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Impact of Altered Early Infant Gut Microbiota Following Breastfeeding and Delivery Mode on Allergic Diseases

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Abstract: The prevalence of allergic diseases among infants is increasing particularly in developed countries. Although, the exact reason is not clear yet, one of the most probable explanations is reducing microbial exposure during early life and consequent alteration of gut microbiota. Various factors including delivery mode, infant`s diet, environment and antibiotics administration by mothers are involved in microbial colonization of infant`s intestine. Since the content of infant`gut microbiota plays a critical role in the maturation and development of the immune system, it determines the risk of immune diseases. Different studies confirmed the important role of vaginal delivery, due to transferring of useful bacteria to the neonatal's intestine, and breastfeeding, owing to the presence of exosomes and different kind of mediators in the milk which modify the pattern of intestinal microflora. As a result, it was proposed that both factors have remarkable effects on reducing allergic diseases. Furthermore, the consumption of probiotic productions by the mother during and after pregnancy possibly induces beneficial impacts on attenuating the allergic diseases.

Keywords: Allergic diseases, breast milk, cesarean, delivery, exosome, probiotic.

INTRODUCTION

Allergy is defined as a kind of hypersensitivity reaction initiated by immunological mechanisms [1]. Allergic diseases, such as atopic asthma, allergic rhinitis, food allergy and eczema, are major public health problems all around the world. Besides, the frequency of allergic diseases is growing rapidly, particularly among children in the developed countries [2-4].

Allergic reactions typically are associated with imbalance of Th1/Th2 cells as majority of T-helper cells in allergic responses are Th2 cells [5]. However, mechanisms that increase the incidence of allergic diseases are not fully understood. Nevertheless, according to some studies, attenuation of microbial exposure (hygiene hypothesis) in early life is the most plausible cause of the enhancement in allergic diseases [2, 13, 14]. The infant's immune system is immature and biased towards Th2 cells. At birth, intestine is sterile, which soon later is colonized by micro-organisms and following consequent outgrowth of Th1 cells and balance of immune cells, the immune system get matured [6-12].

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The composition of the microflora varies throughout the GI tract. The gut microbiota is composed of anaerobic and aerobes bacteria, yeast and fungi [10, 15, 16]. It has been demonstrated that microbial exposure decline in childhood affects gut microbial colonization [5, 17]. Furthermore, several studies have shown that microflora may vary considerably from allergic infants to non-allergic infants. For example, the prevalence of *Bifidobacteria* was low in allergic infants whereas the counts of *Staphylococcus aureus*, *Colstridia* and *Enterobacteria* were higher in comparison with non–allergic infants [18]. Furthermore, various factors could affect gut microbial colonization and consequently impact on maturation of the immune system such as delivery mode, breast milk or formula, genetics, environment, probiotics, administration of antibiotics and mother's diet (Fig. **1**) [15,19, 20]. However, delivery mode and type of feeding are the most imperative elements for intestinal colonization in early life [21, 22]. Breastfeeding has a positive effect on gut microflora, including colonization raising of *Bifidobacteria* and reduction of *Clostridium difficile* incidence [23].

Herein, we focused on the effects of delivery mode (cesarean delivery or vaginal delivery) as well as breastfeeding on the pattern of intestinal microflora in infants and subsequent influences on the allergic diseases.

