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Randomized control trials

Infant formula composition affects energetic efficiency for growth: The BeMIM study, a randomized controlled trial☆

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SUMMARY

Background & aims: Protein source, macronutrient composition and content of long chain-polyunsaturated fatty acids (LC-PUFA) of infant formulae may influence infant growth. We aimed to assess the effect of a modified infant formula on growth.
Methods: In a randomized, double-blind trial, 213 healthy term infants consumed isoenergetic study formulae (intervention formula – IF, control formula – CF) from the first month of life until the age of 120 days. IF (1.89 g protein/100 kcal) contained α-lactalbumin (ALAB) and LC-PUFA, while CF (2.30 g protein/100 kcal) provided standard whey and no LC-PUFA. Anthropometry and dietary intake were regularly assessed. A venous blood sample was obtained on day 120.
Results: Both formulae were well-accepted without significant differences in health related observations. Weight gain was not statistically different between formula groups (IF: 30.2 ± 6.3 vs. CF: 28.3 ± 6.5 g/day, mean ± SD, $P = 0.06$). Length gain was higher in IF (0.11 ± 0.02 vs. 0.10 ± 0.02 cm/day, $P = 0.02$). Energy intake from formula was higher in CF at 90 and 120 days (IF: 509 ± 117 and 528 ± 123 vs. CF: 569 ± 152 and 617 ± 169 kcal/day, $P < 0.01$). Protein intake in CF was significantly higher at each assessment. Growth per energy intake was higher in IF compared to CF for weight (6.45 ± 2.01 vs. 5.67 ± 2.21 g/100 kcal, $P = 0.02$) and length (0.23 ± 0.08 vs. 0.20 ± 0.08 mm/100 kcal, $P = 0.04$).
Conclusions: The modified infant formula with reduced protein content with added ALAB and LC-PUFA, meets infant requirements of protein for adequate growth. The increased energetic efficiency of the new infant formula might result from improved protein composition by added ALAB. Apparently minor differences in composition can markedly affect energetic efficiency for growth.
The study was registered at ClinicalTrials.gov (NCT01094080).

1. Introduction

Infants should be fully breastfed for 6 months whenever feasible.[1] Infants benefit from breastfeeding not only via immediate protection against gastrointestinal and respiratory infections,[2] but also via a lower risk of obesity and diabetes in adult life.[3,4] If full breastfeeding is not possible, safe and suitable infant formulae should be fed.[5]

During the last decades, infant formulae have been improved for example by the inclusion of long chain-polyunsaturated fatty acids (LC-PUFA)[6] and adaptation of content and source of protein.[7,8] Protein intake of infants is lower with breast milk than with standard infant formulae[9] because of a generally higher formula protein content considering the lower nutritive value of cow's milk casein and whey compared to human milk proteins.[10] Differences in the amino acid (AA) composition may require higher amounts of cow's milk protein to ensure adequate supply of essential AA,[10] which puts additional burden on the renal system because of the higher nitrogen intake.[11] According to the "early protein hypothesis"[3] high protein intake causes rapid early growth, which has been associated with an increased risk of obesity and associated disorders in

Abbreviations: AA, amino acids; BeMIM, Belgrade–Munich Infant Milk Trial; BF, breastfed; CF, control formula; FF, formula fed; IF, intervention formula; ITT, intention to treat; LC-PUFA, long chain-polyunsaturated fatty acids; PP, per-protocol; Trp, tryptophan.

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later life.[12,13] Thus, lower protein intake in infancy seems beneficial for long term health.

Davis et al. 2008 investigated the use of an infant formula with α-lactalbumin (ALAB).[14] ALAB, the predominant whey fraction in human milk, is the main source of tryptophan (Trp) of breastfed infants and enables the reduction of protein content in infant formulae, while ensuring sufficient supply of Trp and all other essential AA.[15,16] The composition of milk consumed by infants affects the energy efficiency for growth: Butte et al. 1990 compared the energy efficiency of infants at the ages of 1 and 4 months and found that breastfed infants had an 11% higher weight gain per 100 kcal (energetic efficiency) than formula fed infants.[17]

The inclusion of LC-PUFA into formula aimed to optimize the neuronal development as LC-PUFA are quantitatively and qualitatively important components of nervous tissue and provided by human milk.[18] The LC-PUFAs, arachidonic acid and docosahexaenoic acid, may enhance visual acuity and mental as well as psychomotor development.[19] Moreover, there might be interactions with growth as arachidonic acid has been related to growth and LC-PUFA derived prostaglandin may influence adipocyte differentiation.[20,21]

Since the modification of protein source, macronutrient composition and content of LC-PUFA of infant formulae may influence infant growth and development, modified formula must be tested to ensure they support adequate growth.[22] In present study we compared growth and blood biochemistry of infants fed a modified infant formula with reduced protein content and rich in ALAB as well as added LC-PUFA to a formula with standard protein content and without LC-PUFA, and a reference group of breastfed infants. The randomized controlled trial aimed to assess the suitability of a reduced-protein, ALAB and LC-PUFA containing formula focusing on growth velocities, adverse events, markers of fatty acids and protein status and energetic efficiency in infants until the age of 120 days.

