Infant Formulas: A Long Story

Fórmulas infantis: uma longa estória

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Abstract

The ideal feeding for infants is the breast milk because it has a balanced nutritional composition, which includes all essential nutrients, in addition to many bioactive factors that contribute to the growth and development of the child, as well as to the maturation of the gastrointestinal tract. Among them are immunological factors, antimicrobials and anti-inflammatory components, digestive enzymes, various types of hormones, and growth factors. If human milk is not available, there is an indication of infant formulas that should follow the recommendations of the Codex Alimentarius of the Food and Agriculture Organization/World Health Organization (WHO). In a century of history, infant formulas have gone from a simple combination of cow milk (evaporated or condensed) and water to highly sophisticated products, elaborated by very refined technological processes to produce lactose-free, antiregurgitation, based on soy protein, hydrolyzed protein in various grades, and only amino acids formulas. The major milestones in the modification of infant formulas were the incorporation of nutrients/ingredients such as: iron, nucleotides, alpha lactalbumin, long-chain polyunsaturated fatty acids, prebiotics, probiotics, postbiotics, oligosaccharides similar to human milk, lactoferrin, and milk fat globule membrane. Many of these ingredients have shown benefits on the immunological system. Despite the technological advances, breast milk remains irreplaceable, being the gold standard for infant feeding.

Keywords

- breast feeding
- breast-milk substitutes
- bottle feeding
- infant formula
- infant

Resumo

A alimentação ideal do lactente é o leite materno, por possuir uma composição nutricional equilibrada que inclui todos os nutrientes essenciais, além de muitos fatores bioativos que contribuem para o crescimento e o desenvolvimento da criança, assim como para o amadurecimento de seu trato gastrintestinal. Entre eles, destacam-se fatores imunológicos, antimicrobianos, anti-inflamatórios, enzimas digestivas, vários tipos de hormônios e fatores de crescimento. Ante a impossibilidade do uso do leite humano, existe a indicação de fórmulas infantis que devem seguir as recomendações do Codex Alimentarius da Food and Agriculture Organization/Organização Mundial da Saúde (OMS). Em um século de história, as fórmulas infantis passaram de uma simples combinação de leite de vaca (evaporado ou condensado) e água para produtos

Palavras-chave

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- substitutos do leite humano
- alimentação artificial
- fórmulas infantis
- lactente

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altamente sofisticados, elaborados por processos tecnológicos bastante refinados, surgindo as fórmulas isentas de lactose, antirregurgitação, à base da proteína da soja, com proteína hidrolisada em vários graus e somente de aminoácidos. Os grandes marcos na modificação das fórmulas infantis foram as incorporações de nutrientes/ingredientes tais como: ferro, nucleotídeos, alfa lactoalbumina, ácidos graxos polinsaturados de cadeia longa, prebióticos, probióticos, pósbióticos, oligossacarídeos similares ao leite humano, lactoferrina e membrana do glóbulo de gordura. Muitos destes ingredientes têm mostrado benefícios do ponto de vista imunológico. Apesar dos avanços tecnológicos, o leite materno continua insubstituível, sendo o padrão ouro para a alimentação de lactentes.

Introduction

Knowledge of child nutrition is fundamental in the training of health professionals, as it enables them to deal with frequent situations in the clinical practice. Knowing and understanding these processes, from food acceptance to the use of different nutrients, is a situation of great relevance in the care of the child.

The adequacy of the diet to the needs of the child ensures their nutrition, a process to which all other vital functions are subordinated. Nutrition is one of the main determinants of the health and wellbeing of the human being and assumes special importance in early life.

Subordinates such as the incorporation of nutrients to the body, growth and development, and fundamental characteristics of the child are, consequently, highly dependent on the satisfaction of nutritional needs.