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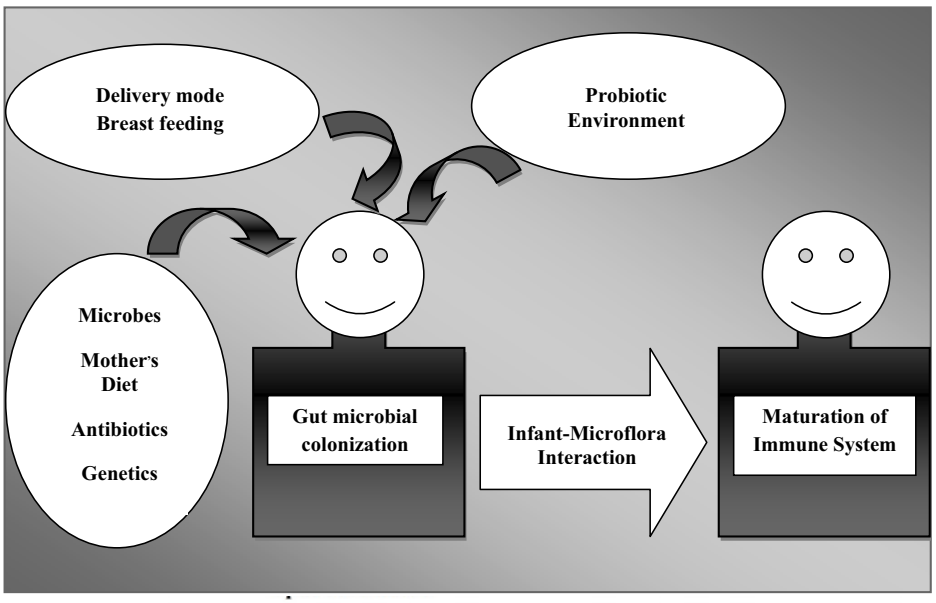

Fig. (1). Factors impact on infant gut microbial colonization such as delivery mode, breast milk or formula, genetics, environment, probiotics, use of antibiotics and mother's diet and consequent intraction infant-microflora impacts on maturation of the immune system.

Mechanism of Allergy

Allergy is extending responses to certain antigens in the host immune system [2, 24]. It is categorized to IgE-mediated allergy and non-IgE-mediated allergy [1]. The IgE-mediated allergic reactions, known by the production of IgE antibody, are often immediate hypersensitivity responses just minutes after repeated exposure to the allergen. After exposure to an allergen, Th2 cells and antigen-specific B cells are activated and IgE antibody is produced. On condition of the exposure to the same allergen, bound IgE on mast cells senses the allergen and trigger secretion of various mast cell-derived mediators, including vasoactive amines, lipid mediators, cytokines (Fig. **2**). Mast cells and IgE antibody play important roles in the pathogenesis of immediate hypersensitivity reactions [25, 26].

Most T-cells in allergic reactions are Th2 cells, which produce IL-4, IL-5, IL-9 and IL-13. IL-4 and IL-13 induce switching B cells to generate IgE. IL-5 promotes proliferating and activating of eosinophils whereas IL-9 is involved in differentiating and growing of mast cells [27-29].

Non-IgE mediated allergic reactions are often late-phase responses that appear 2-24 hours after repeated exposure to an allergen. This reaction occurs owing to the migration of other kinds of leukocytes including neutrophils, lymphocytes (Th1), eosinophils and macrophages to the first site that the allergen has been entered [30-32].

Activation of allergen–specific Th2 cells in IgE-mediated allergic reactions and the polarization and activation of allergen–specific Th1 cells in non-IgE mediated allergic reactions cause tissue damage [25, 26, 31, 32]. Besides, regulatory T-cells, including Th3 cells, T-regulatory type 1 (Tr1) cells, CD4+CD25+ cells, CD8+ -suppressor T-cells and γδ T-cells may suppress the development of allergic reactions [28, 33].

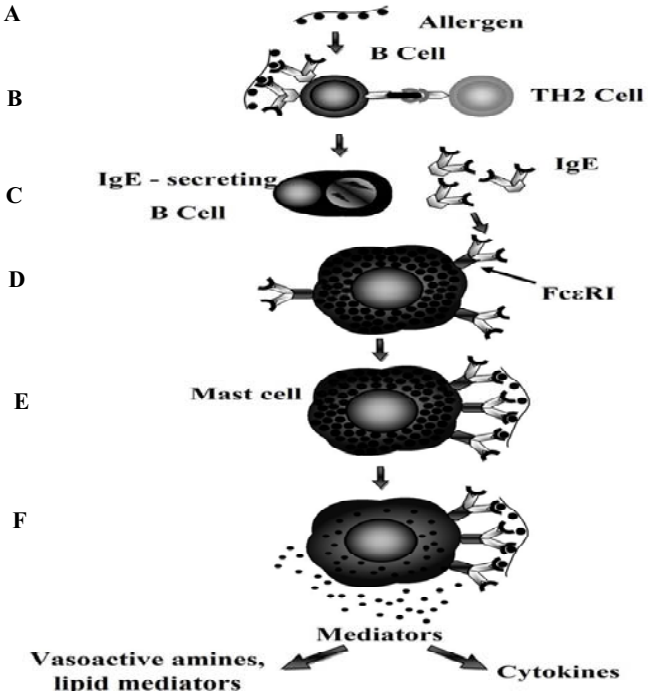

Fig. (2). Mechanism of IgE-mediated allergic reactions. **A**-First exposure to allergen, **B**-Activation of Th2 cells and stimulation of IgE class switching in B cells **C**-Production of IgE, **D-**Binding of IgE to FcεRI on mast cells, **E-** Repeated exposure to allergen, **F-** Activation of mast cell: release of mediators.

