Indian Journal of
Nutrition

Open Science Publications

Volume 8, Issue 2 - 2021

www.opensciencepublications.com

Probiotics in Pregnancy

Review Article

Tania SG*

Head, Department of Obstetrics and Gynecology, GNS Multispeciality Hospital, Chattarpur, New Delhi, India

***Corresponding author:** Tania SG, Head, Department of Obstetrics and Gynecology, GNS Multispeciality Hospital, Chattarpur, New Delhi, India; Tel: 9625930047; Email: taniasingh.ts@gmail.com

Article Information: **Submission:** 22/04/2021; **Accepted:** 28/05/2021; **Published:** 31/05/2021

Abstract

Probiotics are live microorganisms (in most cases bacteria) that are similar to beneficial microorganisms found naturally in the human gut. They are available mainly in the form of dietary supplements and foods, and when administered in adequate amounts confer a health benefit on the host. They are a safe and effective way of enhancing the diversity and health of the microbiome in pregnant women. Probiotics given prenatally are an important way for mothers to safeguard their health during pregnancy as well as the health of their babies.

Colonization of the neonatal gut by beneficial bacteria is important in protecting the neonate from enteric pathogens and local as well as systemic inflammation. Maternal microbiome in pregnancy together with infant diet impacts neonatal microbiome.

Keywords: Microbiota; Dysbiosis; Synbiotics; Bifidobacterium; FODMAP; Lactobacillus; Prebiotics; Pregnancy; Urogenital infections; Infant colic

Introduction

Gut microbiota is a heterogeneous microbial community that includes 10^{14} [1,2] microorganisms comprising predominantly bacteria, along with viruses, archaeans, and protozoa. The gastrointestinal microbiota can be considered as an organ within an organ contributing to host nutrition, developmental regulation of intestinal angiogenesis, protection from pathogens and development of the immune response [3]. Three dominant phyla comprise almost 80% of gut flora [4]: Bacteroidetes, Firmicutes, and Actinobacteria [5].

The neonatal microbiota is highly different compared to the adult one, since the former is characterized by rapid changes especially in the first year of life [6]. Colonization of the neonatal gut by beneficial bacteria is important in protecting the neonate from enteric pathogens and local as well as systemic inflammation. Maternal microbiome in pregnancy together with infant diet impacts neonatal microbiome. Dysbiosis in pregnancy increases the risk of preeclampsia, diabetes, infection, preterm labour, and later childhood atopy. It can also lead to postnatal maternal depression and infant colic. It also plays an important role in necrotizing enterocolitis and sepsis, both of which can occur as a result of prematurity affecting the long term outcomes in neonates. Administration of enteral prebiotics, probiotics, and synbiotics during pregnancy, lactation, and postnatal life appears to be a safe and feasible method to alter the maternal and neonatal microbiome, thus improving pregnancy and neonatal outcomes [7].

Synbiotics refers to a product which has an appropriate combination of both probiotic and prebiotic components. Synbiotics ensures that it has a superior effect when compared to the activity of probiotic or prebiotic alone. It was developed in order to overcome some possible difficulties in the survival of probiotics in the gastrointestinal tract.

Prebiotics

Prebiotics generally refers to a substrate (non-digestible food ingredient) which, when added to the dietary intake, is selectively used by host microorganisms conferring a health benefit [8] by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, especially Bifidobacterium species [9]. Prebiotics evade digestion in the small intestine and must be selectively fermented in the colon.

Prebiotics are typically comprised of nondigestible carbohydrates but can also include non-carbohydrates such as fatty acids, phenolics, and phytochemicals [8].

The most widely accepted prebiotics are together referred to as FODMAPs (Fermentable Oligosaccharides Disaccharides Monosaccharides and Polyols). The types of FODMAPs which hold

ISSN: 2395-2326

prebiotic effects are mainly fructans, galacto-oligosaccharides (GOS), and inulin. Foods high in fructans include wheat products, rye products, onion and garlic. Foods high in GOS include legumes, such as chickpeas and baked beans. Inulin is found in some yoghurts (even some lactose-free), asparagus, garlic/onion, and some confectionary. The reason fructans and GOS are able to act like prebiotics is because our gut doesn't have enzymes to break them down, so they remain undigested like prebiotics [10,11].The down side to a low FODMAP diet is that it often limits the intake of prebiotics (Table 1).

