IBFAN briefing
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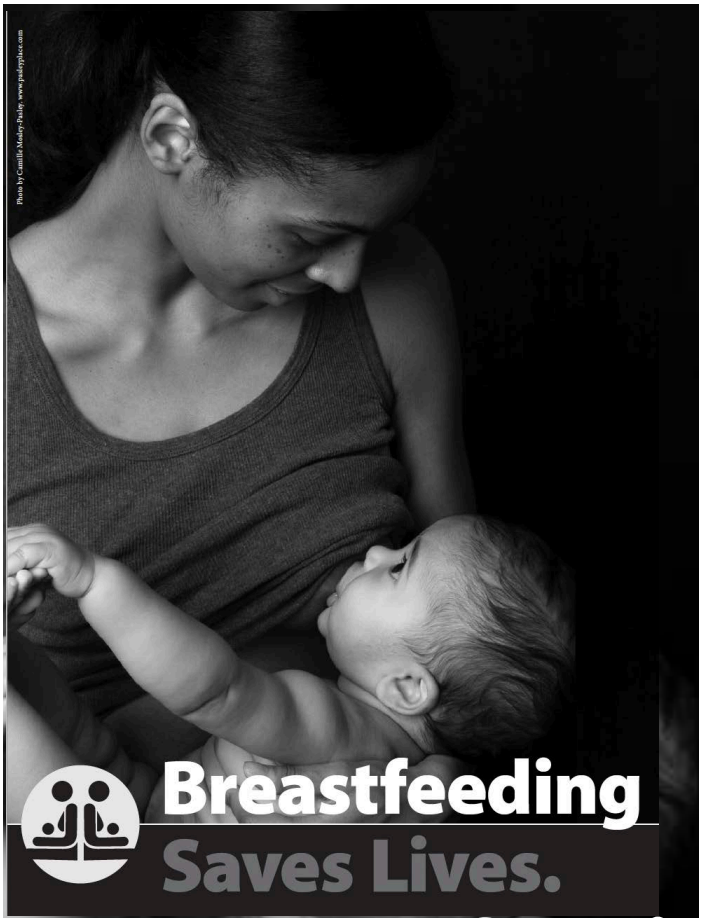
Breastfeeding and the immune system



Whenever someone reports a problem with breastmilk and/or breastfeeding, the question being raised is: are there situations where it is safer to avoid breastfeeding, or shorten its duration, and use formula? In our opinion, the answer is no, except in rare or extraordinary circumstances, such as a newborn affected by galactosemia[1] or the very high levels of dioxin[2] found in breastmilk an industrial disaster like the one that occurred in Seveso, Italy, in 1976. The replacement of breastmilk by its substitutes deprives infants and children, mothers and families, health care systems, the economy and the environment of so many benefits that the balance is always in favour of breastmilk and breastfeeding. This paper focuses on the harms to the immune system caused by totally or partially replacing breastmilk and breastfeeding with formula feeding. Further papers in this series will focus on other arguments against such replacement.

The infant immune system

Breastmilk and breastfeeding evolved during millions of years, first in proto-mammals then in mammals, including human beings, to play an important role in establishing defence mechanisms for infants and young children. In fact, the first evolutionary role of breastmilk and breastfeeding was defence; only much later, in evolutionary terms, did breastmilk and breastfeeding become carriers of important nutrients and the mainstay of infant and young child feeding.[3]

Soon after birth and in the first few months, newborn infants are more susceptible, compared to later in life, to infectious diseases because of their weak capacity to build up a quick and robust inflammatory response. Their immune system is still maturing and their gut microbiota,[4] perhaps the main booster of immunity, is still evolving. Newborn infants are also exposed, in a period in which their immune memory is forming, to a huge variety of antigens that they did not encounter during intrauterine life.[5] In summary, the immune system of newborn infants reacts to infections, but their response is weak and slow. This is one of the reasons why neonatal infections still account for a large proportion of neonatal and infant deaths worldwide.

At the same time, newborn infants need to curb or even silence their immune response, because they have to develop tolerance for antigens that do not cause harm or that may be beneficial, such as those contained in foods. This tolerance will help prevent auto-immune and allergic responses in the early months and later in life. Gut colonization with the right microbiota plays an important role also in this process.

Breastfeeding for the prevention of infectious diseases

The anti-infective properties of breastmilk have been known for almost a century. The first review on breastfeeding and the prevention of infectious diseases was published in 1935.[6] Subsequently, hundreds of articles and dozens of systematic reviews have confirmed those initial findings. The results of a meta-analysis[7] included in an article published in the Lancet in 2016 show that scaling up breastfeeding in 75 high mortality countries to a near universal level could prevent 823,000 annual deaths in children younger than 5 years, mostly due to infectious disease.[8]

This effect is the result of several factors. Breastmilk contains many substances with antibiotic properties, such as lactoferrin, lysozyme and other proteins. In addition, it contains hundreds of different human milk oligosaccharides (HMOs), which are complex sugars with prebiotic and probiotic properties.[9] Every mother has a different set of HMOs, depending on genetic factors, environmental exposures and time of lactation.[10] HMOs lower the risks of viral, bacterial and parasitic infections, shape the infant gut microbiota with beneficial bacteria, and modulate epithelial and immune cell responses.[11] All the above elements interfere with bacterial entry and growth. Other constituents of breastmilk, called growth factors, maintain and repair respiratory and intestinal mucosae to prevent bacterial invasion.