Human milk is considered the ideal food for the newborn and infant. It is known that milk produced by healthy mothers is sufficient to meet all nutritional needs during the 1st 6 months of life, exclusively and up to $\geq$ 2 years old together with complementary feeding.[1]

Human milk has a balanced nutritional composition, which includes all essential nutrients, in addition to many conditionally essential and $\sim$ 45 different types of bioactive factors; many of these factors contribute to the growth and development of the infant, as well as to the maturation of the gastrointestinal tract. Among them, stand out antimicrobial factors, anti-inflammatory agents, digestive enzymes, various types of hormones, and growth factors.[2]

The numerous benefits of breastfeeding for the infant organism include hygienic, immunological, psychosocial, and cognitive aspects, as well as those related to the prevention of future diseases. The economic advantages of breast milk due to its lower cost and contraceptive effect, as well as the benefits of breastfeeding on the organism of the mother, should also be considered. Human milk is undoubtedly the great example of immune nutrition, drastically decreasing infectious diseases, mainly gastrointestinal and respiratory diseases.[2]

Unfortunately, a good portion of infants, for various reasons, do not receive breast milk, and, therefore, the pediatrician has the task of prescribing the best alternative in this situation. In the absence or in the impossibility of feeding the infant with breast milk, there is the indication of infant formulas.

Brief History of Infant Milk Feeding

Feeding infants who do not receive human milk has been a problem for centuries. Wet nurses have already been used (a method that is currently not allowed), and cow and other mammalian animals milk, plus starch and sucrose, with high morbidity for infants due to inadequate preparation techniques and to their composition (high protein content, low bioavailability of iron, excess saturated fatty acids, and high caloric density).[3]

After comparations between the composition of cow and human milks, several efforts were made to make cow milk more similar to human milk, from the point of view of the composition of macronutrients (proteins, carbohydrates, and lipids).[4]

Thus, around 1920, commercial formulas began to be produced; however, these formulas were homemade preparations, using whole cow milk (evaporated or condensed), corn syrup, and water.[3]

These mixtures presented the same problems as fresh cow milk, that is, very high protein content, inadequate lipid profile, with excess saturated fatty acids and very little supply of essential fatty acids and extremely low in vitamins, especially vitamin C, besides presenting a high load of renal solutes, which can lead to hypertonic dehydration and kidney injury.[4]

From 1950 on, safer and easier preparation infant formulas have been designed, with important changes in their composition:[4]

1. Lower protein content and change in the ratio between whey protein and casein;
2. Better lipid profile, with gradual decrease in the content of saturated fatty acids of animal origin and added mixtures of vegetable oils;
3. Addition of lactose and other carbohydrates (maltodextrin);
4. Adjustments in micronutrient content.

A few years later, acidified formulas emerged, which were obtained by adding lactic or citric acids to partially

Table 1 Nutritional characteristics and indications of infant formula

Formula	Kcal/mL	Protein source	Carbohydrate source	Fat source	Fiber source	Indications
Formula based on cow or goat milk	0.6–0.7	Whey protein Casein	Lactose Maltodextrin	Vegetable oils Milk fat Fish oil	FOS GOS	Indicated as routine feeding for children when breast milk is unavailable or insufficient
Soy-based formula	0.6–0.7	Isolated soy protein with methionine	Maltodextrin	Vegetable oils Fish oil	—	Indicated for children with cow milk allergy older than 6 months, lactose intolerance, galactosemia, glycogenosis type I
Lactose-free formula	0.6–0.7	Serum protein Casein	Maltodextrin	Vegetable oils Fish oil	–	Indicated for children with lactose intolerance, galactosemia, glycogenosis type I
Antiregurgitation formula	0.6–0.7	Serum protein Casein	Lactose Maltodextrin Corn starch Rice starch Carob gum	Vegetable oils Milk fat Fish oil	—	Suitable for children with GER
Hydrolyzed formula	0.6–0.8	Hydrolyzed casein Hydrolyzed whey protein	Lactose Maltodextrin Starch	Vegetable oils Fish oil Medium chain triglycerides	—	Indicated for children with cow milk soy allergy (with or without diarrhea), and with malabsorption, such as short bowel syndrome, cystic fibrosis or liver disease
Amino acid formula	0.6–0.8	Free amino acids	Maltodextrin Starch	Vegetable oils Fish oil Medium chain triglycerides	—	Indicated for children who continue with symptoms with the use of extensively hydrolyzed formulas; children with severe malabsorption
Hypercaloric formula	1.0	Serum protein Casein	Lactose Maltodextrin	Vegetable oils Milk fat Fish oil	FOS GOS	Indicated for newborns and infants with increased caloric needs or requiring fluid restriction. Can be used in children with difficulty/ maintaining weight gain.