Prebiotic carbohydrates are a major substrate for bacterial growth, selectively stimulating the growth and/or activity of beneficial members of the gut microbiota, particularly bifidobacteria [12,13].

Short-chain prebiotics are mainly fermented in the cecum and colon ascendens. Long chain oligosaccharides are fermented along the entire colon [14].Thus, prebiotics could, at least in theory, have more global effects on colonization than adding a single probiotic strain. A second, more direct immune effect appears to be mediated by the fermentation products of prebiotics. Gut microorganisms ferment prebiotics to produce short-chain fatty acids (SCFAs) that have direct anti-inflammatory effects [15]. SCFAs also promote intestinal integrity through effects on epithelial cell proliferation and differentiation [16]. Animal and human studies suggest that prebiotics may directly affect both mucosal and systemic immunity [17-19]. However, more studies are needed to confirm that these are clinically relevant effects.

The gastrointestinal microbiota of breastfed babies differ from classic standard formula fed infants. While mother's milk is rich in prebiotic oligosaccharides and contains small amounts of probiotics, standard infant formula doesn't [14]. Different prebiotic oligosaccharides are added to infant formula: galacto-oligosaccharides, fructo-oligosaccharide, polydextrose, and mixtures of these which brings infant formula one step closer to breastmilk.

Prebiotics are present as supplements also, and they're sometimes added to probiotic supplements or yoghurts.

Probiotics

The United Nations Food and Agriculture Organization (FAO) and World Health Organization (WHO) have defined probiotics as "live micro-organisms, which when administered in adequate amounts confer a health benefit on the host" with a wide and varying range of clinical and immunologic capacities [20].The term probiotic means "for life" and it is currently used to name bacteria associated with beneficial effects for humans and animals [21].

The concept of probiotics was introduced in the early 20thcentury by Elie Metschnikoff, the Russian born Nobel Prize winner working at the Pasteur Institute, who suggested that "The dependence of the intestinal microbes on food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes" [22]. At the same time, Henry Tissier, a French paediatrician, observed that children with diarrhea had in their stools a low number of bacteria characterized by a peculiar, Yshaped morphology. These "bifid" bacteria were, on the contrary, abundant in healthy children [23]. He suggested that these bacteria could be administered to patients with diarrhea to help restore a healthy gut flora.

Probiotics, however, have gained momentum in recent past after almost a century, with considerable growth in functional food market.

The concept of probiotic food came from the fact that bacteria are normal inhabitants of humans (as well as the bodies of upper animals and insects) including the gastrointestinal tract, where more than 400 bacterial species are found [24]: half of the wet weight of colonic material is due to bacterial cells whose numbers exceed by 10-fold the number of tissue cells forming the human body. Normally the stomach contains few bacteria (10^3colony forming units per mL of gastric juice) whereas the bacterial concentration increases throughout the gut resulting in a final concentration in the colon of 10^{12} bacteria/g. Bacterial colonization of the gut begins at birth, as newborns are maintained in a sterile status until the delivery begins, and continues throughout life, with notable age-specific changes [25]. Bacteria, forming the so-called resident intestinal microflora, do not normally have any acute adverse effects and some of them have been shown to be necessary for maintaining the wellbeing of their host.

The term probiotic was introduced in 1953 by the German bacteriologist Werner Kollath to mean "active substances essential for a healthy life" [26]. In the last 30 years or so, however, research in the probiotic area has progressed considerably and significant advances have been made in the selection and characterization of specific probiotic cultures and substantiation of health claims relating to their consumption. For use in foods, the probiotic microorganisms should not only be capable of surviving passage through the digestive tract but also have the capability to proliferate in the gut. This means they must be resistant to gastric juices and be able to grow in the presence of bile under conditions in the intestines, or be consumed in a food vehicle that allows them to survive passage through the stomach and exposure to bile. The most commonly used probiotics are lactobacilli

Table 1: Foods High in Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAPs).

