The Journal of Nutrition
Critical Review

Can Nutritional Modulation of Maternal Intestinal Microbiota Influence the Development of the Infant Gastrointestinal Tract?[1,2]

Caroline Thum,[3,4] Adrian L. Cookson,[4,5] Don E. Otter,[3] Warren C. McNabb,[4,6] Alison J. Hodgkinson,[7] Jolon Dyer,[4,8] and Nicole C. Roy[3,4]*

[3]Food Nutrition and Health Team, Food and Bio-based Products Group, AgResearch Grasslands, Palmerston North, New Zealand; [4]Riddet Institute, Massey University, Palmerston North, New Zealand; [5]Rumen Microbiology Team, Animal Nutrition and Health Group, AgResearch Grasslands, Palmerston North, New Zealand; [6]AgResearch Grasslands, Palmerston North, New Zealand; [7]Dairy Foods Team, Food and Bio-based Products Group, AgResearch Ruakura, Hamilton, New Zealand; and [8]Food and Bio-based Products Group, AgResearch Lincoln, Christchurch, New Zealand

Abstract

The gastrointestinal microbiota plays an important role in maintaining host health by preventing the colonization of pathogens, fermenting dietary compounds, and maintaining normal mucosal immunity. Particularly in early life, the composition of the microbiota profoundly influences the development and maturation of the gastrointestinal tract (GIT) mucosa, which may affect health in later life. Therefore, strategies to manipulate the microbiota during infancy may prevent the development of some diseases later in adult life. Earlier research suggested that term fetuses are sterile and that the initial bacterial colonization of the newborn GIT occurs only after the baby transits through the birth canal. However, recent studies have demonstrated that the colonization and/or contact of the fetus with the maternal GIT microbiota may start in utero. After vaginal birth, the colonization of the neonate GIT continues through contact with maternal feces and vaginal bacteria, leading to a relatively simple microbial community that is influenced by feeding type (breast vs. formula feeding). Maternal GIT microbiota, vaginal microbiota, and breast milk composition are influenced by maternal diet. Alterations of the maternal GIT microbiota composition via supplementation with probiotics and prebiotics have been shown; however, transfer of these benefits to the offspring remains to be demonstrated. This review focuses on the influence of maternal GIT microbiota during the pre- and postpartum periods on the colonization of the infant GIT. In particular, it examines the manipulation of the maternal GIT microbiota composition through the use of probiotics and/or prebiotics and subsequent consequences for the health of the offspring. J. Nutr. 142: 1921–1928, 2012.

Introduction

During pregnancy and lactation, the mother needs a diet that provides adequate energy and nutrients to support her metabolism, growth and development of the fetus, and subsequent milk production. Nutritional imbalances or malnutrition during pregnancy are important factors responsible for miscarriage and fetal developmental problems (1). Studies with iron and folic acid supplementation of the mother's diet, e.g., have shown measurable benefits to the offspring such as decreased incidences of neural tube defects and early neonatal death (2,3). More recently, probiotic and prebiotic supplements that improve maternal gastrointestinal tract (GIT)[9] microbiota composition and function have been reported to beneficially affect the development and maturation of the neonatal GIT (4,5). An improved maternal microbiota is likely to provide the beneficial microbes for either direct colonization of the neonatal GIT or for indirect effect on the succession of indigenous intestinal bacteria.

The commensal microbiota of the GIT has important functions for the human host, including development of the immune system (6,7), protection against pathogens (8) and carcinogens (9), nutrient processing (10), stimulation of angiogenesis (11), and regulation of host fat storage (12). Early colonization of the infant GIT is undoubtedly an important factor for infant health and may have additional health benefits in later life. The initial develop-

[1] Supported by Ministry of Science and Innovation, New Zealand (C10X0907). PhD Scholarship is funded by AgResearch.
[2] Author disclosures: C. Thum, A. L. Cookson, D. E. Otter, W. C. McNabb, A. J. Hodgkinson, J. Dyer, and N. C. Roy, no conflict of interests.
* To whom correspondence should be addressed. E-mail: nicole.roy@agresearch.co.nz.

[9] Abbreviations used: GIT, gastrointestinal tract; GOS, galacto-oligosaccharide; Hib, *Haemophilus influenza* type b; HMO, human milk oligosaccharide; LGG, *Lactobacillus GG*.

Manuscript received June 26, 2012. Initial review completed July 6, 2012. Revision accepted August 20, 2012.
First published online September 18, 2012; doi:10.3945/jn.112.166231.

ment and maturation of the fetal/neonatal GIT is under partial control of the maternal environment mediated by 4 main routes: *1*) trans-placental transfer of maternal blood factors to the fetus; *2*) fetal ingestion of amniotic fluid in utero; *3*) microbial colonization of the neonatal GIT by maternal microbiota in the perinatal period; and *4*) maternal milk factors (13). Consequently, the transition between pre- and postnatal life is likely to be a critical window for maternal dietary intervention, thus ensuring normal development of the infant GIT with potential long-term effects on health in adult life.

This review discusses the factors and mechanisms that contribute to the development of the infant GIT and explores the potential that maternal dietary supplementation may play in enhancing the microbiota and mucosal interactions in her GIT, thus offering health benefits to the infant.

Microbiota Colonization of the GIT

Prepartum. Historically, the human fetus has been considered microbiologically sterile, with the first microbial exposure taking place at vaginal birth through contact of the newborn with the maternal vaginal and GIT microbiota and the surrounding environment (14). However, in the last decade, discoveries point to pregnancy as the beginning of bacterial exposure for the developing fetus (15–17). Bacteria from the maternal GIT and/or urogenital region, such as *Enterococcus* species and *Lactobacillus* species, have been isolated and/or detected in umbilical cord blood (17), amniotic fluid (18), meconium (16), and placental (15) and fetal membranes (15,19,20) without any clinical evidence of infection or inflammation in the mother-infant pair. Such findings suggest that term fetuses are not sterile and that a mother-to-fetus efflux of commensal bacteria through the placental barrier may occur. The microbial prevalence in the amniotic fluid and fetal membranes has not been well characterized; however, an association between inflammation leading to preterm birth and altered maternal GIT and genital microbiota have been suggested (21). Therefore, the maternal microbiota, which translocates to the amniotic fluid, is likely to stimulate an inflammatory response or the development of GIT mucosal immune system of the fetus (22).

The low levels of bacteria detected in umbilical cord blood, amniotic fluid, placenta, and fetal membranes suggest that rather than colonize the fetal GIT, their presence may be to prepare the fetal immune system for life outside the uterus. In support of this, microbial RNA and unmethylated DNA CpG islands were shown to exert immune regulatory effects in adult germfree mice (23,24). The absence of adverse neonatal immune responses after microbial exposure in the birth canal supports the existence of complex regulatory mechanisms that are likely to commence during fetal development (25). Therefore, bacteria or their components present in the fetal membranes during pregnancy may contribute to immunological stimulatory and protective or depletory effects for the neonate and may be closely associated with maternal GIT and/or urogenital microbiota (26).

