Chapter

Probiotics in Allergic Diseases

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Abstract

Allergic diseases are the most common chronic diseases in children and no complete agreement on effective measures for primary prevention is available. Atopic family history is one of the most important risk factors for the development of asthma. A decline in microbial diversity due to modern lifestyle particularly in urban areas was proposed to have an important role in allergic epidemic. Recent studies are more focused on the specific mode of prevention such as probiotic usage in early pregnancy and infants period. It is well known that the composition of the gastrointestinal microbiota has been postulated to play a role in the development of allergies because it promotes potentially antiallergenic processes: TH1-type immunity, generation of TGF (which has an essential role in suppression of TH2-induced allergic inflammation and induction of oral tolerance), and IgA production, an essential component of mucosal immune defenses. Probiotic interventions administered during pregnancy and breastfeeding offer a unique opportunity to influence a range of important maternal and infant outcomes.

Keywords: allergy, atopic dermatitis, probiotics

1. Introduction

According to the epidemiological data, half of pediatric population will suffer from allergic diseases until the end of 2020. With that prevalence of more than 30%, they represent the most common disorders of children, adolescents, and adults [1]. A great increase of the prevalence of allergic diseases globally in the last 10 years are best described in a concept of "allergic epidemic" [2]. Germany multi-center allergy study is one of the most important epidemiological studies on allergic diseases, showing age related manifestation of allergic diseases, best described in "allergic march" concept. Allergies start in early infancy as an atopic dermatitis or food allergies, followed with the development of respiratory allergies such as allergic rhinitis and/or asthma [3]. Different from all other chronic diseases such as diabetes mellitus, hypertension, etc., allergic diseases manifest as it has been previously mentioned early in infancy, according to some authors even prenatal. It is well known that allergic diseases are multifactorial, so both environmental and genetic factors may play an important role in their pathogenesis. Identification of prenatal and early postnatal factors is of a great importance for early prevention and intervention [4–6]. Due to many phenotypes and genotypes as well as different patients' needs although a great availability of pharmacological options, treating allergies still represents a great challenge. Detection

of individual risk factors and identification of predictive markers are of a great importance in primary prevention, early intervention, and immune modulation of a natural course of allergic diseases [7]. It is well know that the development of immune system starts in 11 gestation week with the production of IgE antibodies. Detection of specific IgE antibodies on inhalatory and nutritive allergens is not possible in cord core blood. Except dry skin other clinical manifestation of allergies is not presented in infants. Atopic dermatitis will develop in the first year of life in a case of a great transdermal water loss between 2nd day of life and 2nd month of life. As we have already mentioned, both genetic and "in utero" environmental factors are responsible for allergy development. Uni or bilateral positive family history of allergies, diet habits, obesity, smoking, and drug use during pregnancy, season at time of birth as well as gestational age, the way of delivery are known to be an very important risk factors. Primary prevention and early intervention can prevent the development of atopic march. It includes treating skin with emollient creams, breast feeding in the first year of life, probiotics, and vitamin D during pregnancy and during the first year of life, early introduction of solid food as well as allergens [8]. Many hypotheses on causes of the increase in allergic diseases have been suggested. One of the most investigated hypotheses is "hygiene hypothesis", helping us to understand early-life events. It is well known that early exposure to common bacterial triggers such as endotoxins, LPS, or hemlines might have an allergy preventive effect.

The second worldwide accepted concept of reduced exposure (exposure to small amounts of foreign proteins) in exclusively breastfeeding children may rather lead to tolerance than to clinical allergic disease. Other routes of exposure via inhalation or via the skin cannot be totally avoided; interventional studies on avoidance/reduction of indoor allergen exposure (house dust mite and cat) have not shown convincing results. EAACI evidence-based recommendation for prevention of food and respiratory allergy prevention includes: no special diet during pregnancy or for the lactating mother, exclusively breastfeeding for 4–6 months, if needed hypoallergenic formula is recommended, avoids exposure to tobacco smoke, and avoids pets at home [9, 10].

