# A NARRATIVE REVIEW ON EFFECT OF FORMULA FEEDING ON THE HEALTH OF INFANTS

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Breast milk is the best mode of providing nutrition to infants. Worldwide demand of formula is increasing when breastfeeding is not feasible or desirable. Infants fed formula have different growth patterns than those fed breast milk. Formula-fed babies gain more weight in the first year of life relative to their length, which raises their BMI. During their first year of life, infants fed formula grow more lean mass than breastfed infants due to the higher protein: energy ratio of formula. Lack of exposure to bioactive components in breastfeeding that could prevent adipogenesis, or changes in the location of fat deposition or lean mass gain during infancy may be the cause of obesity in later life. Formula feeding has been associated with a less stable microbiome over time, a notably altered bacterial content, and greater diversity and richness of bacteria in comparison to breastfeeding. Breastfed infants had higher levels of *Bifidobacteria*—an key component of a healthy microbiota than formula-fed infants. The serum concentrations of total IgG, IgG1, NK cell activity, and IFN- $\gamma$  showed a notable difference between breastfed and formula-fed infants, with the latter group showing significantly greater levels of these indicators. There is no clear correlation between formula feeding, the creation of gut microbiota, and its long-term health effects, more thorough and in-depth research in these areas is crucial.

## Keywords: Formula, bioactive components, adipogenesis, microbiota

Human milk is the healthiest food for infants, and the combination of its nutritional and bioactive ingredients has a positive impact on the health of infants. From the perspectives of nutrition, physiology, and development, breastfeeding has been shown to provide both immediate and long-term health benefits. Breastfeeding is linked to a lower risk of necrotizing enterocolitis and diarrhea in the early years of life as well as a lower risk of type 2 diabetes, obesity, and inflammatory bowel illnesses in later life (Le Huërou-Luron et al., 2010). In addition to its nutritional value, human milk contains a wide range of bioactive substances, including hormones, cytokines, leukocytes, immunoglobulins, lactoferrin, lysozyme, stem cells, human milk oligosaccharides (HMOs), microbiota, and microRNAs. The World Health Organization strongly advises breastfeeding babies for the first hour after birth and exclusively for the first six months, without the use of any other solid food or water (WHO, 2001). However, despite these recommendations, breastfeeding rates remain low, in India only 54.9% of children under 6 months are exclusively breastfed (NFHS-4, 2015-16). In situations where breastfeeding is not feasible, infants are given formula milk, which is almost similar to human milk in terms of the macro and micronutrient content. The American Academy of Pediatrics (AAP)

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advises against giving nonformula milk or milk substitutes to infants younger than 12 months of age since they may contain excesses of certain nutrients and insufficient amounts of others (Green Corkins, K., and Shurley, T. 2016). Despite improvements in infant formula over its 150 years history, any added ingredients in formula lack the ability to constantly change and adapt like breast milk. The composition of breast milk is dynamic and adapts to the baby's requirements. The higher level of protection and nourishment found in human milk is attributed to the biological actions of certain components as well as the nutritional composition of the milk, which varies during lactation. During the first month of lactation, the protein content of human milk rapidly falls (14–16 g/l during early lactation, 8–10 g/l at 3–4 months, and 7–8 g/l at 6 months and beyond). The primary cause of this decline is the reduction in the concentration of whey protein. After two to three months of breastfeeding, the ratio of whey to casein shifts from 80:20 in the early stages of lactation to 60:40. Consequently, throughout the early stages of breastfeeding, the amino acid composition of human milk similarly varies (Le Huërou-Luron et al., 2010). The nutritional value of infant formula is greatly impacted by processing. Differences in fat structure with respect to size, content, fatty acid profile, and interfacial architecture are caused by a combination of heat and homogenization treatments (Lopez et al., 2015; Cilla et al., 2016). Furthermore, heat causes certain hormones, unsaturated fatty acids, and water-soluble vitamins like C,  $B_1$ ,  $B_6$ , and  $B_{12}$  to partially degrade. Oxygen-sensitive substances, such as unsaturated fatty acids and the majority of fat- and water-soluble vitamins, may degrade while drying and evaporation processes. When heated,  $\alpha$ -lactal burnin's capacity to bind with calcium and zinc is lost, resulting in a decrease in their bioavailability (Golinelli et al., 2014). The amounts of metals in baby formulae are typically far higher than those in breast milk (Sipahi et al. 2014). Formula-fed infants had higher amounts of amino acids in their plasma than breastfed infants did. Increased protein consumption due to formula feeding leads to higher levels of amino acid excretion (Kirchberg et al., 2015). Compared to breastfed infants, formula-fed infants had significantly greater urine C-peptide concentrations, which are used as a measure of insulin secretion (Le Huërou-Luron et al., 2010). The IGF-I axis and insulin release in infancy are stimulated by cow-milk-based infant and follow-up formulae with increased protein content (Socha et al., 2011). This review aims to provide an overview of how infant formula affects the health of infants.