Partum and postpartum. During vaginal delivery, contact with maternal vaginal and intestinal microbiota is an important source of microbiota for colonization of the infant GIT. During cesarean delivery, however, this direct contact is absent and nonmaternally derived environmental and potentially pathogenic bacteria are likely to colonize the infant GIT. The causal relationship among cesarean delivery, the shift in microbiota, and many childhood diseases was recently reviewed by Neu et al. (27). After delivery, the microbiota changes rapidly, presumably influenced by diet. Human milk provides nutrients and nonnutritive components (e.g., Ig, lactoferrin, lysozyme, and oligosaccharides) to the offspring that facilitate the adaptive, functional changes required for optimal transition from intrauterine to extrauterine life (28,29). It also stimulates the immune system, encourages cognitive development, protects from toxins and pathogenic diseases, and colonizes and supports a protective microbiota in the infant GIT (30).

Human milk is a rich and natural source of carbohydrate oligosaccharide polymers that act as a prebiotic. Human milk oligosaccharides (HMO) are capable of improving intestinal microbiota diversity, which, in turn, increases the microbiota metabolism rate, protects the neonate against pathogenic bacteria, and most likely increases the absorption of minerals (31,32). They have also been shown to improve glucose homeostasis (33) and develop the neonatal immune system (34). Of the various components in human milk, oligosaccharides comprise a considerable fraction (5–23 g/L), being the third-most abundant constituent in terms of concentration after lactose and lipids (35). Infants cannot digest HMO, which remain intact until they reach the large intestine; however, although having no apparent direct nutritional role, HMO are involved in promoting the colonization and subsequent signaling between commensal bacteria and their host. These interactions play pivotal roles in the development of the mucosal immune system and prevention of disease (36). HMO are growth-promoting factors for the bifidobacteria-dominated microbiota present in the large intestine of breast-fed infants (37). In addition, HMO facilitate establishment of the microbiota, which is required to activate the mucosal immune system (38) and actively protect the infant from pathogenic infection (39). Therefore, lactation could be considered the second step of "immunological education."

An emerging feature of the structural analysis of HMO is their diversity and specificity among women. Approximately 200 molecular structures differing in size, charge, and sequence have been identified in human milk samples (40). Maternal HMO vary qualitatively and quantitatively with regards to lactation period, maternal Lewis Blood Group, and Secretor status (41). However, diet, lifestyle, ethnicity, and other factors may also contribute to structural variations of HMO. The complexity of the carbohydrate repertoire in breast milk may influence the level of protection transferred to the offspring. It is likely that infants raised in particular environments, or during specific growth stages or physiological states, take advantage of selective variations in the amounts and structural differences of oligosaccharides. For example, it has been shown that oligosaccharides from individuals with Lewis blood group B exhibit preferential binding to pathogens, especially *Helicobacter pylori* (42), and children with Lewis blood group A have increased susceptibility to enterotoxigenic *Escherichia coli* diarrhea (43).

Another minor component of breast milk is bacteria. Culture-dependent methods have long confirmed the presence of bacteria, including *Staphylococcus*, *Streptococcus*, and *Bifidobacterium* species, in aseptically collected human milk (44,45), whereas culture-independent studies utilizing characterization techniques based on the amplification of bacterial 16S rRNA have shown that human milk contains several additional bacterial genera, including *Lactobacillus* and *Enterococcus* species (45–47). Pyrosequencing of 16S rRNA genes in human milk has suggested a core microbiome consisting of 9 bacterial genera such as *Staphylococcus*, *Streptococcus*, *Serratia*, *Pseudomonas*, *Corynebacterium*, *Ralstonia*, *Propionibacterium*, *Sphingomonas*, *and Bradyrhizobiaceae* (48). Other studies using

cultivation and real-time qPCR have shown greater levels of complexity and individuality in the milk microbiota compared with the proposed core microbiome (13,45–47). A microbial composition similar to breast milk was also found in infant feces (49,50), supporting the concept of transfer of microbes from the mother's milk to the neonatal GIT. Exposure of breast-fed infants to the bacteria in milk may educate the infant immune system through the pattern recognition receptor CD14 and toll-like receptor (51) that recognize bacterial cell wall components. These receptors may induce analogous responses to maternal antigens and protect the neonate against pathogens (52,53).

Mechanisms of maternal microbiota transfer during pregnancy and breast feeding. Some studies indicate that the maternal GIT may be the origin of bacteria found in umbilical cord blood and amniotic fluid (17,54,55) as well as in human milk (56) (**Fig. 1**). For example, experiments with pregnant mice orally administered a labeled *Enterococcus faecium* strain showed a low level transfer of the labeled strain to the fetal intestine and a higher level transfer to the mammary glands (17). The mechanisms of maternal bacterial transfer to the fetus and milk are unclear. It has been proposed that maternal dendritic cells and leukocytes play an important role in the bacterial uptake into placenta and milk (52). Dendritic cells in the Peyer's patch can cross the paracellular space of the intestinal epithelium to take up bacteria directly from the intestinal lumen. Once internalized by dendritic cells and/or macrophages, bacteria can spread to other locations, such as those of the respiratory and genitourinary tract, salivary and lachrymal glands, and, most importantly, that of the lactating mammary gland, via lymphatic and blood circulation (56–58). Dendritic cells are relatively ineffective at killing internalized organisms (56,57) and may be responsible for viable bacteria reaching the mammary glands and placenta (52,56,59,60). Once in the blood circulation, maternal-derived bacteria may be transferred to the fetus via the paracellular pathway of the placental barrier (61). This is analogous to the transfer of extracellular pathogens shown to occur across the blood-brain barrier (62), including *Streptococcus pneumoniae* and group B streptococci, bacteria closely related to the predominant species found in human milk. Beginning during prepartum and persisting throughout the postpartum period, the maternal immune system shifts from cell-mediated immunity (63) toward one characterized by humoral immunity (64). This altered maternal immunological state may increase the translocation of bacteria and their components from the maternal GIT into the blood and lymphatic circulation (56). Near term, thinning of the placental barrier increases nutrient, waste product, and gas exchange efficiency between mother and fetus (65) and possibly contributes to the influx of commensal bacteria present in the blood circulation. This influx may initiate the first adaptation of the fetal intestine for life outside the mother.