Abreviatório: FOS, hidro-oligocitemias; GOS, galacticocentricidade.

decremated cow milk. This process improved the digestibility of cow milk and started the growth of enteropathogenic microorganisms due to their acidic pH.[4]

Meanwhile, finding an acceptable alternative to breast milk has proven to be a complicated quest that continues today.

Current View of Infant Formulas: Definition, Classification, and Indications

In the absence of human milk, infant formulas are the appropriate substitutes for infant nutrition. However, these formulas do not reproduce the composition of human milk for several reasons:

1. Human milk contains hormones, growth factors (growth hormone and insulin-like growth factor 1 [IGF-1]), antibodies, enzymes (lysozymes) and living maternal cells (neutrophils, macrophages, T and B lymphocytes), prostaglandins, complement system fractions, and granulocyte colony stimulating factors, which are virtually impossible to be added to infant formulas;[5]
2. Human milk presents the bifidum factor (whey proteins and kappa fractions of casein, short chain fatty acids, and lactose) that stimulates the growth of bifidobacteria, which are microorganisms present in the protective intestinal microbiota;[5]
3. Formulas are mostly developed from cow milk and although the proportion of whey/casein proteins (60:40) of current formulas is similar to mature breast milk, these proteins, of animal origin, are distinct from human milk, besides having a different composition of amino acids;[5]
4. The bioavailability of various nutrients, mainly micronutrients, of infant formulas is lower than that of human milk;
5. Human milk is consumed practically after its synthesis, while the formulas require heat treatment to ensure longer shelf life, with consequent structural change.

Despite the issues described, infant formulas are constantly improved when new information, nutrients, ingredients, and technologies become available.

There are three basic indications of infant formulas:

1. As a substitute for human milk when it is contraindicated (human immunodeficiency virus disease, some inborn errors of metabolism, maternal chemotherapy, use of illicit drugs);
2. As a supplement for breastfed infants whose intake of breast milk does not meet their needs;
3. As a substitute for human milk when the mother does not produce milk or chooses not to breastfeed.

Infant formulas are dairy products modified to obtain a nutritional composition similar to that of human breast milk, defined as a powder or liquid product intended for the feeding of infants (0 to 36 months old), by prescription, in total or partial replacement of human milk, to meet the nutritional needs of this age group. These formulations must follow the nutritional specifications described in the current legislation and they must also meet the Codex Alimentarius standards of the Food and Agriculture Organization/World Health Organization (WHO), be nutritionally adequate and safe, acceptable in taste and odor, and be readily available for acquisition.[6,7]

The formula model is always human milk. For this model to be at least partially achieved, it is necessary to reduce the protein content and to suit the ratio of serum/casein proteins (in breast milk, it is 60:40, and in cow milk, it is 20:80). In addition, there should be a reduction in the content of fats (saturated), addition of vegetable fats (unsaturated), and of essential fatty acids (linoleic and linolenic acids), as well as lactose to make the intestinal pH more acidic, thus improving the absorption of calcium, iron, minerals, trace elements, and vitamins.[8]

Infant formulas should also contain a caloric density between 67 and 70 Kcal/100 ml, so that, with the usual intake of 150 to 200 ml/Kg/d (100 to 135 Kcal/kg/d), there is adequate weight gain (20 to 30 g/d). In general, they have a higher concentrations of nutrients when compared with those of human milk, in order to compensate the lower bioavailability.[9]

Classification of Infant Formulas (►Table 1)

Infant formulas are classified as:[1]

- Complete polymeric (intact macronutrients, especially protein)
- Natural proteins (not used)
- Purified casein-based proteins and/or whey proteins (cow or goat milk)
- Nondairy proteins – soy and rice
- Complete oligomeric
- Partially hydrolyzed
- Extensively hydrolyzed
- Amino acids

The complete formulas are those that provide adequate daily amounts of all nutrients and can be used exclusively. In polymeric formulas, macronutrients, especially protein, are intact. Oligomeric formulas are chemically constituted and composed of predigested nutrients, with partially hydrolyzed proteins, widely hydrolyzed (oligopeptides) or fully hydrolyzed (amino acids).