2. The role of microbiome

All plants, animals, and humans live in close association with microbial organisms. The Human Microbiome Project has showed that the human body contains trillions of microorganisms which outnumber human cells by 10 to 1. Their genes encoded proteins essential for human survival. The role of microbes is of particular importance in gastrointestinal tract where they are involved in break down proteins, lipides, and carbohydrates in monomers suitable for absorption [11]. They are also involved in vitamin synthesis as well as in immuno modulation. Mice raised under germ free conditions have suffered from deficit in innate and adaptive immunity suggesting that the microbiome may play a crucial role in maturation of child immune system. Furthermore, experimental studies in germ free mice showed that those mice developed easily allergic diseases. Reconstruction of neonate mice with a conventional microbic protected the animals from allergic diseases.

The protective role of exposure to a wide diversity of microbial is best described in children raised on traditional farms [12]. Those children have a much lower prevalence of asthma, have fever, and allergic sensitization in comparison to children grown up in urban areas expect those who are exposed to environmental microbes (those who keep dogs indoors) [13].

Gut microbiota is one of the most investigated topics in the last couple of years. Human microbiota represent a community of commensal, symbiotic, and

pathogenic bacteria that live in and on human body with the widest and probably most important community in human gut.

3. History of probiotics

Several thousand years ago, ancient Roman scientist Gaius Plinius Secundus Maior recommended fermented milk to treat gastrointestinal problems. Benefits of probiotics contained in sour milk cream or yogurt are mentioned even in Holy Bible. In 1900, Moro isolated the first bacteria that produced lactic acid Bacillus acidophilus later called Lactobacillus acidophilus. Ilja Iljic Mecnikov was the first scientist who proved benefits of so-called good lactic acid produced bacteria particularly on gastrointestinal tract. In his hypothesis on autointoxication, he claimed that human body is intoxicated with toxins and pathogenic bacteria from food and he proposed consumption of lactic acid bacteria contained in Bulgarian yogurt in treating this disorder. The bacteria isolated from Bulgarian yogurt later became famous under name Lactobacillus delbrueckii strain, substring bulgaricus.

Henri Tiser from Pasteur Institute isolated Bifidobacterium bifidum from the feces of health breastfeeding infants and advised that bacteria for treating infants with diarrhea. Anri Boulardii French microbiologist discovered and isolated Saccharomyces boulardii that was used in South-eastern Asia for thousands of years for treating cholera [14]. Lactobacillus rhamnosus GG strain is one of the most investigated bacteria strain. IT was discovered by two scientists Sherwood Gorbach and Bari Goldin in 1983 [15]. Word probiotic comes from a Greek word pro+bios that means "for life" and it is used for the first time in 1953 when Kollath described organic and nonorganic food additives that are necessary for treating malnutrition. In 1965, Lilly and Still well described probiotics as substances that are produced by one microbe in order to stimulate the growth of another microbe contrary to the term antibiotics.

In 2001, World Health Organization (WAO) defined probiotics as live microbes that can have a positive effects on wellbeing if they use in a proper way and quantities.

In 2002, Food and Agriculture Organization and WHO published recommendation for probiotics in food [16]. In 2014, WHO reviewed probiotic definition in terms of needs for evidence base clinical efficacy of certain probiotics strains. Nowadays, worldwide accepted definition of probiotics is: probiotics are live microbes which benefits and positive effects on human health if they use in adequate quantities are proven in control clinical studies [17, 18]. Old concept of sterile "in utero" development has been abandoned. According to recent studies, colonization of fetal gut started in utero predominantly with maternal oral, vaginal, and gut microbiota. Neither placenta neither amniotic fluid is sterile; fetus received its first dose of probiotics with the ingestion of amniotic fluid [19, 20].

The most relevant prenatal factors for the formation of gut microbiota are maternal hygiene, particularly dental, diet, infectious, and antibiotics usage. Perinatal factors are also antibiotics during delivery, gestational age, the way of delivery, and medical staff in delivery room [21]. Post natal factors include: skin to skin contact, breast feeding, pets, baby bathing, as well as other environmental factors. To summarize all those maternal as well as placental factors have a key role in the development of a child gut microbiota. Moreover, the presence of pathogenic bacteria in amniotic fluid can induce a cascade of inflammatory response and prostaglandin synthesis that leads to the uterus contraction and preterm delivery. In utero infection particularly chorioamnionitis presents key risk factors for preterm delivery.