Most importantly, breastmilk, and colostrum in particular, contains plenty of maternal IgAs, immunoglobulins specialized in fighting against intestinal and respiratory pathogens. These IgAs originate in maternal mucosae and migrate in mammary glands to be incorporated in breastmilk. In addition to direct defence, maternal IgAs help establish the infant gut microbiota.

Breastmilk contains also other maternal immunoglobulins. These are memory antibodies that women produce in response to infections they suffered earlier in their life or during pregnancy. These antibodies enter breastmilk upon stimulus from the baby. If a microbial or viral agent is present in the infant's mouth, it will trigger a response in the mammary gland that will produce specific antibodies, if the mother had previous contact with that agent. This is why studies found antibodies against Sars-Cov-2 in the breastmilk of lactating mothers who had suffered from a Covid-19 infection.[12]

There are many other bioactive components in breastmilk; a full list of these currently known components (many more could be added in future) can be found in a recently published article.[13] The role played by many of these components is still uncertain and may not be directly linked to immunity. It may be linked, for example, with neurodevelopment or with the prevention of cancer later in life, in addition to the obvious nutritional functions. Some components, however, play an important role for immunity. This is the case, for example, of maternal white blood cells that migrate from the infant's gut to lymph nodes, liver and spleen. Similarly, several different maternal cytokines and interleukines probably have a role in regulating the cellular immune response and mucosal defence of breastfed infants.[14]

As mentioned above, breastmilk contains numerous types of immune cells; in addition to white blood cells, there are macrophages, lymphocytes and neutrophils. All these cells assist in the protection of the infant's fragile mucous membranes against microbes and viruses, by preventing entry, transport and proliferation.[15] There is, however, a particular type of cells that may be linked to the development of the infant's immunity: the stem cells. These are cells that are able to migrate to different infant's organs (brain, liver, spleen, thymus, etc.) and to differentiate into different tissues. Some of them may trigger the newborn's immune system.[16]

Finally, breastmilk is not sterile, it is full of good maternal bacteria and it has its own mother-specific microbiome mainly made up of lacto- and bifido-bacteria.[17] In addition to help regulate the newborn's gut microbiota, the breastmilk microbiome controls the presence and growth of other bacteria, including the pathogenic ones. In this way, it is of the utmost importance for the development of the infant's immune response.[18] Formula feeding, and in particular early formula feeding, is associated with an alteration of the infant's gut microbiota, with important harms for infant health.[19]

Breastfeeding for shaping an optimal lifelong immune system

As mentioned above, in addition to helping with the prevention of infectious diseases in early life, breastfeeding and breastmilk are essential to shaping the immune system for the rest of life. This is particularly important for the prevention of immune-dependent diseases such as allergy, type 2 diabetes, obesity and other chronic non-infectious diseases, with all their consequences.[20] This is achieved through the effect of breastfeeding and breastmilk on the infant's gut microbiota and through exposure to antigens and allergens.

The gut microbiota acts as a key factor in the balance between health and disease by regulating the susceptibility to infections and allergy.[21] The prebiotics and probiotics of breastmilk, as well as its antigen specific and non-specific antimicrobial compounds, act as seeds for the gut microbiota and its evolution. Cessation of breastfeeding and addition of formula are associated with a radical change in the composition of the gut microbiota.[22] There is plenty of evidence showing that any upset in the gut microbiota in early life, while the immune system is still developing, can have long-lasting effects on local and systemic immune health.[23]

Breastmilk contains also a variety of antigens and allergens that uniquely varies on the diet of the mother and her previous health and disease history to provide specific protection. When given to the baby via breastmilk, these antigens and allergens induce tolerance, rather than an immune reaction. Breastmilk can also modulate the infant's immune response to antigens and allergens that reach its organs in other ways, for example through breathing or when complementary foods are added to its diet. Such direct and indirect (regulatory) effects of breastmilk are the most likely explanation of the risk reduction against diseases due to malfunction of the immune system achieved through breastfeeding.

