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Milk scenarios and gut microbiota in the first 1000 days of life

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ABSTRACT

Human milk is the gold standard for infant nutrition, and breastfeeding should be started within the first hour of life. Cow's milk, other mammalian milk, or plant-based beverages should not be offered before 1 year of age. However, some infants require, at least in part, infant formulas. Even with subsequent enhancements throughout history, with the addition of oligosaccharides, probiotics, prebiotics, synbiotics, and postbiotics, infant formulas still have room for improvement in reducing the health gap between breastfed and formula-fed infants. In this regard, the complexity of infant formulas is expected to continue to increase as the knowledge of how to modulate the development of the gut microbiota is better understood. The objective of this study was to perform a non-systematic review of the effect of different milk scenarios on the gut microbiota.

Keywords: *microbiota; human milk; infant formulas; cow's milk; dietary supplements.*

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INTRODUCTION

The expression *human microbiota* refers to the bacteria, yeasts, fungi, viruses, archaea, and protozoa that colonize the human body, whereas *microbiome* refers to their genetic material. The first 1000 days of life are a window of opportunity for the development of a healthy gut microbiota,[1] immune programming and maturation, and prevention of chronic diseases.[2] The composition of the microbiota of vaginally delivered infants differs from that of those born via C-section.[3] Vaginal birth involves the swallowing of vaginal lactobacilli.[4] On their part, bifidobacteria are prevalent in breast milk,[5] also favored by oligosaccharides, and are the main gut microbial group of a healthy infant.[6]

Eating habits during pregnancy are decisive for the establishment of the gut microbiota.[7] Doing physical activity regularly, not smoking, and avoiding alcohol and psychotropic drugs promote a better fetal development. Overweight and obesity during pregnancy are negative factors for the neonatal microbiota.[8] A pregnancy in an overweight or obese woman has a higher rate of C-section and antibiotic use.[8]

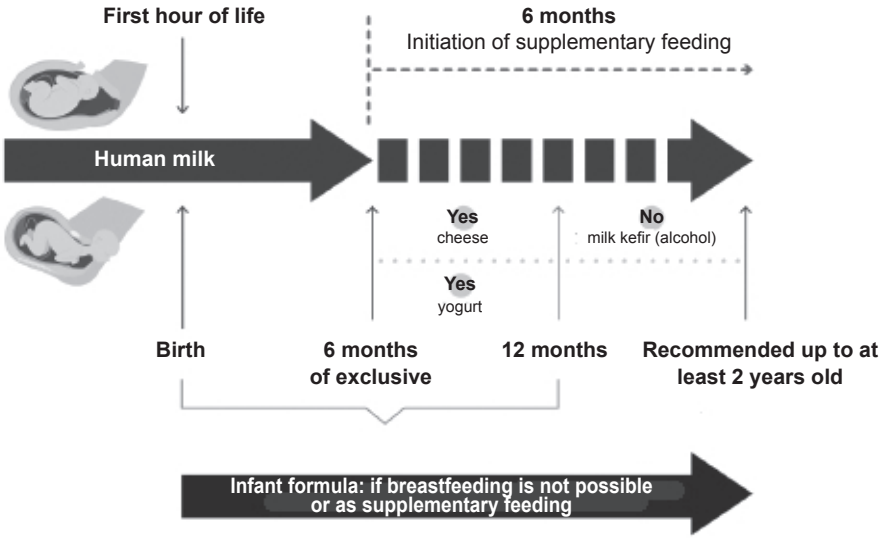
The objective of this study was to perform a non-systematic review of the effect of different milk scenarios on the gut microbiota: breastfeeding, human milk, mammalian milk, plant-based beverages –wrongly defined as "milks"–, and infant formulas.

NUTRITIONAL RECOMMENDATIONS FOR INFANT FEEDING

The timing of breastfeeding initiation, ideally within the first hour of life (the sacred hour), is critical for its continuation and to reduce the mortality risk.[9] If breastfeeding is not possible, the recommendation is to use banked human milk.[10] If this is also not possible, breast milk substitutes should be used under medical prescription.[11] To date, no formula has been developed that matches breast milk and promotes a similar gut microbiota.[12] The World Health Organization (WHO),[12] UNICEF,[13] and the National Ministry of Health of Argentina[14] recommend not offering unmodified milk to infants younger than 1 year. Low intakes of iron, linoleic acid, and vitamin E and excessive intakes of sodium, potassium, and protein have been observed in milk-fed infants (Ministry of Health, Argentina, 2021).[14] Infant formulas should be subject to the Codex Alimentarius standards (UNICEF, 2003).[15]