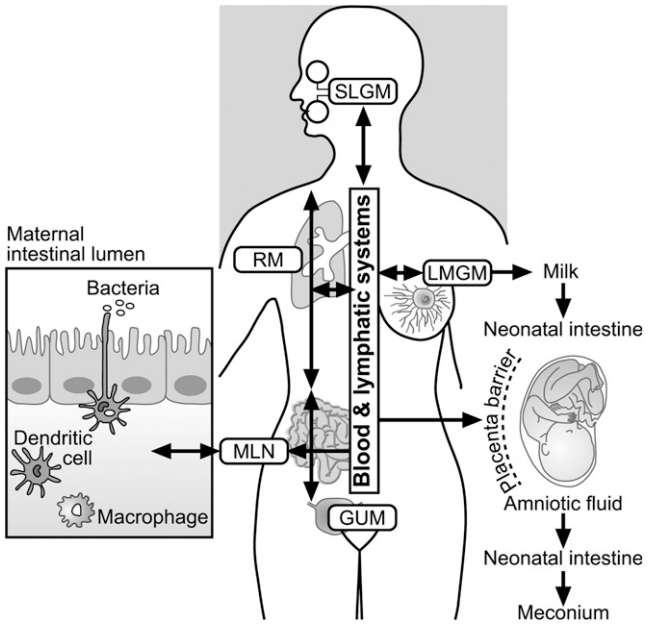

FIGURE 1 A hypothetical model to explain how maternal microbiota and microbial products could be transferred from mother to the fetal and neonatal GIT. Dendritic cells can cross the paracellular space of the intestinal epithelium to take up bacteria directly from the intestine lumen. Circulation of lymphocytes within the mucosal associated lymphoid tissue allows the maternal GIT microbiota to reach distant mucosal surfaces, including those found in the respiratory and genitourinary tracts, salivary and lachrymal glands, and lactating mammary gland. GIT, gastrointestinal tract; GUM, genitourinary tract mucosa; LMGM, mucosa of the lactating mammary gland; MLN, mesenteric lymph node; RM, respiratory tract mucosa; SLGM, mucosa of the salivary and lacrimal gland. The figure was adapted with permission from Martin et al. (13).

Maternal GIT, Microbiota, and Infant Health

Changes in maternal GIT microbiota composition have been associated with alterations to biochemical parameters in the maternal blood (e.g., increased folic acid and ferritin levels and reduced transferrin and cholesterol levels), with possible consequences for pregnancy progression, fetal programming, and, consequently, for newborn health (66,67). The presence of specifically *Actinomyces naeslundii* or Gram-negative anaerobes in the maternal oral cavity, e.g., has been associated with earlier delivery and lower birth weight, whereas the presence of lactobacilli has been linked to term delivery and heavier birth weight (54,67,68). Fak et al. (69) evaluated the effects of maternal GIT microbiota changes on offspring health by orally treating pregnant rats with live, nonpathogenic *E. coli* (strain CCUG 29300T) isolated from human urine (cystitis) before delivery or with broad-spectrum antibiotics before delivery and during lactation (69). Compared with the offspring from untreated mothers, offspring from dams of both treatments had higher concentrations of *Enterobacteriaceae*, which correlated with decreased stomach growth and function, lower total pancreatic protein levels, higher small intestine permeability, and increased plasma levels of the acute-phase protein haptoglobin (69). These findings suggest that specific components of the maternal GIT microbiota or maternal treatment with broad-spectrum antibiotics may influence the diversity of the offspring GIT microbiota and the development and maturation of the offspring mucosal immune system (70, 71).

Studies have shown that many factors affecting the initiation and course of autoimmune diseases appear to act within a narrow window of development, either prenatally or postnatally (72, 73). The maternal immune status seems to affect infant GIT microbiota composition as well as the incidence of allergic diseases. Allergic mothers, e.g., had lower amounts of bifidobacteria in their breast milk and feces and, consequently, decreased counts and diversity of bifidobacteria in the offspring feces (74, 75) compared with nonallergic mothers. The establishment of specific microbiota in infants, such as bifidobacteria

(76), has been shown to alter the signaling reactions that determine T-cell differentiation and/or the induction of tolerance (77, 78).

Maternal exposure to environmental stimuli, particularly bacteria and antigens prenatally, appears to play an important role in postnatal immune responsiveness and the subsequent development of autoimmune disorders (72, 73, 79). For example, cord blood from neonates born to farming families was shown to contain significantly higher levels of IFNγ and TNFα compared with cord blood from infants born to nonfarming families (80). A decreased concentration of IFNγ in cord blood at birth was associated with late onset of allergies in adult life, which might indicate that this cytokine plays an important role in regulating the effects of maternal environmental stimuli to the development of the fetal immune system (81). Maturation of the adaptive immune system and development of functionally active T-cells have been shown to start in utero, are influenced by environmental factors such as bacterial exposure, and are a critical phase in fetal programming of the offspring (82).

Overall, the maternal GIT microbiota appears to influence pregnancy progression and contributes to colonization of the newborn GIT (83). A maternal GIT microbiota rich with bifidobacteria and with fewer *E. coli* may contribute to improve fetal and/or neonatal development and maturation as well decrease the incidence of immune disorders in infants. Dietary manipulation of maternal GIT microbiota during the peri- and postnatal period may thus be an important alternative method to improve offspring health and later life outcomes.

Probiotics and Prebiotics in the Maternal Diet and Infant Health

Probiotics. It is well known that administering probiotic bacteria to adults alters the GIT diversity (84) and provides health benefits (85, 86). Specific lactobacilli and bifidobacteria have traditionally been recognized as potential health-promoting microbes in the human GIT and are, therefore, broadly used as probiotic supplements in foods. The beneficial effects of lactobacilli and bifidobacteria consumption are likely to involve inhibition of pathogen adherence to the mucosa, improvement of barrier function of the intestinal mucosa, production of bacteriocins, increased mucosal IgA production, and reduced mucosal proinflammatory cytokine secretion (87). Probiotic dairy products containing *Lactobacillus* and bifidobacteria have been shown to reduce the risk of spontaneous preterm delivery (88) and preeclampsia (89) as well as increase serum levels of erythrocyte glutathione reductase (90), an enzyme involved in cellular antioxidant activity, when consumed by mothers during pregnancy. Probiotics also enhance disease resistance in infants (91, 92). However, to be effective, probiotics must be continually taken, because they do not persist in infants (93, 94) and adults (95) after administration is discontinued.

Evidence that maternally derived probiotic bacteria colonize the GIT of vaginally delivered and breast-fed infants and persist for 1–2 y comes from studies analyzing the effects of perinatal *Lactobacillus rhamnosus GG* (LGG) supplementation on the development of allergic disorders in offspring (83, 96–98). Blumer et al. (99), e.g., reported that pregnant mice supplemented with LGG had an altered placental proinflammatory cytokine expression, with lower IL-4 and increased TNFα gene expression levels. This was associated with reduced allergic airway inflammation in the offspring (99). Similarly, in a human intervention study, maternal LGG supplementation increased cord blood and breast milk levels of antiinflammatory cytokines, IFNγ, and TGFβ1, in the first week when compared with the placebo group (100). A Finnish study also showed that maternal pre- (1 mo) and postnatal (6 mo) supplementation with LGG reduced the frequency of eczema in the offspring at 1, 2, 4, or 7 y of age but had no effect on atopic sensitization (91, 101–104). Administration of LGG to mothers during pregnancy decreased plasma levels of IgE antibodies to a mixture of food allergens in infants up to 2 y of age (105). The same treatment increased colonization by particular *Bifidobacterium* species (96, 106) but failed to modulate the microbial diversity of 1–wk-old infant GIT (107). In a human-like atopic dermatitis model using NC/NgaTnd mice, perinatal administration of LGG also decreased clinical symptoms of dermatitis, scratching frequency, and plasma IgE levels and increased levels of IFN-γ in skin biopsies (86).