## **Infant Formula**

Infant formula is defined as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk" by the Federal product, Drug, and Cosmetic Act (FDCA). There are three types of infant formulae available: powder, liquid concentrate, and ready to feed. Institutions prefer to employ the liquid products (liquid concentrate, ready to feed) since they are regarded as commercially sterile. Infants are infected with *Enterobacter sakazakii* from the intake of non-sterile powder form of the formula (Green Corkins, K., and Shurley, T. 2016). There are several varieties of infant formula available, such as cow's milk, soy-based, and specialized formulas like lactose-free and hypoallergenic. Among the several varieties of infant formula, cow's milk formula is the most widely used. Standard infant formula (IF) (0–6 months), follow-up formula (6–12 months), and toddler formula (13–36 months) are the three primary categories of

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milk formulae (Rossen et al., 2016). Compared to human milk, cow's milk has a substantially higher protein content of about 3.4% and a distinct whey-to-casein ratio of 20:80. Bovine milk has lower levels of lactose and lactoferrin than human milk. Furthermore, the concentration of alpha-lactalbumin in human milk is two times higher. While beta-lactoglobulin is the predominant protein in the whey fraction of cow's milk, it is absent in human milk (Park, Y.W. and Haenlein, G.F., 2013). Compared to human milk, bovine milk has a lower oligosaccharide concentration and diversity (Fong et al., 2011). Consequently, to replicate a nutrient profile akin to human milk, infant formula makers reformulate or alter cow's milk (Park, Y.W. and Haenlein, G.F., 2013). The use of soy-based formula, extensively hydrolyzed formula, and amino acid-based formula as substitutes for cow's milk formula can help prevent allergies to the protein in cow's milk in the pediatric population (Muraro et al., 2014). Soy-based formula should only be used in infants older than six months because high isoflavone concentrations in soy formula have sparked concerns about the potentiality of the formula to have estrogenic effect on infants' development. Breastfed infants showed greater cognitive development than formula-fed infants despite normal growth (Andres et al., 2012).

### Changes in the body composition of formula-fed infants

Throughout the first year of life, there is a rapid and nonlinear change in body composition. Infants fed formula have different growth patterns than those fed breast milk; by the time they are 12 months old, formula-fed infants weigh 400–600 g more on average than breastfed babies (Gale et al, 2012). Compared to breastfed babies, formula-fed babies gain more weight in the first year of life relative to their length, which raises their weight-for-length, or BMI (body mass index) (Rebhan et al., 2009). During their first year of life, infants fed formula grow more lean mass than breastfed infants; these differences become most noticeable between the ages of 3-4 and 9-12 months. There was less consistency in the relationship between the feeding of the baby and the accumulation of fat mass; at 3-4 and 6 months of age, formula-fed infants had less fat mass, but at 8-9 and 12 months, they had greater fat mass. The lower protein: energy ratio of breast milk may cause less fatfree mass (FFM) to be deposited, with extra energy being stored as fat. Accordingly, the reported higher fat mass compared to formula-fed infants after term may be explained by the reduced protein consumption in breastfed infants (Huang et al., 2016). The protein composition of formula more closely resembles that of mature human milk, ignoring the way that the protein concentration of human milk changes progressively during the breastfeeding phase (Green Corkins, K., and Shurley, T. 2016). The length of exclusive breastfeeding is positively correlated with the proportion of subcutaneous fat mass in babies, but it is not associated with visceral fat mass (Huang et al., 2016). In accordance with the higher fat mass in breastfed babies at 3-4 and 6 months but not at 12 months, circulating leptin is higher in breastfed babies than in babies fed formula at 4 months of age, but not later in infancy (Savino et al., 2002). It is reasonable to infer that the greater fat mass in the early stages of infancy linked to breastfeeding is an evolutionary strategy designed to sustain the baby during the delicate weaning process. Compared to infants who were fed formula with a higher protein concentration, those who got formula milk with a lower protein content had a lower BMI and a decreased risk of becoming obese as adults. Higher absolute weight and faster weight-for-length growth during infancy may be the cause of later childhood and adult obesity, as higher protein consumption in the early years of life has been linked to faster weight gain (Koletzko et al., 2009). Other potential risk factors for obesity in formula-fed infants include variations in solid food consumption habits and the impact of bottle-feeding on feeding self-regulation (Bartok, CJ. and Ventura, AK., 2009), lack of exposure to bioactive components in breastfeeding that could prevent adipogenesis, or changes in the location of fat deposition in infancy rather than its quantity (Gale et al., 2014). On the other hand, lean mass gain during infancy as opposed to adipose tissue gain may be the cause of obesity in later life.