Th3 cells mainly secrete transforming growth-factor beta (TGF-β) and variable amounts of IL-4 and IL-10. IL-10 and TGF-β associate with the induction of oral tolerance while Tr1 cells produce high levels of IL-10, which down-

regulates allergen-specific Th1 and Th2 responses [34, 35]. Several studies illustrated that CD4+CD25+ cells chiefly express transcription factor Foxp3 and exert their suppressive effect *via* negative regulation of T-cell activation and secretion of the immune-suppressive cytokines TGF-β and IL-10 [36-38].

Intestinal Microflora

The gastrointestinal tract of a fetus is sterile and microbial colonization is taken place immediately after birth. The intestinal microflora is a complex environment comprised of around 500 - 1000 microbial species, mostly bacteria [15]. *Streptococcus*, *Lactobacillus*, *Veillonella*, *Bacteroides*, *Bifidobacterium*, *Enterobacteriaceae*, *Clostridium*, *Eubacterium*, *Ruminococcus*, *Coprococcus, Staphylococcus* and yeasts constitute the majority of the intestinal microflora [39, 40]. The most common species in the infant's intestine such as *Bifidobacteria* are acquired only from a human source. In addition, *Lactobacilli* located in the birth canal has been characterized as the earliest source of this species for intestinal colonization [41]. Colonization as well as development of the neonatal intestine microflora are extremely correlated with the maturation of the immune system, protection against pathogenic microorganisms, digestion, fermentation of nutritional fibers and intestinal epithelial cell growth and differentiation [29, 42, 43]. As an example, interaction of Toll like receptors (TLRs) with colonized microbes generate a tolerance to antigens of resident microbes and consequently developed the immune system [44]. In the following section, the mechanism of immune system maturation is explained in more details.

Microflora and Immune System Maturation

The neonatal immune system is a deficient system with a tendency to the Th2 cell response [20]. Also, T cells, B cells, granulocytes and complement system function immaturely and level of cytokines and antibodies is low in newborns [45]. After microbial colonization in the intestine, the immune system promotes gradually. Besides, gut microflora have a steady and dynamic effect on the maturation of gut mucosal and systemic immune system [46].

The mucosal immune system in the gastrointestinal tract consists of the gut-associated lymphoid tissues (GALT) spread throughout the gastrointestinal tract. GALT is comprised of Peyer's patches, solitary lymph follicles, mesenteric lymph nodes (MLNs), lymphocytes in the lamina propria and intestinal epithelium (intraepithelial lymphocytes) [47]. It has been demonstrated that lymphoid follicles located in the small intestine do not evolve in the germ-free mice which confirmed the necessity of an appropriate colonization of gut microflora for the desirable role of GALT [48, 49].

Microflora of the gastrointestinal tract are constantly in contact with epithelial cells and can be recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-like receptors (RLRs) expressed on thr intestinal epithelial cells and innate immune cells (dendritic cells) [50-52]. TLRs are the most important receptors which have different specific types of binding sites for the microbe-associated molecular patterns (MAMPs). Interaction between TLRs and pathogen-associated molecular patterns (PAMP) triggers the induction of TLRs signaling pathway. This pathway is divided to MyD88-dependent pathway commonly stimulated by all TLRs, and MyD88-independent pathway which is specific for the TLR3 and TLR4 signaling pathways [53, 54]. The TLR-MyD88 signaling pathway leads to several responses that are necessary for homeostasis maintenance of intestinal epithelial, repairing damaged epithelium, determining the nature of the immune response and preventing Th2-type allergic responses [29, 55]. Morover, TLR signaling is a mechanism for dendritic cells to swallow bacteria, form the pseudopod between epithelial cells, migrate to the mesenteric lymph node and thereupon activate B cells and T cells (Fig. **3**) [53]. Activated B cells are converted into plasma cells with the ability of IgA secretion. IgA transcytoses across the epithelium and binds to the luminal bacteria and subsequently prevents microbial translocation across the epithelial barrier [56].