Combined probiotic intervention with LGG and *B. lactis* Bb12 and dietary counseling has been shown to ameliorate glucose homeostasis in healthy young females during and after pregnancy (33). Probiotic intervention also reduced the frequency of gestational diabetes mellitus (13% diet/probiotics vs. 36% diet/placebo and 34% control) (108). The same maternal treatment and dietary counseling reduced the proportion of infants with a high 32–33 split proinsulin (a well-characterized metabolic marker of insulin resistance) compared with control/placebo groups (109). Kaplas et al. (110) showed that a combination of a balanced diet and probiotic therapy with LGG and *B. lactis* Bb12 was able to increase placental concentration of phospholipid fatty acids, which are known to exert immunomodulatory effects on the fetus later in pregnancy (111, 112). Increased concentrations of fatty acids available to the fetus showed positive effects with regards to a reduction in food allergy risk and IgE-associated eczema in infants during the first year of life (113) and a lower rate of allergic asthma in 16-y-old children (114). These findings suggest that the beneficial effects of these probiotic strains may at least in part be mediated via the placenta through induction of immunoinflammatory signals and may promote neurological development at an early age (115) as well as reduce the risk of a range of immunoinflammatory disorders (110).

Promising results from previous studies have shown that probiotic supplementation of the mother's diet may have protective effects against allergy development (91, 101–104). There is, however, insufficient scientific evidence to support many of the health claims attributed to probiotics. Because only a limited number of strains, such as bifidobacteria and lactobacillus, have been extensively studied for conferring health benefits, other species, such as *Streptococcus thermophilus* (116), should be investigated. Concerns exist about the overall safety of administering probiotics to high-risk patient groups, including pregnant women, preterm neonates, and infants (117). Invasive infections caused by translocated probiotics into the blood stream have been reported in patients with immune dysfunction/suppression or with an abnormal gastrointestinal mucosal barrier (118, 119). Also, there is a risk of transfer of antibiotic resistance plasmids from some but not all probiotic organisms (120).

Prebiotics. The addition of oligosaccharides resistant to digestion in the small intestine (prebiotics) to the diet of pregnant mothers is possibly a safer alternative than probiotic consumption for influencing the maternal GIT microbiota population for the benefit of the neonate (121). Oligosaccharides affect GIT

function by selectively stimulating the growth and/or activity of beneficial bacteria such as bifidobacteria and lactobacilli, thus improving host health (122). Fujiwara et al. (5, 123) demonstrated that maternal dietary supplementation with fructo-oligosaccharide modulated the GIT microbiota of the offspring and diminished the severity of atopic dermatitis. In contrast, the combined dietary supplementation of galacto-oligosaccharide (GOS) and fructo-oligosaccharide changed the maternal microbiota, but the effect was not transferred to the offspring (121). Another study showed that a GOS and inulin-enriched diet fed throughout pregnancy and lactation was able to increase colon length and thigh muscle mass in the offspring (124).

Consumption of prebiotics by mothers may also increase the production of bacterially derived metabolites, providing benefits both for her and her offspring. Inclusion of inulin and GOS in the mother's diet increased the numbers of bacteria synthesizing folate, the levels of folate in the digesta of the large intestine and, consequently, the levels of folate in the blood stream available for fetal development (125). Suboptimal concentrations of folate during pregnancy have been associated with anemia, neural tube defects, vascular disease, neuropsychiatric disorders, and cancers (126). Another group of metabolites produced by microbial fermentation that may affect the fetus during pregnancy are SCFA. Most SCFA produced by colonic bacteria, predominantly acetate, propionate, and butyrate, are absorbed by colonic epithelial cells and metabolized, contributing to the mother's energy supply and that of the developing fetus (127). For example, butyrate is a histone deacetylase inhibitor that is thought to activate genes by increasing histone acetylation and decreasing DNA methylation (128). There is evidence that SCFA-mediated histone deacetylase inhibition may play a part in gene regulation of fetal globin (129) and hemoglobin (130). This, in turn, may have a role in the normal regulation of human γ- to β-globin gene switching, a process that is important in the formation of hemoglobin.

Synbiotics. Recently, the co-therapy of probiotics with prebiotics (synbiotics) in pregnant women and their infants was tested to assess the prevention of allergic diseases (131,132). A total of 1223 pregnant women carrying infants with a high risk of developing atopic dermatitis were randomly assigned to be given a daily mixture of either 4 probiotic strains with GOS or a placebo for 2–4 wk before delivery. After delivery, infants received either the same probiotic mixture with GOS or the same placebo as the mother for up to 6 mo of age. Synbiotic treatment showed no effect on the incidence of respiratory allergic diseases by 2 y of age but prevented atopic eczema, increased resistance to respiratory infections, and reduced IgE-associated atopic dermatitis (131,132). In the same study, the synbiotic treatment was able to improve the response to *Haemophilus influenzae* type b (Hib) immunization, increasing Hib antibody concentrations compared with the placebo group without impairing antibody responses to diphtheria, tetanus, or Hib.

A mixture of pro- and prebiotics has a synergistic effect by stimulating the growth and/or metabolism of the delivered probiotic bacteria, inducing, e.g., the production of SCFA that have direct antipathogenic and immune-modulating effects. Due to the complexity of the GIT microbiota and its interaction with the immune system, it is difficult to define the specific mechanism underlying the functional effects of pro- and prebiotics. However, the reported relationship between allergic disease and the composition of the intestinal microbiota early in life points to the prenatal and perinatal periods as an opportunity to improve offspring health through maternal supplementation.

In conclusion, during the last decade, important evidence has shown that during pregnancy, maternal GIT microbiota or its products may also be transferred to the fetus/neonate through the placenta or by breast feeding. Moreover, further studies are required to define the mechanisms by which the microbiota present in the mother's GIT and/or genital tract may influence maternal physiology and also the development and maturation of the offspring with health consequences in later life.

Most human intervention studies evaluating the effects of perinatal administration of probiotics and prebiotics to pregnant women and to infants after birth focus primarily on the prevention of atopic dermatitis. Although these findings indicate some positive effects, there are also conflicting results dependent on the specific strains tested, the conditions of use, and the population group. Administration of certain probiotics and/or prebiotics during the perinatal and postnatal period may be a potential prophylactic therapy for other modern-life diseases, such as obesity and metabolic disease. However, there is an urgent need for long-term human intervention studies to support this hypothesis and to widen our knowledge of the interactions between maternal environment and fetus health outcomes.