Start and Follow-up Formula

Start infant formula is the product, in liquid or powder form, used by prescription, especially manufactured to meet, by itself, the nutritional needs of healthy infants during the 1st 6 months of life (5 months and 29 days old). For this, they present a nutritional composition similar to that of human milk, with a caloric density between 0.67 and 0.70 Kcal/ml; osmolality $\sim$ 300mOsm/Kg; amount of protein from 1.2 to 1.4 g/100 ml; serum/casein protein ratio of 60:40 or 70:30; addition of vegetable fat (for the supply of essential fatty acids) and of long-chain polyunsaturated fatty acids of the ω-6 and ω-3 series (docosahexaenoic and arachidonic acids);

addition of lactose (acidifies the intestinal environment improving calcium absorption), minerals, trace elements, vitamins, and nutrients considered conditionally essential such as taurine and carnitine. Some formulas contain partially hydrolyzed proteins in their composition.[9]

Follow-up infant formula is the product, in liquid or powder form, used when indicated, for healthy infants from the 6 month of life up to 12 incomplete months of age (11 months and 29 days), and for healthy children in the early childhood (12 months to 3 years of age), constituting the main net element of a progressively diversified diet. They have protein content similar to that of the start formulas, but higher amounts of iron. Some follow-up formulas contain partially hydrolyzed proteins in their composition.[9]

Infant formulas (start and follow-up) based on goat milk have recently appeared as another safe and appropriate alternative to feeding newborns, infants, and early childhood children who cannot receive breast milk, either partially or exclusively. Goat milk is known to be naturally easier to digest because its protein profile provides the formation of a smoother curdle in the stomach, conferring better digestibility.[10]

Soy-based Formulas

Soy-based formulas (isolated and purified soy protein) are lactose-free and should also be free of sucrose, and maltodextrin is the predominant carbohydrate. Fats are derived from vegetable oils and polyunsaturated long-chain fatty acids of the ω-6 and ω-3 series (docosahexaenoic and arachidonic) should preferably be added, as well as methionine to improve the biological quality of protein.[11]

The American Academy of Pediatrics, through its Nutrition Committee, recommends the use of formulas based on the isolated and purified soy protein in the following situations: galactosemia, lactase deficiency and allergy to IgE-mediated cow milk protein. This same committee does not recommend the use of these formulas in children <6 months old.[11]

Lactose-free Formulas

Lactose intolerance is caused by a lactase deficiency, which can be congenital or acquired. Secondary or transient deficiency is the most common type of lactase deficiency and originates from lesions suffered by brush cells of the intestinal mucosa that lose the ability to produce the enzyme. This deficiency, most often a temporary condition, can occur after an intestinal infection by bacteria, viruses, protozoa and/or fungi.[12]

When there is clinical suspicion of a lactase deficiency, the first step is the exclusion of lactose from the diet. This is of great important in infants, whose main food source is milk. This clinical condition also implies the suspension of human milk, which may be transient or definitive, and the introduction of a lactose-free infant formula or of a formula based on soy protein, since these formulas are also lactose-free.[13]

Currently, there are lactose-free formulations, which have been developed with the objective of meeting the nutritional and diet therapeutic demands of newborns and infants with lactose intolerance. Usually, the predominant carbohydrate is maltodextrin, which has high caloric density, with little effect on osmolality, which reduces complications such as diarrhea, malabsorption, and necrotizing enterocolitis. Protein is whey and casein, and fats are composed of vegetable oils. Basically, lactose-free formulas have the same composition as infant formulas based on cow milk. Long-chain polyunsaturated fatty acids of the ω-6 and ω-3 series (docosahexaenoic and arachidonic) should also preferably be added.[12,13]

Antiregurgitation Formulas

Gastroesophageal reflux (GER), which manifests in the form of regurgitation, is common in newborns. It can be considered physiological during the neonatal period, and it is estimated that it occurs in about half of the children from birth to 2 months of life.[14]

Among the several factors that contribute to the high incidence of GER and regurgitation among infants are immaturity of the lower esophageal sphincter, small size of the stomach, short esophagus, and peristaltic dysfunction. However, as the function of the sphincter, as well as the anatomy and function of the esophagus, mature with age, these causes of regurgitation tend to be resolved as the child develops.[14]