Furthermore, dendritic cells act as an inhibitor, regulator and stimulator of T cell subsets (Th1, Th2, Treg). T cells come back to the mucosal sites through the lymphatic vein and the bloodstream [57, 58]. Another function of dendritic cells is the maintenance of tolerance towards the commensal microflora which may be due to the differentiation of Treg cells from naive T cells [59]. Additionally, it was shown that gut microflora influences on the development, function and number of various immune cells, including Th17, regulatory T cells, invariant natural killer T (iNKT) cells and innate lymphoid cells (ILCs) [60, 61].

Role of Pregnancy in the Immune Maturation

During the prenatal period, the fetus has a limited association with the extrauterian environment. As a result, microbial exposure in pregnancy is provided only by the mother and occurred through the placenta, spreading from the fallopian tubes and retrograding from the birth canal [62]. However, there is some evidence stated the positive effect of microbial exposures on the infant immunity. As an example, it was reported that the risk of developing eczema decreases in the infants born from farmer women, probably because of high encountering to animals and their microbial content [63]. Furthermore, it has been shown that contact of maternal mucosal to *Acinetobacter lwoffi*/F78 attenuated the risk of developing asthma [64]. Also, the alteration of TLR gene expression in both mentioned studies has been suggested as a cause of immune modulation. Moreover, DNA of bacteria such as *Lactobacillus* Spp. and *Bifidobacterium* Spp. which belongs to the gut bacteria has been isolated from placenta. These DNAs can alter the expression of genes involved in TLR-mediated innate immune system in the gut of the fetus [65]. Besides, broad-spectrum antibiotic administeration by a mother might lead to some changes in the gut microbial colonization in both the mother and her child [41].

Role of Mode of Delivery in the Immune Maturation

Mode of delivery plays an effective role in the colonization of the infant gut microflora [66]. During the pregnancy period, the fetus is fed through the placenta and

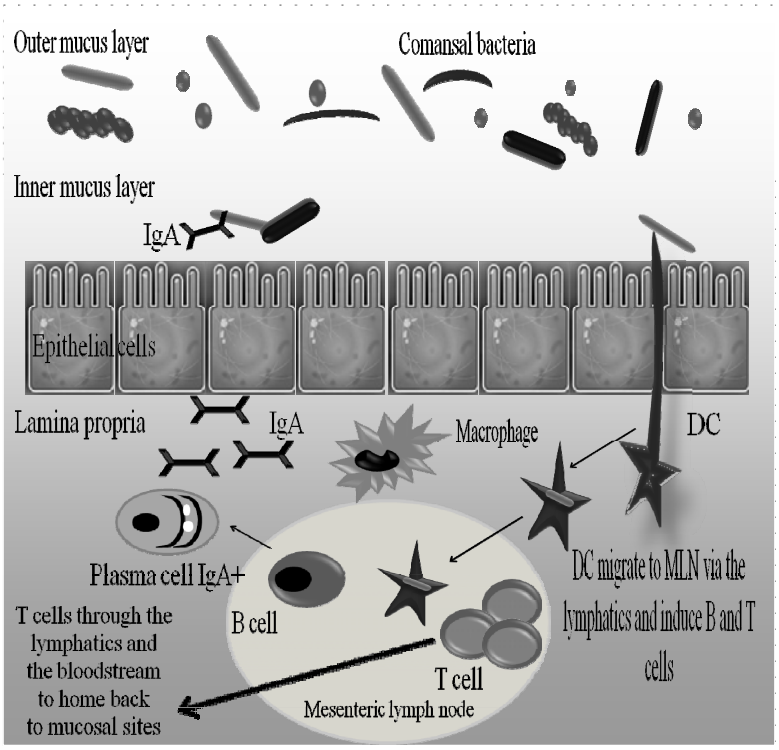

Fig. (3). Dendritic cells form the pseudopod between epithelial cells, swallow bacteria *via* TLR signaling, migrate to the mesenteric lymph node and induce B and T cells. Activated B cells are converted into plasma cells with the ability of IgA secretion. This IgA transcytoses across the epithelium and binds to the luminal bacteria and subsequently prevents microbial translocation across the epithelial barrier. T cells come back to mucosal sites through the lymphatics' vein and the bloodstream.