## **Effect on Gut Health**

The gut microbiota has a major impact on the short- and long-term health of infants by influencing body composition and infant growth. Breastfeeding is linked to a decreased risk of inflammatory bowel illnesses, type 2 diabetes, and obesity in later life as well as a lower incidence of digestive tract diseases such as necrotizing enterocolitis and diarrhea (Le Huërou-Luron et al., 2010). Future health outcomes are significantly influenced by the early colonization of the microbiome in the infant's gut. Neonates' gut microbiome composition is closely related to their birth circumstances, including full-term or preterm delivery, vaginal delivery or cesarean section, formula or human milk feeding, and care provided by their mothers or in a neonatal intensive care unit (NICU). According to research, early-life microbiome may be able to predict a person's likelihood of contracting diseases like type 1 diabetes, obesity, and atopic disorders (Uusitalo et al., 2016). Formula feeding has been associated with a less stable microbiome over time, a notably altered bacterial content, and greater diversity and richness of bacteria in comparison to breastfeeding (Thompson et al., 2015). Research has indicated that breastfed infants had higher levels of Bifidobacteria an key component of a healthy microbiota than formula-fed infants (Lee et al., 2015). As a result, faecal shortchain fatty acids SCFAs—the primary metabolites of HMOs fermentation—have varying levels in breastfed and formula-fed infants. Formula-fed babies at 3 and 6 months of age had higher concentrations of SCFAs, such as free amino acids, butyrate, propionate, acetate, and 5-amino valerate. Because of increased HMOSs fermentation, the breastfed infants also had greater faecal levels of succinate and lactate (Martin et al., 2014). Improvements in the formulation and production of infant formula milk have been made in an attempt to create a gut microbiota profile similar to that of breastfed infants. For example, the whey-to-casein ratio has been optimized, and prebiotics have been added to the formula milk, which has been shown to increase the abundance of Bifidobacterium in formula-fed babies (Hascoët et al., 2011). Probiotic strains such as Lactobacillus rhamnosus GG (LGG), Streptococcus thermophilus, Lactobacillus casei, Bifidobacterium lactis, or Lactobacillus reuteri have been added to infant formula (Ackerberg et al., 2012). Infants who received formula supplemented with Lactobacillus fermentum showed lower incidence rates of gastrointestinal infections (Gil-Campos et al., 2012). Since enriched formulae are typically started early in infancy, if not at birth, the ESPGHAN Committee on Nutrition specifically highlighted concern about the crucial factor of timing (Braegger et al., 2011). Thus, adding outside elements—like probiotics—while the gut microbiota is still forming may impact and irreversibly alter the development of ecosystem, resulting in uncertain modifications. Lastly, the duration of treatment raises further concerns because it is possible to administer supplemental products for extended periods of time leading to obscure consequences. Prebiotic