Figure 1 depicts the possible milk scenarios in the first 2 years of life. Breastfeeding or human milk is recommended within the first hour of life, on demand and exclusively until 6 months of

Figure 1. Milk scenarios and feeding in the first 1000 days of life



Cheese and yogurt may be offered as of 6 months old, while milk kefir should not be offered because of its variable alcohol content.
Source: Developed by the authors.

age. Once supplementary feeding is initiated, it is suggested to continue breastfeeding until at least 2 years of age. In relation to other products within the milk scenario, the clinical practice guidelines on supplementary feeding by the National Ministry of Health of Argentina[16] establish: "It was concluded that introducing cheese as of 6 months old instead of 9 months old may have nutritional benefits over uncertain risks. However, its implementation could lead to the use of greater resources, with a negative impact on equity. For this reason, it was decided to conditionally recommend the introduction of soft and semi-soft cheese, because of its lower sodium content, as of 6 months old, based on family possibilities and preferences." In relation to yogurts, the same guidelines state: "If yogurt is introduced as of 6 months old, whole-milk yogurt, with lower sugar content and no artificial colors should be chosen. It was concluded that introducing yogurt as of 6 months old may have nutritional benefits over uncertain risks. However, its implementation could lead to the use of greater resources, with a negative impact on equity and the environment. For this reason, it was decided to conditionally recommend the introduction of yogurt as of 6 months old, based on family possibilities and preferences." Milk kefir should not be offered because of its variable alcohol content (0.6–3.5% w/v).[17] If breastfeeding is not possible, infant formulas should be adapted to the child's age and condition. Some formulas may also be supplemented with probiotics, prebiotics, synbiotics and/or postbiotics. Cow's milk is not recommended in the first year of life due to its excess and deficit of certain nutrients.

At approximately 6 months of age, nutritional requirements begin to exceed those provided by human milk or infant formula, making it necessary to start supplementary feeding (SF).

Only during emergencies (natural disasters), cow's milk could be given to children under 6 months of age, as long as it is pasteurized, diluted 1:2 or 6% reconstituted powdered milk, with 5% sugar and 2% oil (pure sunflower, corn, soybean oil).[14,18] For children aged 6–12 months, it should be diluted 2:3 or reconstituted to 10% in the case of powdered milk.[14] Also, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) does not recommend the use of other mammalian milks (sheep, buffalo, mare, or goat) or plant-based beverages (soy, almond, oat, rice, or others) due to their inadequate composition.[19]

The early introduction (4–6 months of age) of supplementary feeding with certain potential allergens in infants with a family history of allergy may induce the development of oral tolerance.[20] Given the uncertain risks of initiating supplementary feeding at 4 months old, as well as its potential benefit, it is recommended to maintain exclusive breastfeeding until 6 months old.[21] This is a desirable goal, but if it is not possible, exclusive breastfeeding for shorter periods is also valuable.[22]

Microorganisms and oligosaccharides in breast milk

The oligosaccharide content of breast milk (human milk oligosaccharides, HMO) is 5 to 15 g/L, while that of cow's milk is 0.05 g/L. As the latter is not recommended, no studies of its impact on the gut microbiota have been carried out using metagenomics, a massive sequencing tool of the genetic material of the microbiota that makes it possible to identify the microorganisms present. However, considering that the oligosaccharide content of cow's milk is significantly lower than that of human milk,[23] it is likely that its consumption results in a microbiota different from that generated by human milk, and most likely, less functional.

Metagenomic studies of breast milk indicate that it may contain more than 200 bacterial species, contributing more than 30% of the bacteria to the infant's microbiota.[24] HMOs are molecules of 5 monosaccharides, including lactose,[25] and are the food of bifidobacteria in infants, responsible for guiding gut colonization, immune system maturation, and development of oral tolerance.[26]

Lactose, the main carbohydrate in breast milk and infant formulas, plays a prebiotic role,[27] as it is present in most HMOs. The acidity generated by its fermentation in the gut facilitates calcium absorption,[28] is a very important source of energy at the hepatic level, and represents a structural component of the brain during infant development.[29]

BIOTICS IN INFANT FORMULAS

Although it is impossible to reproduce the microbiological and physicochemical composition and the dynamic succession of nutrients and microorganisms found in breast milk in an infant formula, in the past 30 years, there have been advances in the development of bioactive compounds (biotics) capable of providing some of the functions of breast milk.