FODMAP	Foods high in FODMAPs
Excess fructose	Fruits: apple, clingstone peach, mango, nashi pear, pear, sugar snap pea, tinned fruit in natural juice, watermelon Honey sweeteners: fructose, high-fructose corn syrup Large total fructose dose: concentrated fruit sources, large servings of fruit, dried fruit, fruit juice
Lactose	Milk: regular and low-fat cow, goat, and sheep milk; ice cream Yogurts: regular and low-fat yogurts Cheeses: soft and fresh cheeses
Oligosaccharides (fructans and/or galactans)	Vegetables: artichoke, asparagus, beetroot, broccoli, brussel sprouts, cabbage, fennel, garlic, leek, okra, Cereals: rye and wheat cereals when eaten in large amounts (e.g. biscuits, bread, couscous, crackers, pasta) Legumes: baked bean, chickpea, lentil, red kidney bean Fruits: custard apple, persimmon, rambutan, watermelon, white peach
Polyols	Fruits: apple, apricot, avocado, cherry, longon, lychee, nashi pear, nectarine, peach, pear, plum, prune, watermelon, Vegetables: cauliflower, mushrooms, snow peas sweeteners: isomalt, maltitol, mannitol, sorbitol, xylitol, and other sweeteners ending in "-ol"

Citation: Tania SG. Probiotics in Pregnancy. Indian J Nutri. 2021;8(2): 231.

and bifido bacteria strains [27-28], but not exclusively, as other micro-organisms have also been used as probiotics, including the yeast Saccharomyces boulardii.

Probiotic microorganisms are generally LAB belonging to the species Lactobacillus acidophilus, L. gasseri, L. helveticus, L. johnsonii, L. (para)casei, L. reuteri, L. plantarum, L. rhamnosus, and L. fermentum, while members of the genus Bifidobacterium are also used, e.g., Bifidobacterium bifidum, B. longum, B. animalis, and B. breve [29-31]. On the basis of the currently available literature, probiotics can balance intestinal microbiota, and thereby regulate proper intestinal function and be effective in the prevention or treatment of several gastrointestinal disorders such as infectious diarrhea, antibiotic-related diarrhea, irritable bowel syndrome or Crohn's disease [32]. Other examples of health benefits promoted by probiotics supplied via dairy products are immunomodulatory effects (L. casei CRL431), reduction of serum cholesterol level (L. reuteri NCIMB 30242) and antihypertensive effects (L. plantarum TENSIATM) [33-35]. Of late, probiotics seems to be quite helpful in the management of rheumatoid arthritis.

Some foods naturally contain probiotics, while others have probiotics added during preparation. Foods containing probiotics include:

Live yoghurt

Live yoghurt drinks

Fermented and unfermented milk

Miso and tempeh, which are made from fermented soya beans

Some juices and soya drinks

Probiotics are available as supplements also.

Importance of Probiotics in pregnancy and otherwise

Bifidobacteria are the most important constituent of the dominant active flora [36]. Lactobacilli are part of the sub-dominant flora and are under control by the dominant flora. Dietary and environmental changes constitute the transient flora, which is exogenous and does not colonize the GI tract.

Since probiotics normally exist in our digestive system, their intake is generally considered safe. But effectiveness in treating specific symptoms or conditions is strain specific. Before starting a regimen of probiotics, it is wise to look for the right strain in that particular health condition.

GastroIntestinal Symptoms

Constipation

Constipation is one of the most common conditions that can cause discomfort in pregnancy. Hormones of pregnancy often result in relaxation of smooth muscle in the gastrointestinal (GI) tract, therefore, dietary manipulation that includes increasing fibre and fluids can help reduce constipation [37]. Over years, several studies have found that yogurt can treat constipation, of these few studies have been done in pregnant population. In one such randomized controlled trial of 60 women, researchers found that 300 g of probiotic-enriched yogurt (Bifidobacterium and Lactobacillus 4.8×10^{10} [CFU]) per day alleviated constipation better than conventional yogurt among pregnant women [38].

Few researchers have recommended including probiotic foods such as fermented dairy products like yogurt and kefir every day over probiotic supplements. They also mention the need for prebiotics in the form of fibre, recommending at least 30 g of fibre each day from whole foods such as whole grains, fruits and vegetables (including legumes), and nuts and seeds in the diet during pregnancy.

The proposed mechanisms by which probiotics can help in constipation are:

First, probiotics modify the gastrointestinal microbiota, which is known to be altered in constipation [39-40].

Second, probiotic metabolites may alter gut function, including sensation [41-42] and motility [43-44].