umbilical cord. Consequently, the gastrointestinal track is just exposed to amniotic fluid [41]. Throughout the vaginal delivery, the neonate encounters to several sources of bacteria *via* the physical contact with maternal vaginal and intestinal microbes [67]. Thus, diverse bacteria are colonized in newborn body and its immune response is developed during the first year of the child's life.

Today, Despite serious harmful implications, the rate of caesarean deliveries has dramatically increased during recent decades [66]. In caesarean delivery mode, microbial composition of infant's gut, is fewer compared to vaginal delivery mode [68]. Several studies have shown that infants born by cesarean section are less colonized with *Bacteroides*, *Bifidobacterium* and *Lactobacilli* species in contrast to infants born *via* vaginal delivery (Table **1**).

In addition, some studies demonestrated lower number of *Bifidobacteria* Spp. in the allergic infants, but higher counts of *Staphylococcus aureus, Colstridia* and *Enterobacteria* [71, 72]. Therefore, it could be suggested that the increaseing risk of allergic diseases in infants is related to caesarean

Table 1. Colonization Pattern in Infants Born *via* Cesarean Section and Vaginal Delivery

Study Type	Sample Size	Outcome	References
Clinical trial	165 consecutive children from allergic families	Infants delivered by caesarean section less colonized with *bifidobacteria* at an early age	[66]
Clinical trial	Goteborg (116 children) London (108 children) Rome (100 children) 3 centers (324 children)	Infants delivered by cesarean section were colonized later and less frequently by *Bifidobacterium* species, *Bacteroides* species. *E. coli* and *Clostridium* species were more prevalent	[19]
Clinical trial	1032 infants at 1 month of age	Infants born through cesarean section had lower numbers of *bifidobacteria* and *Bacteroides*	[69]
Clinical trial	46 infants: 23 infants delivered by caesarean section and 23 infants delivered by Vaginal delivery	Infants delivered by cesarean delivery is characterized by an absence of Bifidobacteria species	[22]
Clinical trial	64 infants: 30 infants delivered by caesarean section and 34 infants delivered by Vaginal delivery	Infants delivered by caesarean section was delayed colonized with *bifidobacteria* and *Lactobacillus* and less colonized with *Bacteroides* at 1 month of age	[70]

Table 2. Connection Between Mode of Delivery and Allergic Manifestations

Study Type	Sample Size	Outcome	References
Clinical trial	432 children with a parental history of atopy followed from birth to age 9 years.	Children born by cesarean section had 2-fold higher odds of atopy than those born by vaginal delivery	[73]
Cohort study	8953 children aged 3–10 years	Caesarean sections may be associated with an increase risk of developing allergic rhino conjunctivitis in childhood	[74]
Clinical trial	219 children 113 infants delivered by caesarean section and 106 infants delivered by Vaginal delivery	Caesarean section delivery may be associated with a high prevalence of atopic asthma	[75]
Clinical trial	865 healthy full term neonates with parental history of allergy	Caesarean delivery might be a risk factor for sensitization in infants with a family history of allergy	[76]
Clinical trial	3464 children born on or after 37 weeks of gestation with a birth weight of 2500 grams or greater	Caesarean section or processes associated with it may increase the risk for atopic disease in childhood	[77]
Clinical trial	Infants born in 1984-96 (N=863846)	Caesarean sections may be associated with an increased risk of developing allergic manifestations in children	[78]
Cohort study	87 500 Swedish sibling pairs born in Sweden from June 1993 to June 1999	An increase risk of asthma was shown in children born *via* Caesarean section	[79]
Meta-analysis	33 studies Sample sizes ranged from 131 to 863,233 participants (N=1206679)	A 20% increase in the subsequent risk of asthma was reported in caesarean children	[80]
Meta-analysis	26 studies (N=1308387)	Caesarean section delivery is associated with a moderately increased risk of allergic rhinitis, asthma, hospitalizations for asthma, and possibly food allergy in the offspring	[81]
Cohort study	1756700 children born between 1967 and 1998, followed up to age 18 years or the year 2002	A moderately increase risk of asthma in the children delivered by Caesarean section was observed	[82]
Cohort study	2917 children were followed for 8 years	Children born by caesarean section have a higher risk of asthma than those born by vaginal delivery, particularly children of allergic parents	[83]
Cohort study	6330 first-born and 5438 second-born twins from birth cohorts 1991–2000.	Twins born by caesarean section had a higher risk of developing asthma compared to twins born vaginal delivery. However, this difference was only observed for first born twins born at term	[84]
Cohort study	11147 mothers and their babies of which 7119 mother-child pairs	No evidence of being that delivered *via* caesarean section have an increase risk of asthma	[85]
Clinical trial	29238 children with a median Follow-up time of 2.9 years	No convincing evidence to suggest that babies born by caesarean had an increased risk of developing allergic disease	[86]
Clinical trial	279 Korean children aged ≤16 years	Delivery by cesarean section may not be associated with the subsequent development of asthma, allergic rhinitis, or atopic dermatitis in Korean children	[87]