Gastroesophageal reflux may also be secondary to some pathological conditions such as cow milk allergy and some specific abnormalities of gastrointestinal motility, when it is then called GER disease.[15]

There are efficient and economical treatments to reduce the symptoms of GER and at the same time ensure that the child receives the amount of nutrients necessary for its growth and development. Since 1996, the European Society of Gastroenterology, Hepatology and Pediatric Nutrition (ESPGHAN) has had standards for the management of the condition, including reassurance of parents and dietary management through thickened formulas.[16]

In general, antiregurgitation formulas have a composition similar to that of standard infant formulas, following the regulation of the Codex Alimentarius. The main difference is in the source of carbohydrates. Usually, the carbohydrate found in these formulas, in addition to lactose and maltodextrin, is pregelatinized rice or corn starch, which thickens in contact with the acidic pH of the stomach, preventing regurgitation, or carob gum, which is naturally already a thickener. Polyunsaturated long-chain fatty acids of the ω-6 and ω-3 series should also be added.[16]

Hydrolyzed Formulas

Hydrolyzed formulas have the protein subjected to a hydrolysis process, resulting in oligopeptides and amino acids, which are small molecules that trigger less immune response. Therefore, they were developed for children unable to digest the intact protein from milk (cow or goat) or who are allergic to it. They should contain a mixture of 40 to 50% peptides $< 1{,}500$ daltons and 40 to 50% of free amino acids.[17]

In the clinical practice, hydrolyzed formulas are usually used in cases of cow milk or soy protein allergy, and in cases of malabsorption, either by gastrointestinal or hepatobiliary disease, such as cystic fibrosis, short bowel syndrome, bile duct atresia, cholestasis, chronic or persistent diarrhea.[18]

They have a protein content ranging from 0.20 to 0.25g/ml and the protein source can be serum protein, casein or rice, always widely hydrolyzed.[17]

In general, they are free of lactose and sucrose and the carbohydrate source is a mixture of maltodextrin and modified complex starches.

Lipids are a mixture of vegetable oils and medium chain triglycerides, at $\sim$ 40%, in order to facilitate absorption. Polyunsaturated long-chain fatty acids of the ω-6 and ω-3 series should also be added.[18]

Amino Acid Formulas

Amino acid formulas are those that have in their protein composition 100% free amino acids.[16] They generally have the same characteristics as hydrolyzed formulas regarding other nutrients, and have specific clinical indications, such as severe cases of intestinal dysfunction or of food allergies.[17]

Regarding cow milk protein allergy, amino acid formulas are indicated for children in whom treatment with extensively hydrolyzed formulas has not been successful, because the more extensive hydrolysis determines lower antigenicity.[19]

Incorporation of New Nutrients/Ingredients into Infant Formulas

In the advancement of developments in human milk research and food engineering technology, several nutrients/ingredients have been incorporated into infant formulae: nucleotides, iron, α-lactalbumin, long-chain polyunsaturated fatty acids, prebiotics, oligosaccharides similar to human milk, probiotics (not allowed in Brazil), postbiotics (not yet presented in Brazilian formulas), lactoferrin (not yet presented in Brazilian formulas), and cow milk fat globule membrane.

Nucleotides

Human milk has a higher concentration of nucleotides (from 30 to > 70 mg/L), which are believed to be important for the growth and maturation of the gastrointestinal tract and in the development of neonatal immune function, besides iron absorption and carbohydrate, lipid, protein and nucleic acid metabolism (because nucleotides are the structural units of nucleic acids, RNA and DNA, and are essential compounds in the energy transfer systems).[20]

Nucleotides were first identified in human milk in 1960 and represent between 2 and 5% of the nonprotein nitrogen in human milk. Synthesized de novo by the body utilizing amino acid precursors or salvaged from degraded nucleic acids, nucleotides can be considered essential nutrients in certain conditions in which the needs of the body are greater than the amounts of nucleotides synthesized or salvaged, such as rapid growth, limited nutrient intake or disturbed endogenous synthesis and certain diseases.[21]