There is a substantial body of evidence supporting transplacental immune regulation during pregnancy. Maternal IgGs loaded with, for example, microbial

components from the mother cross the fetal-maternal barrier by an active process from 13 weeks gestation [22], conveying temporary passive immunity [23] and influencing fetal innate immune development [24]. In contrast, cellular components are generally separated by the placenta, with some leakage in both directions without preference toward a specific cell type [25]. This cellular leakage is functionally important, as maternal cells residing in fetal lymph nodes induce fetal regulatory T cells that suppress antimaternal immunity [26]. Transplacental immune regulation may be further mediated by cytokines and hormones [27], through bacterial products such as short-chain fatty acids or lipopolysaccharides (LPS) [28, 29].

Santner-Nanan et al. have demonstrated a strong correlation of peripheral blood Treg cells between the mother and the fetus [30]. In contrast, there was no significant Treg cell correlation between the father and the fetus, implicating that the specific context of pregnancy, that is, the placental environment, rather than haploidentical genetic parental similarity to the fetus, is responsible for this correlation. Maternal infant alignment in Treg cells appeared to be mediated by IL-10, a pleiotropic cytokine with potent immunoregulatory properties [31]. Treg cells are characterized by increased expression of the IL-10 receptor-α (IL-10RA), making them more sensitive to the effects of IL-10. The IL-10 regulates Bcl-2 expression in Treg cells, which could contribute to Treg cell survival in both the mother and the infant [32].

In the context of alignment between maternal and infant Treg, the evidence that has been studied suggesting an association between complicated pregnancy with preeclampsia and an increased risk of asthma, as well as allergic offspring sensitization [32]. A potential antecedent common to both mother and child is the mother's microbiome and its metabolic products, including short-chain fatty acids (SCFA).

Maternal IgG may play a key role in mediating the association between the maternal microbiome and fetal immune development. Of the five immunoglobulin classes, maternal IgG is the only antibody that significantly crosses the human placenta [22]. The active transport of IgG occurs via the neonatal Fc receptor (FcRn) within the syncytiotrophoblast (ST) cells at the surface of the chorionic villi of the placenta. Once bound to the FcRn receptor, IgG is packaged in endosomes and protected from degradation until it dissociates into the fetal circulation [33, 34].

This materno-fetal IgG transport is an important mechanism that confers passive humoral immunity to the fetus, so that after birth, the infant is protected against infections while its own immune system develops [22, 28]. Allergen-specific maternal IgG also plays a role in the induction of immune tolerance in infant [35]. Until recently, maternal IgG transfer during gestation had only been linked to fetal humoral immunity, but there is now good evidence that maternal IgG also plays a crucial in fetal innate immune development [24]. 61.1% of bacteria isolated in meconium of preterm infants (younger than 33 gestational weeks) are those that are also isolated from amniotic fluid, the majority of them belong to the three strains: Enterobacteria, Enterococcus, Lactobacillus, Photorhabdus, and Tanarella. Those bacteria are found to have a negative correlation with gestational age which suggests their important role in initiation of preterm delivery [36, 37].

4. Gestational age is a second important factor in the development of infant gut microbiota

Studies have been already proven that certain bacteria in amniotic fluid can provoke preterm labor. Preterm babies in comparison to term babies have more anaerobe bacteria. This fact can be described with several facts: preterm babies are at high risk of postnatal complications such as asphyxia, acute respiratory distress development, neonatal sepsis, necrotic enterocolitis, etc. In terms of that