Third, some probiotics increase the production of lactate and short-chain fatty acids, reducing luminal pH, which some researchers have proposed will enhance colonic peristalsis and shorten whole gut transit time (GTT) [45-46].

A meta-analysis by Dimidi et al [47] indicated that overall probiotics positively affected and significantly improved the cardinal symptoms of constipation such as bloating, sensation of incomplete evacuation, occurrence of hard stools, ease of stool expulsion. There was a decrease in GTT by half a day. This latter finding was consistent with a meta-analysis by Miller et al [48] who had earlier shown that gut transit time is significantly decreased with probiotics.

B.lactis plays a significant role in increasing the stool frequency and improving stool consistency [49]. Normal stool frequency ranges from 3 to 21 bowel movements per week [50-51] and an increase of 1.3 bowel movements per week through probiotic consumption could normalize bowel frequency in adults with functional constipation.

Acute diarrhea

Probiotics can potentially provide an important means to reduce the problems associated with acute diarrhea, which is a major health problem globally, especially among children. The strongest evidence of a beneficial effect of defined strains of probiotics had been established using Lactobacillus rhamnosus GG and Bifidobacterium lactis BB-12 for prevention [52-53] and treatment [54-58] of acute diarrhea mainly caused by rotaviruses in children. A systematic review that included 12 randomized, controlled trials in the Cochrane database (the majority from affluent countries) concluded that probiotics reduced the mean duration of acute diarrhea in children by 29.2 hours in a fixed-effects model and by 30.48 hours in a random-effects model [59]. Two meta-analyses that evaluated similar studies found statistically significant but modest reductions of diarrhea duration [60]. Two RCTs evaluated probiotics for children with persistent diarrhea and reported dramatic reductions in diarrhea duration—4.8 and 3.9 days in Argentina [61] and India [62] respectively. Two trials evaluated probiotics for diarrhea prevention; children in Peru had 13% fewer diarrheal episodes after 15 months of Lactobacillus rhamnosus [63], whereas diarrhea frequency was reduced by 14%

among children in India who received daily doses of Lactobacillus casei for 12 weeks, with a 12-week follow-up period [64].

In the prevention of antibiotic-associated diarrhea (AAD), meta-analyses of published results of RCTs provide evidence for efficacy of a number of probiotic strains, such as S. boulardii [65-69]. Approximately one in seven cases of AAD was prevented by the use of a probiotic [65]. According to another review, administration of lactobacilli reduces AAD in adults, but not in children [66].

Diarrhea occurs in up to 34% of pregnant women, and its' causes in pregnancy mirror those of the non pregnant state, with the most common being infectious agents (e.g, Salmonella, Shigella, and Campylobacter species; Escherichia coli; protozoans; viruses). Food poisoning, medications, and irritable bowel syndrome are other common causes. Exacerbations of inflammatory bowel disease can also occur in pregnancy. Gastroenteritis symptoms, when severe, can cause dehydration and even preterm labour in cases that go untreated. Therefore, addition of probiotics would definitely make a difference.

Activity against Helicobacterpylori

Another development for probiotic applications is activity against Helicobacterpylori (H. pylori), a Gram negative pathogen responsible for type B gastritis, peptic ulcers and gastric cancer. Epidemiological studies show a close association between the prevalence of H. pylori and dyspeptic symptoms. Data from various studies suggests that most of the Lactobacillus and Bifidobacterium strains possess properties of acid tolerance and antimicrobial activity [70-72].

A study by Chen et al reported that probiotics, L. rhamnosus (GMNL-74) and L. acidophilus (GMNL-185), possess potent activity to inhibit H. pylori adhesion to epithelia, thereby inhibiting the release of inflammatory cytokines, and alleviating gastric inflammation [73]. The results are consistent with study done by Martinez et al [74]. A persistent stomach infection with H. pylori induces secretion of proinflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α, which are closely linked to MALT-lymphoma and gastric adenocarcinoma [75]. In addition, H. pylori infection alters gastric microbiota, leading to dysbiosis that favours H. pylori colonization and development of gastric cancer [76].

It has been further reported that probiotics exhibit anti-obesity effects by lowering serum cholesterol [77-78]. High serum cholesterol levels in humans leads to an increased risk of being infected with H. pylori and induction of pathogenesis [79-80].

