in the first six months post term. Two matched groups of VLBW infants were randomly assigned to either PDF (n° 10) or TF (n° 10) at 40 weeks' CA. Anthropometric parameters of growth, and measurements of bone speed of sound (SOS), indicating bone strength and bone turnover markers were evaluated at term and at three and six months' CA. The anthropometric parameters of infants fed PDF and TF were comparable at 3 and 6 months' CA. No statistically significant differences were found between the two groups regarding growth and bone SOS measurements. Thus, the authors concluded that PDF feeding after term CA in VLBW infants had no short-term beneficial effects on growth, on bone strength, or on bone turnover..

Post-Discharge Breast Feeding

Mature human milk is designed to meet the needs of the term infant and not those of the preterm infant. During hospitalisation, preterm infants who are fed human milk usually have slower growth rates and lower degrees of bone mineralisation than formula fed infants (21,44). Recommendations state that human milk should be fortified with additional nutrients (10). The main limit to the use of human milk fortifiers is the dynamic variation in the composition of human milk, whose quantity and quality vary from person to person and throughout the duration of breast milk feeding.

The use of human milk fortifiers is usually discontinued at the time of hospital discharge. There are few data regarding the adequacy of human milk in feeding VLBW infants post-discharge from hospital. The available data however, do indicate that the preterm infants fed unfortified human milk versus nutrient-enriched formulas have slower growth rates and lower bone mass during infancy (30,38, 45-49). Wauben et al. (50), examined body composition after hospital discharge and found that infants who had been fed human milk had lower bone mineral content and increased fat accretion as compared to those who had been fed enriched-nutrient formula.

On the basis of these findings, Hall et al. (51), suggested that post- discharge calcium, phosphorus and vitamin D supplementation may be necessary in up to 50% of breast-fed infants whose birth weight is below 1,880 g.

The differences in body composition with regards to the kind of feeding that is provided support the idea that " we are what we eat". Not only do insufficient energy and protein intake lead to less growth, but they also result in less lean mass and more fat mass. If mineral intake is inadequate, not only will infants show poorer growth, but anomalies in bone mineral accretion and metabolism will also be observed.

Early under-nutrition of infants may have negative consequences on growth and on neurological development. The early growth deficit in VLBW newborns is part of the complex concept of " programming",which implies that stimulation during the critical phase of development may have long-term biological effects. The consequences of nutritional programming may be of the endocrinological, metabolic, or cardiovascular type. Recent data have shown that low birth weight and quick catch-up may lead to disorders in the adult age, such as cardiovascular disease and non insulin depent diabetes mellitus (52).

Concluding Remarks

Some comments and some questions have arisen based on the results of studies dedicated to the nutrition of preterm infants after discharge.

The first issue regards the methodological differences among several studies and the consequent difficulty in obtaining comparable results.

Meta-analysis of the data taken from the most significant trials reached different conclusions as compared to those stated by the authors. With regards to post discharge administration of nutrient-enriched formula versus standard formula in preterm infants, most studies showed greater, though not statistically significant, growth. Not only do the effects on growth vary depending on the type of formula, but they also depend on the type of parameters that are evaluated and the time of evaluation. The anthropometric variables of growth that are usually evaluated, i.e., weight, length, and head circumference, have varying trends, which are not always comparable among studies.

Neurodevelopmental outcomes also improve with nutrient-enriched formula, but the long term effects are still unclear.There is currently no evidence that calorie and protein-enriched formula milk increases head growth or improves neurodevelopmental outcomes, when assessed at 18 months' CA.

Another aspect concerns the composition of the formula with respect to the characteristics of the newborn. The energy, protein and mineral content of the nutrient enriched formulas used in the studies varies, as does the typology of the newborns. Of course, the characteristics of preterm VLBW differ from those of ELBW, and nutritional needs vary depending on the differences between intra and extra uterine conditions in preterm infants.

Another issue that emerges from the studies concerns the different results that are obtained with respect to the length of time the formula is administered. Nutrient-enriched formula must be administered for at least 6 months in order to ensure a beneficial effect.

The most spontaneous questions that arise from these issues are the following;

Which formulas are most suitable to fill the needs of the former preterm infants during the first year of life?

How long should this formula be administered?

What are the effects of nutrition on the first phase of life beyond 18 months (which is the maximum term used in the trials)?

There are no easy answers to these questions. Further research and more in-depth, easily comparable studies are needed, not only on enriched formulas, but also on the complementary feeding that is administered after 4 month' CA, but that none of the studies that were analysed took into consideration.

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