Nucleotides have numerous biological effects, most of which have been demonstrated in experimental animal models. It has been shown that the intestinal tissues of animals fed nucleotide-supplemented diets have more mucosal protein and DNA, higher villus height and disaccharidase activities, and better recovery after intestinal injury than those of animals fed nucleotide-free diets, and studies in infants indicate that dietary nucleotides may protect against diarrheal disease.[21,22]

Regarding the immune system, several studies in infants indicate an effect of dietary nucleotides as higher serum concentrations of *Hemophilus influenzae* type b and diphtheria antibodies after immunization, greater natural killer cell activity, and higher concentrations of immunoglobulin G antibody to β-lactoglobulin.[23]

Iron

Iron is an essential nutrient that is critically important for normal growth and development, particularly of the brain. Iron deficiency and iron-deficiency anemia are the most common nutritional deficiencies worldwide. They affect every age group but are a particular concern in infants and young children, since they undergo rapid growth and development.[24]

The American Academy of Pediatrics (AAP) Committee on Nutrition stated more than a quarter century ago that "the early use of fortified formula results in augmentation of iron stores which help prevent later development of iron deficiency".[25] The strategy to improve iron stores during the 1st year was a response to the high rates of iron deficiency before the 1970s, when the rate of cow milk consumption during the 1st year and the concordant rate of iron deficiency were unacceptably high. Since then, the formulas have been fortified with iron at levels that vary considerably globally due to the wide range of iron levels offered by expert recommendations and by regulatory agencies.

Knowledge about the factors that influence iron status during the 1st year of life as well as the benefits and risks of iron supplementation during the 1st year of life evolved over time, motivating an "Iron Expert Panel" to make recommendations for the appropriate level of iron in formulas designed for infants from 0 to 12 months old.[26]

The panel members proposed the following recommendations for iron fortification intended for healthy term infants, based on their expert opinion and available evidence: for healthy full-term infants from birth to 3 months old, iron stores accumulated during gestation are sufficient to support the requirements of the infant, and there is no need to provide iron in any form, including iron-fortified infant formula; some healthy full-term infants deplete their endogenous iron stores and become iron deficient as early as at 4 months old, and formulas based on cow or goat milk protein or protein hydrolysates designed for infants from 3 up to 6 months old should contain between 2 and 4 mg/L of iron, and formulas based on soy protein should contain between 3 and 6 mg/L of iron. Since the iron stores present at birth inevitably become depleted after between 5 and 6 months of age, the panel recommends that formulas (based on cow or goat milk protein or on hydrolysate protein) designed for infants from 6 up to 12 months of age contain between 4 and 8 mg/L of iron, and that formulas based on soy protein should contain between 6 and 12 mg/L of iron (L).[26]

α-Lactalbumin

Originally, infant formulas were based on unmodified cow milk protein and, therefore, had a protein profile comprising 80% casein and 20% whey proteins.[27] During all the years that infant formulas have been available, much research has been devoted to improving especially protein quality, resulting in formulas with a protein profile closer to that of human milk that have a high proportion of whey proteins, with the whey and casein protein fractions constituting ~ 60 and 40% of the total, respectively, until the 100th day, when the ratio of whey to casein declines to ~ 50:50.[28]

In 1961, the first whey-dominant infant formula was developed and, since then, the proportion of α-lactalbumin has increased in products over time. The method of producing whey-dominant formulae lowered the renal solute load and protein concentration delivered to the infant.[29]

α-Lactalbumin has an amino acid composition that is high in essential amino acids and comparatively rich in tryptophan, lysine, cysteine, and the branched-chain amino acids leucine, isoleucine, and valine that may lead to improvements in intestinal health, immune responses, and growth, as well as to increased absorption of essential trace elements like iron and zinc. Therefore, this increase in the proportion of α-lactalbumin in infant formulae while reducing total protein content is beneficial.[30]

Human milk proteins, along with the peptides released during digestion, exert physiological effects on gastrointestinal function, including motility (glutamate and quinolinic acid, produced by tryptophan degradation, influence intestinal motility and immune competence) and antimicrobial activity (peptide fractions have been shown to resist digestion and exert their antibacterial activity in the colon; some seem to stimulate the phagocytic activity of macrophages; others have prebiotic activity by stimulating the growth of bifidobacteria). Thus, since α-lactalbumin stimulates the growth of beneficial microorganisms, which reduce pH in the intestinal tract, it may enhance mineral absorption.[28]