they are prescribed more often both oxygen and antibiotics treatment that are together increase hospitalization days particularly in NICU – Neonatal Intensive Care Unit. Only three bacteria strains are found in preterm babies at 10 days of life: Enterobacteria (*E. coli* and *Klebsiella*), Enterococcus faecalis and *Staphylococcus aureus*, and haemolyticus. On the other side, colonization with bifidobacteria in preterm infants is postponed [38]. The way of delivery is the third factor for gut microbiota development. A great number of data suggested that cesarean section alongside with the intrapartal antibiotics usage is independent risk factors for gut disbiosis. During vaginal delivery, an infant become colonize with maternal vaginial bacteria. Grounlad and authors showed that even 6 months after delivery gut of infants born on caesarian section contain less bacteria of Bacteroides fragilis strains. Finland study has proven more bacteria of Clostridium strain in children born on vaginal way in comparison to those born via cesarean section. Lactobacillus, Prevotella, and Sneathia strains are predominant in gut microbiota of children born vaginal way, while on the other side, Staphylococcus, Corynebacterium and Propioni bacterium strains are dominant in another group of children born on caesarian session [39]. Postnatal prevention includes at the first place breast feeding followed with the onetime introduction of solid food and allergens. Breastfed children are proved to have predominantly bifidobacteria strains in their gut microbiota while infants fed with formulas had more bacterioides strains. It is well know that mothers milk contain special ingredients that can have immuno modulation effects on infants immune system. Rutava and authors showed that there is a special interaction between gut microbiota and transforming growth factor beta from human milk that are most potent antiinflammatory factor of a great importance also for maturation of intestinal tract as well as the production of IgA antibodies. According to this hypothesis bacteria from uterus have been actively transported in breast gland and secrete in human milk and in that way transfer immune tolerance to the infants. Moreover, it is proven that if mother use probiotics particularly Lactobacillus strain during breast feeding increase the number of bifidobacteria in gut of breast-fed infants [40].

Intestinal microbiology of early life has been best described in the first thousand days concept (PAI 2014). According to that hypothesis, the first thousand days of early life (230 days prenatal and 2 years postnatal) are crucial for establishing of symbiosis for the whole life. This is one of the most important mechanisms of evolution f as intestinal microbiota is in close relation with etiopathogenesis of allergic, autoimmune disease, and tumors [41].

5. Probiotic in prevention of atopic march

The development of allergic diseases is best described in a concept of atopic march. Allergies start in early infancy with atopic dermatitis, followed by IgE mediated food allergies and asthma development ended up with allergic rhinitis. As we have already mentioned early, intervention is crucial for interrupt atopic march and preventing allergies.

It is very well known for almost 20 years that *Lactobacillus rhamnosus* GG strain 1 × 106 cfu/g given to atopic pregnant women followed with 6 months of postnatal administration to infants can significantly prevent the development of atopic dermatitis at the age of 2 years. Furthermore, protective effects were long lasting for two more years. On the other side, significant increase of atopic dermatitis prevalence has been recorded in the control group in the follow up period [42]. Double blind, randomized, placebo control PandA study investigated the preventive effects of three strains combination Bifidobacterium