section delivery. However, few observations conflicted with this assumption (Table **2**).

Role of Breastfeeding in the Immune Maturation

Human milk contains various components such as immunoglobulins, immune cells, oligosaccharides, lysosyme, exosomes, bacteria, fat and discrepant proteins [88-90]. The presence of immune mediators in breast milk makes it an immunoprotective agent against different kinds of diseases. Also, it generates long-term beneficial effect through modulating the composition of gut microbiota and immune responses, potentially [91]. As described above, breast milk consists of various bacteria which can be colonized in the infant's gut. Some of these bacteria are reviewed by Rautava and colleagues [41]. It is revealed that maternal peripheral blood mononuclear cells (PBMC) and cells in the breast milk contain bacteria and bacterial DNA. These cells are able to translocate to the local lymph node *via* intestinal epithelial barriers. Hence, the similarity between the quantity and quality of *Bifidobacteria* in breast milk and feace of both mother and her infant is explainable [92-94].

Recent studies have established the presence of exosomes in breast milk which may play a critical role in modulating immune responses in early lifetime [95]. Exosomes, endogenous 30-100 nm nanovesicles with a bilayared membrane, are released by all animal cells and include different proteins, lipids, mRNAs and miRNAs. These vesicles contribute in the cell-cell communication *via* transporting materials between the cells. The content of them is closely associated with the cell released from [96]. Admyre and colleagues reported the presence of exosomes in breast milk which contains CD63, HLA-DR, MUC-1, HSC70, MFG-E8, CD86, MHC I, II, lactadherin and tetraspanin proteins. Furthermore, it was found that colostrum contents are different from mature milk. For instance, the amount of HLA-DR is higher in the exosome of

colostrum. Besides, 500μg/ml of milk exosomes is able to decrease IL-2 and IFN-γ production of autologous and allogeneic PBMC *in vitro*. Moreover, they demonstrated the higher number of $CD4^{+}CD25^{+}FOXP3^{+}$ in PBMC exposed to milk exosomes than non exposed one. However, it is unclear which mechanism is involved in and further study is necessary [95].

Since the milk exosomes can tolerate the acidic pH of the gastric environment of newborns (mostly pH=5), they can cross from the gastrointestinal tract and release to the circulation. Kosak and colleagues illustrated that breast milk has several microRNAs which can endure harsh conditions including very acidic pH, freeze-thawing and RNAse treatment. They suggested that this stability is due to the packaging of these microRNAs in the structure such as exosomes. Moreover, they reported the presence of mir-181a and mir-17 in breast milk exosomes. These findings are consistent with results published before illustrating the exosomes derived from milk can justify the regulatory T cells population in newborns [97].

The presence of several RNAs in this type of exosomes has been showed by Lesser and colleagues. Exosome may be an important mediator between a mother and her child leading genetic alterations. Zhou and colleagues found that breast milk exosome was enriched from immune related microRNAs, mir-148a-3p, mir30b-5p, mir182p, mir200a-3p [98]. Accordingly, it is possible that exosomes are capable of developing tolerance toward immunological food allergy.