Long-chain Polyunsaturated Fatty Acids

The n-6 and n-3 series of long-chain polyunsaturated fatty acids (LCPUFAs) have an important role during gestation, lactation, and infancy since they are constituents of cell membrane phospholipids and precursors of eicosanoids. Besides, they are considered essential for the maturation of the developing brain, the retina and other organs.[31]

Long-chain polyunsaturated fatty acids are biosynthesized from essential fatty acids linoleic acid (LA) and linolenic acid (LNA) by successive desaturation and elongation steps in the intestine, the liver, and the brain.[31]

Originally, infant formulas were not supplemented with LCPUFAs; they contained only LA and LNA. Over the past few years, some manufacturers, due to the recommendations of some international organizations such as the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Nutrition Committee, have added LCPUFAs to infant formulae.[32]

Recent reviews that aimed to assess whether supplementation of milk formula with LCPUFAs is both safe and beneficial for full-term infants, while focusing on effects on visual function, neurodevelopment, and physical growth, concluded that most of the included randomized controlled trials reported no beneficial effects of LCPUFAs supplementation on neurodevelopmental outcomes of formula-fed full-term infants and no consistent beneficial effects on visual acuity.[32,33]

Regarding preterm newborns, the conclusions of the most recent reviews were similar, although the overall quality of evidence was considered low. The authors concluded that infants enrolled in the trials were relatively mature and healthy preterm infants, and the assessment schedule, methodology, dose, and source of supplementation and fatty acid composition of the control formula varied between trials.[33,34]

However, intervention studies have shown that LCPUFAs supplementation has positive developmental outcomes that resemble trajectories seen in infants fed human milk regarding cognitive function, visual acuity, and immune response. Infants that are fed formulas supplemented with LCPUFAs have higher levels of DHA and AA in plasma or red blood cells compared with infants that are fed formulae that are not supplemented. As such, all formulae for both term and preterm infants are currently supplemented with LCPUFAs.[35,36]

Prebiotics

Prebiotics are nondigestible carbohydrates, primarily oligosaccharides that pass through the small intestine and stimulate the growth of beneficial microorganisms, such as bifidobacteria, in the lower intestine.[37] They are found in high concentrations in human milk and, thus, it seems to be imperative for product manufacturers to fortify infant formulae with them. Products are most often supplemented with galacto-oligosaccharide, fructo-oligosaccharide or polydextrose, which can mimic the prebiotic effects of human milk, which has been demonstrated to beneficially impact the gut microbiota composition and activity as well as the immune system, showing a reduced risk of allergies and infections.[38,39]

Human Milk Oligosaccharides

Human milk oligosaccharides (HMOs) are complex, nondigestible carbohydrates that are the 3rd largest fraction in human milk (between 12 and 15 g/l). More than 200 HMOs have been