Acknowledgments

The authors thank Pauline Hunt for drawing Figure 1 and Drs. Rachel Anderson, Wayne Young, Eric Altermann, Julie Dalziel, and Shalome Bassett (AgResearch) for critical review of this manuscript. All authors designed the approach for the review; C.T. conducted the literature search, review, and wrote the manuscript; and C.T. and N.C.R. had primary responsibility for final content. All authors read and approved the final manuscript.

Literature Cited

1. Belkacemi L, Nelson DM, Desai M, Ross MG. Maternal undernutrition influences placental-fetal development. Biol Reprod. 2010;83:325–31.
2. Breimer LH, Nilsson TK. Has folate a role in the developing nervous system after birth and not just during embryogenesis and gestation? Scand J Clin Lab Invest. 2012;72:185–91.
3. Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. Bull World Health Organ. 2011;89:B402–11.
4. Sanz Y. Gut microbiota and probiotics in maternal and infant health. Am J Clin Nutr. 2011;94 (Suppl 6):S2000–5.
5. Fujiwara R, Takemura N, Watanabe J, Sonoyama K. Maternal consumption of fructo-oligosaccharide diminishes the severity of skin inflammation in offspring of NC/Nga mice. Br J Nutr. 2010;103:530–8.
6. Ivanov II, Littman DR. Modulation of immune homeostasis by commensal bacteria. Curr Opin Microbiol. 2011;14:106–14.
7. Gaskins HR, Croix JA, Nakamura N, Nava GM. Impact of the intestinal microbiota on the development of mucosal defense. Clin Infect Dis. 2008;46 Suppl 2:S80–6; discussion S144–51.
8. Asahara T, Nomoto K, Shimizu K, Watanuki M, Tanaka R. Increased resistance of mice to Salmonella enterica serovar Typhimurium infection by synbiotic administration of Bifidobacteria and transgalactosylated oligosaccharides. J Appl Microbiol. 2001;91:985–96.
9. Le Leu RK, Hu Y, Brown IL, Woodman RJ, Young GP. Synbiotic intervention of Bifidobacterium lactis and resistant starch protects against colorectal cancer development in rats. Carcinogenesis. 2010;31:246–51.
10. Xu J, Mahowald MA, Ley RE, Lozupone CA, Hamady M, Martens EC, Henrissat B, Coutinho PM, Minx P, Latreille P, et al. Evolution of symbiotic bacteria in the distal human intestine. PLoS Biol. 2007;5:e156.
11. Stappenbeck TS, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. Proc Natl Acad Sci USA. 2002;99:15451–5.

12. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA. 2004;101:15718–23.
13. Martín R, Langa S, Reviriego C, Jimenez E, Marin ML, Olivares M, Boza J, Jimenez J, Fernandez L, Xaus J. The commensal microflora of human milk: new perspectives for food bacteriotherapy and probiotics. Trends Food Sci Tech. 2004;15:121–7.
14. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. Am J Clin Nutr. 1999;69:S1035–45.
15. Pettker CM, Buhimschi IA, Magloire LK, Sfakianaki AK, Hamar BD, Buhimschi CS. Value of placental microbial evaluation in diagnosing intra-amniotic infection. Obstet Gynecol. 2007;109:739–49.
16. Jiménez E, Marin ML, Martin R, Odriozola JM, Olivares M, Xaus J, Fernandez L, Rodriguez JM. Is meconium from healthy newborns actually sterile? Res Microbiol. 2008;159:187–93.
17. Jiménez E, Fernandez L, Marin ML, Martin R, Odriozola JM, Nueno-Palop C, Narbad A, Olivares M, Xaus J, Rodriguez JM. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. Curr Microbiol. 2005;51:270–4.
18. Hitti J, Riley DE, Krohn MA, Hillier SL, Agnew KJ, Krieger JN, Eschenbach DA. Broad-spectrum bacterial rDNA polymerase chain reaction assay for detecting amniotic fluid infection among women in premature labor. Clin Infect Dis. 1997;24:1228–32.
19. Satokari R, Gro«nroos T, Laitinen K, Salminen S, Isolaur E. Bifidobacterium and Lactobacillus DNA in the human placenta. Lett Appl Microbiol. 2009;48:8–12.
20. Steel JH, Malatos S, Kennea N, Edwards AD, Miles L, Duggan P, Reynolds PR, Feldman RG, Sullivan MH. Bacteria and inflammatory cells in fetal membranes do not always cause preterm labor. Pediatr Res. 2005;57:404–11.
21. DiGiulio DB. Diversity of microbes in amniotic fluid. Semin Fetal Neonatal Med. 2012;17:2–11.
22. Wagner CL, Taylor SN, Johnson D. Host factors in amniotic fluid and breast milk that contribute to gut maturation. Clin Rev Allergy Immunol. 2008;34:191–204.
23. Eberle F, Sirin M, Binder M, Dalpke AH. Bacterial RNA is recognized by different sets of immunoreceptors. Eur J Immunol. 2009;39:2537–47.
24. Obermeier F, Strauch UG, Dunger N, Grunwald N, Rath HC, Herfarth H, Scholmerich J, Falk W. In vivo CpG DNA/toll-like receptor 9 interaction induces regulatory properties in CD4+CD62L+ T cells which prevent intestinal inflammation in the SCID transfer model of colitis. Gut. 2005;54:1428–36.
25. Mold JE, Michaelsson J, Burt TD, Muench MO, Beckerman KP, Busch MP, Lee TH, Nixon DF, McCune JM. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science. 2008;322:1562–5.
26. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005;122:107–18.
27. Neu J, Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol. 2011;38:321–31.
28. German JB, Dillard CJ, Ward RE. Bioactive components in milk. Curr Opin Clin Nutr Metab Care. 2002;5:653–8.
29. Boehm G, Stahl B. Oligosaccharides from milk. J Nutr. 2007;137:S847–9.
30. German JB, Freeman SL, Lebrilla CB, Mills DA. Human milk oligosaccharides: evolution, structures and bioselectivity as substrates for intestinal bacteria. Nestle Nutr Workshop Ser Pediatr Program. 2008;62:205–18, discussion 18–22.
31. Perez Conesa D, Lopez G, Ros G. Effects of probiotic, prebiotic and synbiotic follow-up infant formulas on large intestine morphology and bone mineralisation in rats. J Sci Food Agric. 2007;119:1059–68.
32. Scholz-Ahrens KE, Ade P, Marten B, Weber P, Timm W, Acil Y, Gluer CC, Schrezenmeir J. Prebiotics, probiotics, and synbiotics affect mineral absorption, bone mineral content, and bone structure. J Nutr. 2007;137:S838–46.
33. Laitinen K, Poussa T, Isolauri E. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr. 2009;101:1679–87.
34. Innis SM. Human milk: maternal dietary lipids and infant development. Proc Nutr Soc. 2007;66:397–404.
35. Zivkovic AM, German JB, Lebrilla CB, Mills DA. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. Proc Natl Acad Sci USA. 2011;108 (Suppl 1):4653–8.
36. Gnoth MJ, Kunz C, Kinne-Saffran E, Rudloff S. Human milk oligosaccharides are minimally digested in vitro. J Nutr. 2000;130:3014–20.
37. Coppa GV, Zampini L, Galeazzi T, Gabrielli O. Prebiotics in human milk: a review. Dig Liver Dis. 2006;38 Suppl 2:S291–4.
38. Hosea Blewett HJ, Cicalo MC, Holland CD, Field CJ. The immunological components of human milk. Adv Food Nutr Res. 2008;54:45–80.
39. Newburg DS, Ruiz-Palacios GM, Morrow AL. Human milk glycans protect infants against enteric pathogens. Annu Rev Nutr. 2005;25:37–58.
40. Ninonuevo MR, Park Y, Yin H, Zhang J, Ward RE, Clowers BH, German JB, Freeman SL, Killeen K, Grimm R, et al. A strategy for annotating the human milk glycome. J Agric Food Chem. 2006;54:7471–80.
41. Thurl S, Munzert M, Henker J, Boehm G, Muller-Werner B, Jelinek J, Stahl B. Variation of human milk oligosaccharides in relation to milk groups and lactational periods. Br J Nutr. 2010;104:1261–71.
42. Borén T, Falk P, Roth KA, Larson G, Normark S. Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. Science. 1993;262:1892–5.
43. Ahmed T, Lundgren A, Arifuzzaman M, Qadri F, Teneberg S, Svennerholm AM. Children with the Le(a+b-) blood group have increased susceptibility to diarrhea caused by enterotoxigenic Escherichia coli expressing colonization factor I group fimbriae. Infect Immun. 2009;77:2059–64.
44. Heikkilä MP, Saris PE. Inhibition of Staphylococcus aureus by the commensal bacteria of human milk. J Appl Microbiol. 2003;95:471–8.
45. Martín R, Jimenez E, Heilig H, Fernandez L, Marin ML, Zoetendal EG, Rodriguez JM. Isolation of bifidobacteria from breast milk and assessment of the bifidobacterial population by PCR-denaturing gradient gel electrophoresis and quantitative real-time PCR. Appl Environ Microbiol. 2009;75:965–9.
46. Martín R, Heilig HG, Zoetendal EG, Jimenez E, Fernandez L, Smidt H, Rodriguez JM. Cultivation-independent assessment of the bacterial diversity of breast milk among healthy women. Res Microbiol. 2007;158:31–7.
47. Collado MC, Delgado S, Maldonado A, Rodriguez JM. Assessment of the bacterial diversity of breast milk of healthy women by quantitative real-time PCR. Lett Appl Microbiol. 2009;48:523–8.
48. Hunt KM, Foster JA, Forney LJ, Schutte UM, Beck DL, Abdo Z, Fox LK, Williams JE, McGuire MK, McGuire MA. Characterization of the diversity and temporal stability of bacterial communities in human milk. PLoS ONE. 2011;6:e21313.
49. Solís G, de Los Reyes-Gavilan CG, Fernandez N, Margolles A, Gueimonde M. Establishment and development of lactic acid bacteria and bifidobacteria microbiota in breast-milk and the infant gut. Anaerobe. 2010;16:307–10.
50. Martín V, Maldonado-Barragan A, Moles L, Rodriguez-Banos M, Campo RD, Fernandez L, Rodriguez JM, Jimenez E. Sharing of bacterial strains between breast milk and infant feces. J Hum Lact. 2012;28:36–44.
51. Stagg AJ, Hart AL, Knight SC, Kamm MA. The dendritic cell: its role in intestinal inflammation and relationship with gut bacteria. Gut. 2003;52:1522–9.
52. Perez PF, Dore J, Leclerc M, Levenez F, Benyacoub J, Serrant P, Segura-Roggero I, Schiffrin EJ, Donnet-Hughes A. Bacterial imprinting of the neonatal immune system: lessons from maternal cells? Pediatrics. 2007;119:e724–32.
53. Labéta MO, Vidal K, Nores JE, Arias M, Vita N, Morgan BP, Guillemot JC, Loyaux D, Ferrara P, Schmid D, et al. Innate recognition of bacteria in human milk is mediated by a milk-derived highly expressed pattern recognition receptor, soluble CD14. J Exp Med. 2000;191:1807–12.
54. Dasanayake AP, Li Y, Wiener H, Ruby JD, Lee MJ. Salivary Actinomyces naeslundii genospecies 2 and Lactobacillus casei levels predict pregnancy outcomes. J Periodontol. 2005;76:171–7.
55. Bearfield C, Davenport E, Sivapathasundaram V, Allaker R. Possible association between amniotic fluid micro-organism infection and microflora in the mouth. BJOG. 2002;109:527–33.
56. Donnet-Hughes A, Perez PF, Dore J, Leclerc M, Levenez F, Benyacoub J, Serrant P, Segura-Roggero I, Schiffrin EJ. Potential role of the intestinal microbiota of the mother in neonatal immune education. Proc Nutr Soc. 2010;69:407–15.
57. Macpherson AJ, Uhr T. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. Science. 2004;303:1662–5.