Finally, in addition to all the above components, it has been recently established that breastmilk contains myriads of fragments of microRNA[24] derived from the mammary gland. More than 1400 different types of microRNA have been identified so far in breastmilk; their composition is affected by maternal genetics, diets and environmental factors. While the specific functional role of these fragments of microRNA is still a matter of research, in particular for their epigenetic effects, it is very likely that many of them may play a role in the development and performance of the immune system.[25]

Conclusions and key messages:

- Formula may provide basic though sub-optimal nutrition for an infant; breastfeeding and breastmilk provide optimal nutrition, immune protection and developmental support.
- Breastmilk is a dynamic, living fluid that contains thousands of different molecules, growth factors, hormones, microorganisms, cells and genetic material.
- Breastfeeding and breastmilk provide infants with protection against infection via the robust maternal immune system and support to the modulation of the immature infant immune system.
- Breastfeeding is an interactive process, not just the delivery of a product; breastmilk is continuously adapted to meet the newborn infant demands.
- The overwhelming evidence allows us to give a firm answer to our initial question: the replacement of breastmilk with formula should be avoided, apart from exceptional circumstances.
- The longer the duration of breastfeeding, the greater are the benefits. Thus, exclusive breastfeeding up to around six months and continues breastfeeding alongside bio-diverse nutritious foods for two years and beyond should be a goal both for individual mother and infant dyads, but also for public health policies and programmes.
- Breastfeeding saves lives; its protection, promotion and support should be a global priority, if not an imperative.

ENDNOTES:

1 A rare hereditary disease that affects the baby's ability to convert to glucose the galactose contained in breastmilk.
2 A highly toxic pollutant causing cancer, reproductive and development disorders. It is harmful to the immune system and it can interfere with hormones.
3 Vorbach C, Capecchi MR, Penninger JM. Evolution of the mammary gland from the innate immune system? BioEssays 2006;28:606-16
4 The term microbiota refers to the type of microorganisms (bacteria, viruses, fungi, etc.) that are found within a specific environment, the gut in this case.
5 The term antigen refers to any foreign substance which induces an immune response in the body.
6 Grulee CG, Sanford HN, Schwartz H. Breast and artificially fed infants: a study of the age incidence in the morbidity and mortality in twenty thousand cases. J Am Med Assoc 1935;104:1986-8
7 A statistical method that allows to combine the results of several studies to calculate an overall effect.
8 Victora CG, Bahl R, Barros AJ et al: Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet 2016; 387: 475-490
9 Prebiotics act as food for the gut microbiota. Probiotics act as microorganisms that maintain or improve the gut microbiota.
10 Triantis V, Bode L, Joost van Neerven RJ. Immunological effects of human milk oligosaccharides. Front Pediatr 2018;6:190
11 Plaza-Diaz J, Fontana L, Gil A. Human milk oligosaccharides and immune system development. Nutrients 2018;10:1038
12 Favara DM, Ceron-Gutierrez ML, Carnell GW et al. Detection of breastmilk antibodies targeting SARS-CoV-2 nucleocapsid, spike and receptor-binding-domain antigens. Emerg Microbes Infect 2020;9;2728-31
13 Bardanzellu F, Peroni DG, Fanos V. Human breast milk: bioactive components, from stem cells to health outcomes. Curr Nutr Rep 2020;9:1-13
14 Cytokines and interleukines are proteins made in response to pathogens and other antigens; they regulate and mediate inflammatory and immune responses.
15 Ballard O, Morrow A. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am 2013;60:49-74
16 Kaingade PM, Somasundaram I, Nikam AB et al. Assessment of growth factors secreted by human breastmilk mesenchymal stem cells. Breastfeed Med 2016;11:26-31
17 The term microbiome refers to the collection of genomes from all the microorganisms found in a given environment, the mammary gland in this case.
18 Rautava S. Early microbial contact, the breast milk microbiome and child health. J Dev Orig Health Dis 2016;7:5-14
19 Pärnänen KMM, Hultman J, Markkanen M et al. Early-life formula feeding is associated with infant gut microbiota alterations and an increased antibiotic resistance load. Am J Clin Nutr 2022;115:407-21
20 C amacho-Morales A, Caba M, García-Juárez M et al. Breastfeeding contributes to physiological immune programming in the newborn. Front Pediatr2021;9:744104
21 Hand TW, Vujkovic-Cvijin I, Ridaura VK, Belkaid Y: Linking the microbiota, chronic disease, and the immune system. Trends Endocrinol Metab 2016;27:831-43
22 Backhed F, Roswall J, Peng Y et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 2015;17:690-703
23 van den Elsen LWJ, Garssen J, Burcelin R, Verhasselt V. Shaping the gut microbiota by breastfeeding: the gateway to allergy prevention? Front Pediatr 2019;7:47
24 Small fragments of RNA (ribonucleic acid) derived from full RNA molecules contained in human and non-human cells.
25 Hatmal MM, Al-Hatamleh MAI, Olaimat AN et al. Immunomodulatory properties of human breast milk: microRNA contents and potential epigenetic effects. Biomedicines 2022;10:1219

International Baby Food Action Network (IBFAN) was founded in 1979 and is a global network of more than 148 public interest groups in over 108 countries. Members include health worker, parent, consumer and development organisations. Social justice, human rights and environmental protection underscore all our work.

IBFAN members help governments bring in legislation to support and protect families and health workers. Our work on breastfeeding and young child feeding is just one element in the global action to ensure an environment in which children can survive and reach the highest attainable standard of health.

IBFAN does not seek or accept financial or other supports from manufacturers or distributors of infant and young child feeding and related products (or their trusts or foundations). IBFAN is also cautious about funding from any for-profit entities since this can lead to loss of reputation and raise questions about IBFAN's integrity.

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