bifidum W23B (1 × 109 cfg/g), Bifidobacterium lactase W52 (1 × 109 cfu/g) and Lactococcus lactic W58 (1 × 109cfu/l). Administration of this combination to atopic mothers in the last 6 weeks of pregnancy and infants in the first year of life showed preventive effects in the first 3 months of life with the significant changes in intestinal microbiota and decrease in the level of IL-5 production [43]. Those results are in accordance with the results of Zhang meta-analysis who showed that prenatal and postnatal administration of probiotics may reduce the risk of atopic disease in families under risk of allergy and hypersensitivity reaction to food. According to those authors, administration of probiotics to infants born via cesarean section can even benefit more from probiotics [44]. Probiotics are also have positive impact on SCORAD reduction in placebo control study on 27 infants with atopic dermatitis who were breast-fed and received Bifidobacterium lactose Bb-12 1 × 109 cfu/g and Lactobacillus GG 3 × 108 cfu/g in comparison to place group [45]. Majamaa and collaborators showed significant improvement of atopic dermatitis and reduction in fetal concentration of antitripsin-1 and TNF as well as up regulation of Il-10 and down regulation of pro inflammatory cytokines and total IgE antibodies level in infants on hypoallergenic milk formulas who concomitantly received Lactobacillus rhamnosus GG 5 × 108 cfu/g in comparison to placebo group [46]. Pessi's study showed similar Il-10 level improvement in children allergic to cow milk proteins who received Lactobacillus rhamnosus GG 2 × 1010 cfu/g pro doses [47]. Those results are controversial in terms of asthma and wheezing prevention. Two meta-analysis of Elazab and coauthors and Azad and coauthors have failed to prove positive effects of probiotics administration in pregnancy and postnatal on the asthma and wheezing development. Recent meta-analysis of randomized control study of Wei and coauthors did not find enough results to support recommendation of probiotics for asthma prevention in infants [48]. In Filipovic and coauthors study, it is found that *Lactobacillus rhamnosus* GG (LGG) formulation with Zn and vitamin D3 supplementation during the postnatal period (in infancy and early childhood) reduce the severity of atopic dermatitis. Type of delivery, type of feeding breast-feeding versus adapted milk formulas were not found to be statistically associated with risk of atopic dermatitis [49]. According to European Academy for Allergy and Clinical Immunology, there is no official recommendation for probiotic treatment in patients with food allergy [50]. Overall probiotics are proven to have positive effects in primary prevention of allergies even prenatal. According to the results from several studies probiotics have both local and systemic effects. They act locally on the intestinal tract via promoting immune tolerance. Systemically, they act antiinflammatory reducing Th17 response and stimulating TLR and Th1 immune response [51, 52].

6. Conclusion

According to the epidemiological data, allergic diseases have been increasing in the last decades, despite a great variety of effective treatment available. Standard pharmacological treatment of allergies is only symptomatic without the capability to change the natural course of allergic disease. Immunotherapy is the only treatment with the immunomodulatory effects. The second option is probiotics that are not only capable to prevent atopic march but also to prevent the development of allergic disease prenatal. Despite a great number of placebo control randomized studies and meta-analysis, we are still looking for the best probiotic and adequate dose for each level of intervention: prenatal, early postnatal as well as for different manifestation of allergic diseases (atopic dermatitis, food allergies, asthma, and allergic rhinitis).

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References

[1] Matricardi PM. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Controversial aspects of the 'hygiene hypothesis'. Clinical and Experimental Immunology. 2010;**160**(1):98-105

[2] Prescott S, Allen KJ. Food allergy: Riding the second wave of the allergy epidemic. Pediatric Allergy and Immunology. 2011;**22**(2):155-160. DOI: 10.1111/j.1399-3038.2011.01145.x

[3] Bergmann RL, Bergmann KE, Lau-Schadensdorf S, Luck W, Dannemann A, Bauer CP, et al. Atopic diseases in infancy. The German multicenter atopy study (MAS-90). Pediatric Allergy and Immunology. 1994;**5**:19-25

[4] Holguin F. The atopic march: IgE is not the only road. The Lancet Respiratory Medicine. 2014;**2**:88-90

[5] Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatric Allergy and Immunology. 2015;**26**:431-437

[6] Grabenhenrich LB, Gough H, Reich A, Eckers N, Zepp F, Nitsche O, et al. Early-lifedeterminants of asthma from birth to age 20 years: A German birth cohort study. The Journal of Allergy and Clinical Immunology. 2014;**33**:979-988

[7] Caminati M, Duric-Filipovic I, Arasi S, Peroni DG, Zivkovic Z, Senna G. Respiratory allergies in childhood: Recent advances and future challenges. Pediatric Allergy and Immunology. December 2015;**26**(8): 702-710. DOI: 10.1111/pai.12509

[8] Hayward AR. The human fetus and newborn: Development of the immune response. Birth Defects Original Article Series. 1983;**19**(3):289-294

[9] Halken S. Prevention of allergic disease in childhood: Clinical and epidemiological aspects of primary and secondary allergy prevention. Pediatric Allergy and Immunology. 2004;**15**(Suppl 16):9-32

[10] Illi S, Weber J, Zutavern A, et al. Perinatal influences on the development of asthma and atopy in childhood. Annals of Allergy, Asthma & Immunology. February 2014;**112**(2):132-139