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supplementation to infants may be linked to a beneficial alteration of microbiome composition and metabolic activity, which encourages the formation of an intestinal environment that is more akin to that of breastfed infants. Galactooligosaccharides (GOS), polydextrose (PDX), fructooligosaccharides (FOS), 20fucosyllactose, lacto-N-neo-tetraose, inulin, oligofructose, and galactofructose are the most widely used and researched prebiotic ingredients. GOS, FOS, and/or PDX, as well as mixtures of GOS/FOS-the most extensively studied is a 9:1 mixture of short-chain GOS and long-chain FOS-are the most commonly used and studied prebiotic ingredients. These ingredients are largely studied to promote the establishment and maintenance of a healthy gut environment, more closely resembling that of breastfed infants (Sierra et al., 2015). Necrotizing enterocolitis and a number of other chronic illnesses, such as inflammatory bowel disease, allergies, obesity, diabetes, asthma, cancer, and neurological disorders connected to the gut-brain axis, have all been linked to disruption in the gut microbiota, or dysbiosis (LaTuga et al., 2014). Fast gut maturation brought on by infant formula feeding results in an increase in the number of several *Clostridium* species, especially C. difficile, which leads to the development of atopy (Yang et al., 2016). The bacteria in the gut may be impacted by the structure of triglycerides. High-palmitate infant formula raised the number of Bifidobacterium and Lactobacillus in 6-week-old infants' faces at quantities comparable to those of breastfed children, as compared to infants receiving a low-palmitate formula (Yaron et al., 2013). Emulsifiers as an additive reduce the variety of gut microbiota by elevating Verrumicrobia and lowering Bacteroides abundance. These changes in the gut microbiota induced dysbiosis and encouraged colitis, chronic gut inflammation, and metabolic syndrome (Chassaing et al., 2015). Infants fed formula have higher counts and frequencies of Clostridium perfringens, while infants fed breast milk typically have higher counts of C. difficile (Mountzouris et al., 2002). Regardless of the fetal age at delivery, measurements of intestinal permeability in vivo in human neonates consistently show a greater permeability in formula-fed compared with breast-fed neonates (Le Huërou-Luron et al., 2010).

### Immune development

The newborn's immune system has low levels of gastrointestinal tract acidity (chemical barrier), low levels of antioxidant and anti-inflammatory activity in the respiratory and gastrointestinal tract, underdeveloped physical barriers (such as tight junctions), delayed T-cell function, and decreased immunoglobulin secretion, particularly of secretory immunoglobulin A (IgA). Human milk bioactives have been shown to influence gut microbiota composition, provide healthy gastrointestinal tract mucosal stimuli, and support the developing immune system of the infant. Human milk lactoferin had a greater ability to inhibit bacterial growth in comparison to bovine lactoferrin (Jiang *et al.*, 2014). The characteristics of lactoferrin isolated from human and bovine milk are highly comparable, though not quite the same (Vogel, 2012). The serum concentrations of total IgG, IgG1, NK cell activity, and IFN- $\gamma$  showed a notable difference between breastfed and formula-fed infants, with the latter group showing significantly greater levels of these indicators. Infants fed formula had higher serum IgA levels than infants fed breast milk, however after three months there is no significant difference in serum IgA levels. Since infants start to be fed formulas with a higher likelihood of containing environmental antigens than breast milk does leading to a cross-talk between environmental antigens and

intestinal flora colonization, which could raise serum IgA concentrations. Piglets raised in containment facilities on bovine-based infant formula display variations in their microbiomes and the mucosal immune system, such as more B-cells, less regulatory T-cells, and a faster recruitment of antigen-presenting cells (Lewis et al., 2012). The network of differentially expressed genes was found to be significantly denser in breastfed infants compared to infants fed formula, indicating a higher level of biomolecular cross talk based on feeding style (Praveen *et al.*, 2015).

## .Conclusion

Although breastfeeding is the best mode of feeding for infants, if exclusive breastfeeding is not feasible, breast milk substitute must be considered. Researchers are experimenting with diverse ingredient combinations to create formula milk in a variety of ways. The focus is increasingly changing toward the addition of useful bioactive substances that support immune system function, and cognitive function in addition to physical growth. Heat processing of infant formula deteriorates infant formula. Several non-thermal solutions have been applied at various phases of the infant formula production process to mitigate the negative effects of heat treatments on nutrient loss. A thorough comprehension of the physiological characteristics of infant formula throughout handling, storage, and transit needs to be assessed. As there is no clear correlation between formula feeding, the creation of gut microbiota, and its long-term health effects, more thorough and in-depth research in these areas is crucial.

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