58. Goldman AS, Goldblum RM. Transfer of maternal leukocytes to the infant by human milk. Curr Top Microbiol Immunol. 1997;222:205–13.
59. Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R, Granucci F, Kraehenbuhl JP, Ricciardi-Castagnoli P. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. Nat Immunol. 2001;2:361–7.
60. Nagl M, Kacani L, Mullauer B, Lemberger EM, Stoiber H, Sprinzl GM, Schennach H, Dierich MP. Phagocytosis and killing of bacteria by professional phagocytes and dendritic cells. Clin Diagn Lab Immunol. 2002;9:1165–8.
61. Uhlig HH, Powrie F. Dendritic cells and the intestinal bacterial flora: a role for localized mucosal immune responses. J Clin Invest. 2003;112:648–51.
62. Nassif X, Bourdoulous S, Eugene E, Couraud PO. How do extracellular pathogens cross the blood-brain barrier? Trends Microbiol. 2002;10:227–32.
63. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann N Y Acad Sci. 2011;1221:80–7.
64. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis. 2006;12:1638–43.
65. Włoch S, Palasz A, Kaminski M. Active and passive transport of drugs in the human placenta. Ginekol Pol. 2009;80:772–7.
66. Santacruz A, Collado MC, Garcia-Valdes L, Segura MT, Martin-Lagos JA, Anjos T, Marti-Romero M, Lopez RM, Florido J, Campoy C, et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr. 2010;104:83–92.
67. Africa CW. Oral colonization of Gram-negative anaerobes as a risk factor for preterm delivery. Virulence. 2011;2:498–508.
68. Durand R, Gunselman EL, Hodges JS, Diangelis AJ, Michalowicz BS. A pilot study of the association between cariogenic oral bacteria and preterm birth. Oral Dis. 2009;15:400–6.
69. Fåk F, Ahrne S, Molin G, Jeppsson B, Westrom B. Microbial manipulation of the rat dam changes bacterial colonization and alters properties of the gut in her offspring. Am J Physiol Gastrointest Liver Physiol. 2008;294:G148–54.
70. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sanchez PJ, Ambalavanan N, Benjamin DK, Jr. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics. 2009;123:58–66.
71. Wang Y, Hoenig JD, Malin KJ, Qamar S, Petrof EO, Sun J, Antonopoulos DA, Chang EB, Claud EC. 16S rRNA gene-based analysis of fecal microbiota from preterm infants with and without necrotizing enterocolitis. ISME J. 2009;3:944–54.
72. Rowe J, Kusel M, Holt BJ, Suriyaarachchi D, Serralha M, Hollams E, Yerkovich ST, Subrata LS, Ladyman C, Sadowska A, et al. Prenatal versus postnatal sensitization to environmental allergens in a high-risk birth cohort. J Allergy Clin Immunol. 2007;119:1164–73.
73. Ege MJ, Bieli C, Frei R, van Strien RT, Riedler J, Ublagger E, Schram-Bijkerk D, Brunekreef B, van Hage M, Scheynius A, et al. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol. 2006;117:817–23.
74. Mikami K, Takahashi H, Kimura M, Isozaki M, Izuchi K, Shibata R, Sudo N, Matsumoto H, Koga Y. Influence of maternal bifidobacteria on the establishment of bifidobacteria colonizing the gut in infants. Pediatr Res. 2009;65:669–74.
75. Grönlund MM, Gueimonde M, Laitinen K, Kociubinski G, Gronroos T, Salminen S, Isolauri E. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin Exp Allergy. 2007;37:1764–72.
76. Dong P, Yang Y, Wang WP. The role of intestinal bifidobacteria on immune system development in young rats. Early Hum Dev. 2010;86:51–8.
77. Ogra PL, Welliver RC Sr. Effects of early environment on mucosal immunologic homeostasis, subsequent immune responses and disease outcome. Nestle Nutr Workshop Ser Pediatr Program. 2008;61:145–81.
78. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci USA. 2010;107:12204–9.
79. Herberth G, Hinz D, Roder S, Schlink U, Sack U, Diez U, Borte M, Lehmann I. Maternal immune status in pregnancy is related to offspring's immune responses and atopy risk. Allergy. 2011;66:1065–74.
80. Pfefferle PI, Buchele G, Blumer N, Roponen M, Ege MJ, Krauss-Etschmann S, Genuneit J, Hyvarinen A, Hirvonen MR, Lauener R, et al. Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy: the PASTURE Study. J Allergy Clin Immunol. 2010;125:108–15 e1–3.
81. Prescott SL, Noakes P, Chow BW, Breckler L, Thornton CA, Hollams EM, Ali M, van den Biggelaar AH, Tulic MK. Presymptomatic differences in Toll-like receptor function in infants who have allergy. J Allergy Clin Immunol. 2008;122:391–9, 9 e1–5.
82. Marsh LM, Pfefferle PI, Pinkenburg O, Renz H. Maternal signals for progeny prevention against allergy and asthma. Cell Mol Life Sci. 2011;68:1851–62.
83. Tannock GW, Fuller R, Smith SL, Hall MA. Plasmid profiling of members of the family Enterobacteriaceae, lactobacilli, and bifidobacteria to study the transmission of bacteria from mother to infant. J Clin Microbiol. 1990;28:1225–8.
84. Rauch M, Lynch SV. The potential for probiotic manipulation of the gastrointestinal microbiome. Curr Opin Biotechnol. 2012;23:192–201.
85. Nishijima K, Shukunami K, Kotsuji F. Probiotics affects vaginal flora in pregnant women, suggesting the possibility of preventing preterm labor. J Clin Gastroenterol. 2005;39:447–8.
86. Tanaka A, Jung K, Benyacoub J, Prioult G, Okamoto N, Ohmori K, Blum S, Mercenier A, Matsuda H. Oral supplementation with Lactobacillus rhamnosus CGMCC 1.3724 prevents development of atopic dermatitis in NC/NgaTnd mice possibly by modulating local production of IFN-gamma. Exp Dermatol. 2009;18:1022–7.
87. Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. Nat Rev Gastroenterol Hepatol. 2010;7:503–14.
88. Myhre R, Brantsaeter AL, Myking S, Gjessing HK, Sengpiel V, Meltzer HM, Haugen M, Jacobsson B. Intake of probiotic food and risk of spontaneous preterm delivery. Am J Clin Nutr. 2011;93:151–7.
89. Brantsaeter AL, Myhre R, Haugen M, Myking S, Sengpiel V, Magnus P, Jacobsson B, Meltzer HM. Intake of probiotic food and risk of preeclampsia in primiparous women: the Norwegian Mother and Child Cohort Study. Am J Epidemiol. 2011;174:807–15.
90. Asemi Z, Jazayeri S, Najafi M, Samimi M, Mofid V, Shidfar F, Shakeri H, Esmaillzadeh A. Effect of daily consumption of probiotic yogurt on oxidative stress in pregnant women: a randomized controlled clinical trial. Ann Nutr Metab. 2012;60:62–8.
91. Kim JY, Kwon JH, Ahn SH, Lee SI, Han YS, Choi YO, Lee SY, Ahn KM, Ji GE. Effect of probiotic mix (Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. Pediatr Allergy Immunol. 2010;21:e386–93.
92. Mohan R, Koebnick C, Schildt J, Schmidt S, Mueller M, Possner M, Radke M, Blaut M. Effects of Bifidobacterium lactis Bb12 supplementation on intestinal microbiota of preterm infants: a double-blind, placebo-controlled, randomized study. J Clin Microbiol. 2006;44:4025–31.
93. Lee SJ, Cho SJ, Park EA. Effects of probiotics on enteric flora and feeding tolerance in preterm infants. Neonatology. 2007;91:174–9.
94. Petschow BW, Figueroa R, Harris CL, Beck LB, Ziegler E, Goldin B. Effects of feeding an infant formula containing Lactobacillus GG on the colonization of the intestine: a dose-response study in healthy infants. J Clin Gastroenterol. 2005;39:786–90.
95. Tannock GW, Munro K, Harmsen HJ, Welling GW, Smart J, Gopal PK. Analysis of the fecal microflora of human subjects consuming a probiotic product containing Lactobacillus rhamnosus DR20. Appl Environ Microbiol. 2000;66:2578–88.
96. Gueimonde M, Sakata S, Kalliomaki M, Isolauri E, Benno Y, Salminen S. Effect of maternal consumption of lactobacillus GG on transfer and establishment of fecal bifidobacterial microbiota in neonates. J Pediatr Gastroenterol Nutr. 2006;42:166–70.
97. Schultz M, Gottl C, Young RJ, Iwen P, Vanderhoof JA. Administration of oral probiotic bacteria to pregnant women causes temporary infantile colonization. J Pediatr Gastroenterol Nutr. 2004;38:293–7.
98. Buddington RK, Williams CH, Kostek BM, Buddington KK, Kullen MJ. Maternal-to-infant transmission of probiotics: concept validation in mice, rats, and pigs. Neonatology. 2010;97:250–6.
99. Blümer N, Sel S, Virna S, Patrascan CC, Zimmermann S, Herz U, Renz H, Garn H. Perinatal maternal application of Lactobacillus rhamnosus GG suppresses allergic airway inflammation in mouse offspring. Clin Exp Allergy. 2007;37:348–57.