[11] Herbst T, Sichelstiel A, Schär C, Yadava K, Bürki K, Cahenzli J, et al. Dysregulation of allergic airway inflammation in the absence of microbial colonization. American Journal of Respiratory and Critical Care Medicine. 2011;**184**(2):198-205

[12] von Mutius E, Vercelli D. Farm living: Effects on childhood asthma and allergy. Nature Reviews. Immunology. 2010;**10**(12):861-868

[13] Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al. Exposure to environmental microorganisms and childhood asthma. The New England Journal of Medicine. 2011

[14] Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics--approaching a definition. The American Journal of Clinical Nutrition. 2001;**73** (2 Suppl):361S-364S. DOI: 10.1093/ajcn/73.2.361s

[15] Conway PL, Gorbach SL, Goldin BR. Survival of lactic acid bacteria in the human stomach and adhesion to intestinal cells. Journal of Dairy Science. 1987;**70**(1):1-12

[16] Živković Z, Filipović I, Filipović Đ. Probiotics for acute gastroenteritis – pediatrician's thinking and decision. Preventive Pediatric. 2020;**6**(1-2):9-11

[17] Guidelines for the Evaluation of Probiotics in Food. Available from: www.who.int/foodsafty/fs_managment/en/probiotic_guidelines.pdf [Accessed: April 2020]

[18] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The international scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews. Gastroenterology & Hepatology. 2014;**11**(8):506-514. DOI: 10.1038/nrgastro.2014.66

[19] Perez-Muñoz ME, Arrieta MC, Ramer-Tait AE, Walter J. A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: Implications for research on the pioneer infant microbiome. Microbiome. 2017;**5**(1):48. DOI: 10.1186/s40168-017-0268-4

[20] Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Science Translational Medicine. 2014;**6**(237):237-265. DOI: 10.1126/scitranslmed.3008599

[21] Teshome A, Yitayeh A. Relationship between periodontal disease and preterm low birth weight: Systematic review. The Pan African Medical Journal. 2016;**24**:215

[22] Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. Clinical & Developmental Immunology. Hindawi Publishing Corporation Clinical and Developmental Immunology. Vol. 2012. 2012. Article ID 98564. p. 13. DOI: 10.1155/2012/985646

[23] Firan M, Bawdon R, Radu C, et al. The MHC class I-related receptor, FcRn, plays an essential role in the maternofetal transfer of gamma-globulin in humans. International Immunology. 2001;**13**:993-1002

[24] Gomez de Agüero M, Ganal-Vonarburg SC, Fuhrer T, et al. The maternal microbiota drives early postnatal innate immune development. Science. 2016;**351**:1296-1302

[25] Loubière LS, Lambert NC, Flinn LJ, et al. Maternal microchimerism in healthy adults in lymphocytes, monocyte/macrophages and NK cells. Laboratory Investigation. 2006;**86**:1185-1192

[26] Mold JE, Michaëlsson J, Burt TD, et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science. 2008;**322**:1562-1565

[27] Lacković M, Mihajlović S, Bakić T, Marina L, Stefan Šojat A, Ilić M, et al. Imunski sistem u trudnoći. Preventive Pediatric. 2020;**6**(1-2):37-40

[28] Thorburn AN, McKenzie CI, Shen S, et al. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. Nature Communications. 2015;**6**:7320

[29] Voltolini C, Battersby S, Etherington SL, et al. A novel antiinflammatory role for the short-chain fatty acids in human labor. Endocrinology. 2012;**153**:395-403

[30] Conrad ML, Ferstl R, Teich R, et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe Acinetobacter lwoffii F78. The Journal of Experimental Medicine. 2009;**206**:2869-2877

[31] Santner-Nanan B, Straubinger K, Hsu P, et al. Fetal-maternal alignment of regulatory T cells correlates with IL-10 and Bcl-2 upregulation in pregnancy. Journal of Immunology. 2013;**191**:145-153