Biotics consist of probiotics, prebiotics, synbiotics, and postbiotics. Probiotics are live microorganisms capable of having a beneficial effect when administered in adequate amounts.[30] Prebiotics are ingredients selectively fermented by the host's microbiota.[31] The combination of probiotics and prebiotics is called synbiotics,[32] whereas postbiotics are preparations of inanimate microorganisms and/or their cellular components that confer a health benefit.[33] It has also been possible to synthesize, or produce by microbial fermentation, some of the HMOs found in breast milk so that they can be added to some infant formulas.[34]

IMPACT OF THE TYPE OF EARLY FEEDING ON THE GUT MICROBIOTA

The type of feeding during the first year of life is critical in the development of the gut microbiota. The microbiota of formula-fed infants shows a different colonization pattern dominated by bifidobacteria and with fewer *Clostridia* when compared to infants who are fed with human milk. Formula-fed infants have a more heterogeneous microbial composition, with lower levels of bifidobacteria.

The microbial profile induced by human milk has been associated with a lower incidence of infections. In addition, human milk provides antibodies, which prevent the translocation of aerobic bacteria in the gut, decrease the risk of inflammatory disease, and promote intestinal homeostasis with superior effects on the intestinal barrier integrity.[35]

The *Bifidobacterium* genus is the most abundant and relevant in the gut ecosystem in the first year of life, since it modulates the immune system,[26] produces vitamins, reduces rotavirus infection, and prevents overweight and obesity, among other benefits.[36] Differences in the gut microbiota of infants fed with human milk or formula are associated with a greater predisposition to develop atopic dermatitis in formula-fed infants.[37]

Several studies on biotics combined with human milk or infant formula and on birth by vaginal delivery or C-section have demonstrated that the gut microbiota developed in infants is more similar to that induced by human milk, with a predominance of bifidobacteria when infant formulas with added biotics are used. This has been observed even in unfavorable initial situations, such as C-section, which in these cases contributes to a partial correction of the resulting dysbiosis.[38–40]

After breastfeeding, the next major influence on the development of the microbiota is supplementary feeding. With it, the number of *Bacteroidetes* increases, which break down complex plant polysaccharides, thus accelerating the maturation of the gut microbial community.[41] The differences between the microbiota of infants fed with human milk versus those fed with formula decrease progressively after the introduction of supplementary feeding, so the composition of diet also affects the short- and long-term health of infants.

A high protein intake, a low consumption of fruits, vegetables, and fish, and a poor ratio of saturated to unsaturated fats are associated with obesity, type 2 diabetes, and dyslipidemia. The current recommendation suggests a diet with a lower protein intake (30% less, compared to previous guidelines), the introduction of long-chain polyunsaturated fatty acids (LCPUFAs), and a low intake of saturated fatty acids. These LCPUFAs, found in fish and fish oils, have been associated with a lower risk of asthma, atopic disease, and infections during childhood.[42]

A high-fiber (fruits and root vegetables) and low-fat diet promotes a more diverse and abundant microbiota, with a greater production of short-chain fatty acids, in which microorganisms adapted to obtain energy and nutrients from plant fibers predominate.[43] In addition, industrialized food—rich in low-quality fats, proteins, sugars, and starches and poor in fiber content—causes the microbiota to have a predominance of less beneficial microorganisms and a decrease in strict anaerobic species that produce short-chain fatty acids that metabolize complex carbohydrates from vegetables. This eating pattern promote a more patent gut.

CONCLUSION

The diet and habits of pregnant women, the possibility of receiving human milk, and the type and quality of supplementary feeding are the factors that determine the configuration of a healthy gut microbiota. Human milk is a dynamic biological tissue adapted to the changing needs of the baby. Early feeding may have long-lasting metabolic and immunologic effects during childhood and adulthood. Breast milk is the gold standard; however, some infants require, at least in part, infant formulas. Cow's milk and plant-based formulas are discouraged in the first year of life. The complexity of infant formulas

is expected to continue to advance as more is learned about how to modulate the gut microbiota through probiotics, prebiotics, synbiotics, and postbiotics. ■

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