100. Prescott SL, Wickens K, Westcott L, Jung W, Currie H, Black PN, Stanley TV, Mitchell EA, Fitzharris P, Siebers R, et al. Supplementation with Lactobacillus rhamnosus or Bifidobacterium lactis probiotics in pregnancy increases cord blood interferon-gamma and breast milk transforming growth factor-beta and immunoglobin A detection. Clin Exp Allergy. 2008;38:1606–14.
101. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet. 2001;357:1076–9.
102. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet. 2003;361:1869–71.
103. Kalliomäki M, Salminen S, Poussa T, Isolauri E. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2007;119:1019–21.
104. Wickens K, Black PN, Stanley TV, Mitchell E, Fitzharris P, Tannock GW, Purdie G, Crane J. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2008;122:788–94.
105. Abrahamsson TR, Jakobsson T, Bottcher MF, Fredrikson M, Jenmalm MC, Bjorksten B, Oldaeus G. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2007;119:1174–80.
106. Lahtinen SJ, Boyle RJ, Kivivuori S, Oppedisano F, Smith KR, Robins-Browne R, Salminen SJ, Tang ML. Prenatal probiotic administration can influence Bifidobacterium microbiota development in infants at high risk of allergy. J Allergy Clin Immunol. 2009;123:499–501.
107. Ismail IH, Oppedisano F, Joseph SJ, Boyle RJ, Robins-Browne RM, Tang ML. Prenatal administration of Lactobacillus rhamnosus has no effect on the diversity of the early infant gut microbiota. Pediatr Allergy Immunol. 2012;23:255–8.
108. Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr. 2010;103:1792–9.
109. Aaltonen J, Ojala T, Laitinen K, Poussa T, Ozanne S, Isolauri E. Impact of maternal diet during pregnancy and breastfeeding on infant metabolic programming: a prospective randomized controlled study. Eur J Clin Nutr. 2011;65:10–9.
110. Kaplas N, Isolauri E, Lampi AM, Ojala T, Laitinen K. Dietary counseling and probiotic supplementation during pregnancy modify placental phospholipid fatty acids. Lipids. 2007;42:865–70.
111. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr. 2006;83:S1505–19.
112. Herrera E, Amusquivar E, Lopez-Soldado I, Ortega H. Maternal lipid metabolism and placental lipid transfer. Horm Res. 2006;65 Suppl 3:59–64.
113. Furuhjelm C, Warstedt K, Larsson J, Fredriksson M, Bottcher MF, Falth-Magnusson K, Duchen K. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr. 2009;98:1461–7.
114. Olsen SF, Osterdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, Henriksen TB. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. Am J Clin Nutr. 2008;88:167–75.
115. Gíl-Sanchez A, Demmelmair H, Parrilla JJ, Koletzko B, Larque E. Mechanisms involved in the selective transfer of long chain polyunsaturated Fatty acids to the fetus. Front Genet. 2011;2:57.
116. Guandalini S, Magazzu G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, Sibal A, Romano C, Canani RB, Lionetti P, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr. 2010;51:24–30.
117. Neu J. Routine probiotics for premature infants: let's be careful! J Pediatr. 2011;158:672–4.
118. Boyle RJ, Robins-Browne RM, Tang ML. Probiotic use in clinical practice: what are the risks? Am J Clin Nutr. 2006;83:1256–64, quiz 446–7.
119. Luong ML, Sareyyupoglu B, Nguyen MH, Silveira FP, Shields RK, Potoski BA, Pasculle WA, Clancy CJ, Toyoda Y. Lactobacillus probiotic use in cardiothoracic transplant recipients: a link to invasive Lactobacillus infection? Transpl Infect Dis. 2010;12:561–4.
120. van Reenen CA, Dicks LM. Horizontal gene transfer amongst probiotic lactic acid bacteria and other intestinal microbiota: what are the possibilities? A review. Arch Microbiol. 2011;193:157–68.
121. Shadid R, Haarman M, Knol J, Theis W, Beermann C, Rjosk-Dendorfer D, Schendel DJ, Koletzko BV, Krauss-Etschmann S. Effects of galactooligosaccharide and long-chain fructooligosaccharide supplementation during pregnancy on maternal and neonatal microbiota and immunity–a randomized, double-blind, placebo-controlled study. Am J Clin Nutr. 2007;86:1426–37.
122. Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, et al. Prebiotic effects: metabolic and health benefits. Br J Nutr. 2010;104 Suppl 2:S1–63.
123. Fujiwara R, Watanabe J, Sonoyama K. Assessing changes in composition of intestinal microbiota in neonatal BALB/c mice through cluster analysis of molecular markers. Br J Nutr. 2008;99:1174–7.
124. Desbuards N, Gourbeyre P, Haure-Mirande V, Darmaun D, Champ M, Bodinier M. Impact of perinatal prebiotic consumption on gestating mice and their offspring: a preliminary report. Br J Nutr. 2011:1–4.
125. Aufreiter S, Kim JH, O'Connor DL. Dietary oligosaccharides increase colonic weight and the amount but not concentration of bacterially synthesized folate in the colon of piglets. J Nutr. 2011;141:366–72.
126. Iyer R, Tomar SK. Folate: a functional food constituent. J Food Sci. 2009;74:R114–22.
127. Roediger WE. Utilization of nutrients by isolated epithelial cells of the rat colon. Gastroenterology. 1982;83:424–9.
128. Bhatia H, Hallock JL, Dutta A, Karkashon S, Sterner LS, Miyazaki T, Dean A, Little JA. Short-chain fatty acid-mediated effects on erythropoiesis in primary definitive erythroid cells. Blood. 2009;113:6440–8.
129. Fathallah H, Weinberg RS, Galperin Y, Sutton M, Atweh GF. Role of epigenetic modifications in normal globin gene regulation and butyrate-mediated induction of fetal hemoglobin. Blood. 2007;110:3391–7.
130. Kaneda R, Ueno S, Yamashita Y, Choi YL, Koinuma K, Takada S, Wada T, Shimada K, Mano H. Genome-wide screening for target regions of histone deacetylases in cardiomyocytes. Circ Res. 2005;97:210–8.
131. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2007;119:192–8.
132. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. Pediatrics. 2008;122:8–12.