[32] Mosser DM, Zhang X. Interleukin-10: New perspectives on an

old cytokine. Immunological Reviews. 2008;**226**:205-218

[33] Kumpel BM, Manoussaka MS. Placental immunology and maternal alloimmune responses. Vox Sanguinis. 2012;**102**:2-12

[34] Schneider H, Miller RK. Receptor-mediated uptake and transport of macromolecules in the human placenta. The International Journal of Developmental Biology. 2010;**54**:367-375

[35] Shreiner A, Huffnagle GB, Noverr MC. The "microflora hypothesis" of allergic disease. Advances in Experimental Medicine and Biology. 2008;**635**:113-134

[36] Ardissone AN, de la Cruz DM, Davis-Richardson AG, et al. Meconium microbiome analysis identifies bacteria correlated with premature birth. PLoS One. 2014;**9**(3):e90784

[37] Magne F, Suau A, Pochart P, Desleux JF. Fecal microbial community in preterm infants. Journal of Pediatric Gastroenterology and Nutrition. 2005;**41**:386-392

[38] Arboleya S, Sánchez B, Solís G, et al. Impact of prematurity and perinatal antibiotics on the developing intestinal microbiota: A functional inference study. International Journal of Molecular Sciences. 2016;**17**(5):649

[39] Grönlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: Permanent changes in intestinal flora after cesarean delivery. Journal of Pediatric Gastroenterology and Nutrition. 1999;**28**(1):19-25

[40] Rautava S, Luoto R, Salminen S, Isolauri E. Microbial contact during pregnancy, intestinal colonization and human disease. Nature Reviews. Gastroenterology & Hepatology. 2012;**9**(10):565-576

[41] Wopereis H, Oozeer R, Knipping K, Belzer C, Knol J. The first thousand days - intestinal microbiology of early life: Establishing a symbiosis. Pediatric Allergy and Immunology. 2014;**25**(5):428-438. DOI: 10.1111/pai.12232

[42] Kalliomaki M, Salminen S, Arvilommi H, Pentti K, Pertti K, Isolauri E. Probiotics in primary prevention of atopic disease: A randomised placebo- controlled trial. Lancet. 2001;**357**:1076-1079

[43] Niers L, Martín R, Rijkers G, Sengers F, Timmerman H, van Uden N, et al. The effects of selected probiotic strains on the development of eczema (the PandA study). Allergy. 2009;**64**(9):1349-1358

[44] Zhang G-Q, Hu H-J, Liu C-Y, Zhang Q, Shakya S, Le Z-Y. Probiotics for prevention of atopy and food hypersensitivity in early childhood. Medicine. 2016;**95**(8):e2562

[45] Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clinical and Experimental Allergy. 2000;**30**:1604-1610

[46] Majamaa H, Isolauri E. Probiotics: A novel approach in the management of food allergy. The Journal of Allergy and Clinical Immunology. 1997;**99**:179-185

[47] Pessi T, Sutas Y, Hurme M, Isolauri E. Interleu-kin-10 generation in atopic children following oral Lactobacillus rhamnosus GG. Clinical and Experimental Allergy. 2000;**30**:1804-1808

[48] Azad MB, Coney JG, Kozyrskyj AL, Field CJ, Ramsey CD, Backer AB, et al. Probiotic supplementation during

pregnancy or infancy for the prevention of asthma and wheeze: Systematic review and meta-analysis. BMJ. 2013;**347**:f6471

[49] Filipovic I, Ostojic O, Vekovic V, Lackovic M, Zivkovic Z. Combination of Lactobacillus Rhamnosus LGG, vitamin D3 and Zn in preventing atopic dermatitis in infancy. American Journal of Pediatrics. 2020;**6**(3):280-284. DOI: 10.11648/j.ajp.20200603.26

[50] Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy. 2014;**69**(5):590-601

[51] Ozdemir O. Various effects of different probiotic strains in allergic disorders: An update from laboratory and clinical data. Clinical and Experimental Immunology. 2010;**160**(3):295-304

[52] Özdemir Ö. Any benefits of probiotics in allergic disorders? Allergy and Asthma Proceedings. 2009;**31**:103-111