On the other side, indigestible oligosaccharides in breast milk involve in the growth and activity of commensal bacteria, especially *Bifidobacteria* Spp. [99]. Therefore, breastfeeding can result in the colonization of gut micrbiota enriching *Bifidobacteria* and *Lactobacillus* species. In addition, it has been reported that lower incidence of allergies in the breastfed infants correlates with higher levels of *Bifidobacteria* in comparison with those fed with formula [100]. *Bifidobacteria* and *Lactobacillus* are members of probiotic bacteria. Probiotic bacteria are defined as "live micro-organisms, which when administered in adequate amounts, confer a health benefit on the host" [101, 102]. Several clinical trials suggest that probiotic bacteria (*Bifidobacteria* and *Lactobacillus*) contribute to the prevention, reduction and treatment of allergic diseases [29, 103-105]. Consuming probiotics by the mother during the breastfeeding has beneficial effects on the maturation and modulation of the newborn's immune system. In a study performed by Rutava and colleges, it was observed that the administration of *L. rhamenosus GG* by a mother in a time of breastfeeding gave rise of TGF-β2, an immunomodulatory cytokine, and decrease the risk of infant atopic eczema [104]. This cytokine may contribute to immune tolerance and modify the inflammatory responses [106]. Based on confirming outcomes from various studies, breastfeeding may function as a bioactive tool to participate in immune modulation which prevent and reduce allergic reactions in infants (Table **3**).

CONCLUSION

It is revealed that the interaction between microbiota and immune cells in the infant`s intestine is necessary to maturate the immune system. The presence of some useful species such as *Bifidobacteria* and *Lactobacilli* in gut microflora composition results in generating the tolerance to some allergens. These bacteria, which exist in breast milk

Table 3. Connection Between Breastfeeding and Allergic Manifestations

Study Type	Sample Size	Outcome	Reference
Clinical trial	861 children: 480 children with short (<6 months) and 381 children with prolonged (≥6 months) breastfeeding duration	A protective effect of prolonged Breastfeeding in developing allergic disease, particularly hay fever, in children born from the non-allergic parents	[13]
Systematic review and meta-analysis	18 prospective studies: 4158 participants were included in these trials	Exclusive breastfeeding during the first 3 months of life is associated with lower incidence rates of atopic dermatitis during childhood in children with a family history of atopy	[107]
Clinical trial	1500 Qatari infants and pre-school children with an age range of 0-5 years were surveyed during the period from October 2006 to September 2007	The risk of allergic diseases, eczema, wheeze were lower in children with prolonged breastfeeding (>6 months) than in those with short-term breast feeding duration (<6 months)	[108]
Systematic review and meta-analysis	12 prospective studies: 8183 participants were included	Exclusive breastfeeding during the first months after birth is associated with lower asthma rates during childhood	[109]
Cohort study	8583 Tasmanian children born in 1961	Exclusively breastfed babies with a maternal history of atopy were less likely to develop asthma before the age of 7 years, but more likely to develop asthma after the age of 7 years	[110]
Systematic review	132 studies were selected, 56 were regarded as conclusive	Protective effect against development of allergic diseases, especially among children with an atopic heredity	[111]
Systematic review and meta-analysis of prospective cohort studies	21 articles were evaluated (34227 participants)	Find no significant protective effect of breastfeeding for children with a family history of atopy	[112]
Cluster randomized trial	17 046 mother-infant pairs were enrolled, of whom 13 889 (81.5%) were followed up at age 6.5 years	No protective effect of prolonged and exclusive breastfeeding on asthma or allergy	[113]

and the birth canal, transfer to newborns during vaginal delivery and breastfeeding. Furthermore, breast milk contains various immune modulating mediators being able to develope the immune response and its maturation. Moreover, the presence of immune related genetic materials in the breast milk exosomes directly adjusts the infant's immune system. Accordingly, it is concluded the vaginal delivery and breastfeeding play important roles in modifying the pattern of intestinal microflora and consequently they could possibly reduce the allergic diseases. Also, the consumption of probiotics during pregnancy and breastfeeding may be an efficient strategy to improve the infant`s health and helpful for reducing the rate of allergic diseases in the world.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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