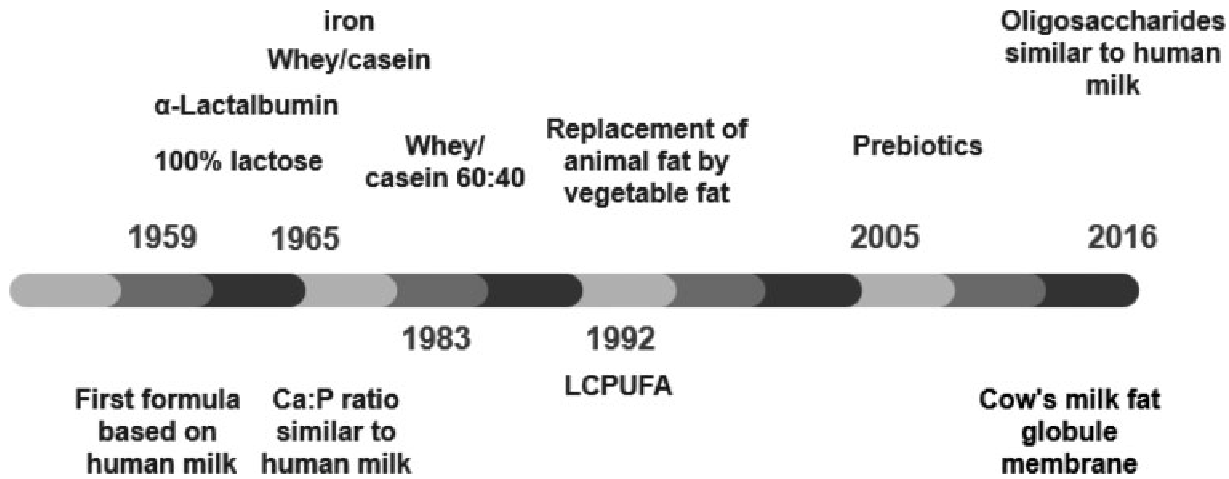

Fig. 1 Infantile formula timeline.[38,51,52]

discovered in human milk, where 2-fucosyllactose and lacto-N-neotetraose are the most abundant.[40] They were discovered >60 years ago, but their biological roles and functions have been studied more extensively only in recent years, especially in the past 10 years.[41] They are known to exert a beneficial impact on the immune system of infants, primarily through the promotion of a balanced gut microbiota.

Human milk oligosaccharides are not digested by the infant. Thus, they arrive in the intestinal colon intact, where part of them is fermented by bacteria probiotics such as bifidobacteria, while some HMOs bind to potentially pathogenic bacteria, such as *Escherichia coli* and *Campylobacter jejune*, inhibiting their adhesion to the intestinal epithelium and, consequently, infections.[41] Even without being digested, a small number of HMOs is absorbed from the intestine and reaches the systemic circulation, acting on other systems and organs. Thus, current evidence has suggested effects of HMOs that go beyond the intestinal ones acting directly on the immune cells, for example.[42] Certain acidic HMOs reduce the expression of proinflammatory cytokines IL-1β and IL-6 in macrophages stimulated by lipopolysaccharide and in other immune cells, indicating that they alter the immune response.[43] A clinical study with 200 infants showed that the levels of studied immunological markers were similar between breastfed and breastfed infants who received infant formula supplemented with 2'-FL.[44]

Furthermore, some HMOs contain sialic acid, which is an important structural component of the nervous system. It has been observed that the sialic acid concentration in the brain of exclusively breastfed infants is significantly larger than that in the brains of infants fed infant formulas. Therefore, sialic acid present in HMOs can contribute to the neurological and cognitive advantages provided by breastfeeding the infant.[45]

Cow Milk Fat Globule Membrane

The human milk fat globule is a heterogeneous structure varying in diameter, triglyceride content, membrane, and fatty acid composition. The lipid droplets of milk fat globules (including those found in breast milk) are stabilized by a 3-layered membrane called milk fat globule membrane (MFGM). which is highly structured and contains various components, such as specific proteins (mainly glycoproteins), choline, sialic acid, polar lipids (phospholipids and glycosphingolipids), and no polar lipids (cholesterol and cerebrosides). This membrane acts as an emulsifier and protects the globules from coalescence and enzymatic degradation.[46]

The milk fat globule membrane has been studied for the purpose of enhancing the efficacy of infant nutrition formulae. A recent review by Brink et al. examined MFGM and its components regarding resistance to infections, cognitive development, establishment of gut microbiota, and infant metabolism. The authors concluded that the addition of this ingredient in infant formulae is safe and warranted because the membrane fraction is an inherent component of all mammalian milk, and its biological value is lost in infant formulae due to the use of vegetable oils for fat. Furthermore, to date, clinical evidence support the beneficial effects of adding back this fraction on infant health and development.[47]

Figure 1 shows the timeline of the evolution of infant formulae.

Final Considerations

Infant formulae are infant-specific foods and should only be indicated in the absence and/or in the impossibility of using human milk.

In almost a century of history, we have left the condition of using fresh cow milk in the composition of highly complex formulas, always in accordance with the current legislation and better meeting the nutritional needs of this age group, besides being quite safe.

Major milestones in the modification of the composition of infant formulae were the incorporation of nucleotides, LCPUFAs, and prebiotics, among others, showing benefits to the immunological status.

Despite advances in knowledge and technology, breast milk remains irreplaceable, being the gold standard for infant feeding.

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Conflict of Interests
The authors have no conflict of interests to declare.

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