2. Subjects and methods

2.1. Power calculation and randomization

Based on previous findings a weight gain between birth and age 4 months of life of 30 g per day with a standard deviation of 6 g was assumed for sample size estimation.[23–26] The non-inferiority study assumed a power of 85% and 2.5% risk of α-error to detect a difference of 0.5 standard deviations (one-sided test) as statistically significant required studying 70 infants per formula group. Assuming a total loss to follow-up rate of up to 30% 100 infants were enrolled into each formula arm.

Double blinded randomized allocation of infants to the study formulae was stratified for gender and a block size of four was applied. A random allocation sequence was generated by the study sponsor. The blinded allocation was concealed for participants, support staff and investigators until all laboratory and data analyses had been performed.

2.2. Ethical considerations

The study was approved by the Clinical Center Serbia Ethical Committee. Written informed consent was obtained from all parents prior to study start after the experimental protocol had been explained to them in detail.

The study was registered at ClinicalTrials.gov (NCT01094080).

2.3. Study design

The BeMIM study (Belgrade–Munich Infant Milk Trial), a randomized, double-blind, controlled study with parallel design, was performed with two formula groups (intervention formula – IF and control formula – CF) and a reference group of breastfed infants (BF). Infants were recruited until the age of 28 days. Children of mothers, who could not breastfeed their healthy newborn babies for reasons not related to this study, or who decided – in spite of all benefits of breast milk – to start full formula-feeding within the first 28 days of life, were randomized double blinded into one of the two formula groups. Formula infants (FF) were fully formula fed until the age of 120 days. A reference group of breastfed infants was recruited with intended duration of breastfeeding for at least 4 months. During the first 28 days (Baseline) and at 30, 60, 90 and 120 days of life infants were examined and anthropometric measures were taken. During three days before each study examination parents recorded the volume of consumed formula and completed questionnaires on formula acceptance, consistency and color of stool, occurrence of colic, flatulence, regurgitation, and vomiting.

Weight was determined with a Seca 336 scale (Seca, Hamburg, Germany) equipped with a measuring rod (Seca 232) for measuring recumbent length, and head circumference was measured with a tape (Seca 212). All measurements were performed in duplicate and documented with an accuracy of 10 g for weight and 0.1 cm for length and head circumference, respectively. The equipment was regularly checked and calibrated to ensure accuracy of measurements. These checks were done with a calibrated weight of 5 kg every 4 weeks. There was never an aberration of more than 10 g. Therefore, the scales were never reset.

2.4. Study population

From Jan 2010 to May 2011, 505 infants were enrolled verbally at the maternity ward and with flyers providing study information and contact data of the principal investigator at the Institute for Gynecology and Obstetrics of the Clinical Center of Serbia in Belgrade, Serbia. Eligible infants had to be born apparently healthy from singleton pregnancies after 37–41 weeks of gestation, with a birth weight between the 3rd and 97th weight-for-age percentile according to the EURO-Growth charts.[27] Infants with malformations, congenital heart defects, congenital vascular diseases, severe diseases of gastrointestinal tract, kidney, liver, central nervous system, or metabolic disease were excluded from study participation.

2.5. Study diets

Study formulae were provided free of charge to families by HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany) in 600 g cartoons and labeled by random numbers. The products were packed in identical white boxes and labeled with the same product name. IF complied with the EU-directive of 2006[28] and CF with the corresponding 1999 EU-directive.[29] The formulas had identical whey/casein ratios of 60/40 and energy contents of 67 kcal/100 mL, but differed in protein, fat and carbohydrate content (Table 1). IF had a protein content of 1.89 g/100 kcal and a fat content of 5.3 g/100 kcal,

Table 1
Composition of study formulae and human milk.

	Infant formula		Human milk[a]
	Intervention	Control	
Whey:casein ratio	60:40	60:40	60:40
Energy (kcal/100 mL)	67	67	67 ± 7.6
Protein (g/100 kcal)	1.89	2.2	–
Protein (g/100 mL)	1.3	1.5	1.2 ± 0.2
Lipids (g/100 mL)	3.6	3.3	3.6 ± 0.7
Carbohydrates (g/100 mL)	7.5	7.8	7.4 ± 0.2

[a] Nommsen et al. 1991, Food and Nutrition Board 2001.[52,53]

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