Regulation of blood sugar levels in pregnancy

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance first diagnosed during pregnancy [81]. Maternal pregnancy complications in GDM include preeclampsia and instrumental or operative delivery. Fetal complications include macrosomia, polyhydramnios, preterm birth, shoulder dystocia and neonatal complications of admission to neonatal ICU, respiratory distress, hypoglycaemia, and jaundice. Both women with GDM and their infants are at increased risk of diabetes mellitus and metabolic dysfunction later in life [82-83]. A study examining probiotics in pregnancy suggested a benefit in reducing the incidence of gestational diabetes [84]. Supplementation with probiotics has been shown to improve glycaemic control in men and women with type 2 diabetes [85-86]. The gut microbiome is thought to influence obesity and type 2 diabetes through modification of energy extraction, inflammation, hunger and satiety, as well as lipid and glucose metabolism [87-89]. Probiotics may regulate glucose metabolism and metabolic syndrome [90-92], and the regulation of glucose metabolism is associated with improvement in type 2 diabetes and hyperglycemia. Probiotic supplementation during pregnancy may help maintain the density of the intestinal flora, thereby reducing the metabolic imbalance in pregnant women [93-94]. They are helpful in preventing worsening of insulin resistance in late pregnancy [95].

A recent Cochrane review studying the role of probiotics in GDM involving 256 women showed a 60% decrease in the rate of diagnosis of gestational diabetes mellitus in women taking probiotics from early pregnancy [96]. A systematic review and meta-analysis looking at the effect of treatment of GDM on pregnancy outcomes showed that treatment significantly reduced the risks of fetal macrosomia, large-for-gestational-age births, shoulder dystocia and gestational hypertension, as well as a tendency to reduction of perinatal/neonatal mortality and birth trauma [97].

In a randomized controlled trial, published in January 2017, subjects either took Lactobacillus rhamnosus HN001 or a placebo. Those who took the probiotic had a significantly lower incidence of GDM than those who didn't (2.1% vs 6.5%) [98]. A previously published randomized controlled trial found no protection against gestational diabetes with the use of Lactobacillus salivarius UCC118, perhaps indicating the difference in efficacy of the strain [99]. Other factors could be dosage, duration of treatment, timing of delivery (early vs later in pregnancy), or other genetic or environmental differences between the study groups.

A very recent study by Callaway et al [100] studied the role of probiotics in the prevention of GDM in overweight and obese women, in a total of 411 participants fulfilling the criteria. Probiotics containing strains Lactobacillus rhamnosus and Bifidobacterium animalis subspecies lactis were administered from the second trimester in these women. Assessment by OGTT (oral glucose tolerance test) was done at 28 weeks' gestation. The probiotics used in this study did not prevent GDM in overweight and obese pregnant women.

The diet therapy (including specific fat and fibre intake recommendations) was given to all patients enrolled. Diet together with probiotic group had a significantly reduced rate of gestational diabetes mellitus when compared to controls in a study conducted by Baral M including 256 women [101]. Probiotic treatment included Lactobacillus rhamnosus GG and Bifidobacterium lactis. Each probiotic was taken at 10 billion CFU per day. Specific bacterial ratios will either encourage or discourage obesity later in life and even predict obesity development [102]. High numbers of bifidobacteria and low numbers of Staphylococcus aureus in infancy can help protect against overweight and obesity in children, possibly revealing a key reason that breastfed infants enjoy a healthier metabolic outcome.

Probiotics help modulate the immune system and therefore

inflammation [103]. Obesity can lead to a state of low-grade systemic inflammation, possibly explaining the increased incidence of asthma in obese patients [104]. Since obesity and inflammation are related, it can be postulated that the probiotic control of inflammation plays a role in obesity prevention.

Probiotics use in preventing urogenital infections

The microbial species that inhabit the vaginal tract play an important role in the maintenance of health, and prevention of infection. Over 50 microbial species have been recovered from the vaginal tract [105-107]. These species do not exist independently, and studies in vitro and in humans have shown that a multispecies microbiota, usually associated with bacterial vaginosis (BV), are present in dense biofilms [108-111], while a lactobacilli dominant microbiota can be sparsely distributed on the epithelium [108-109,112]. Despite the close proximity of the vagina to the anus, the diversity of microbes present in the vagina is much lower than in the gut. The reason for this lower diversity is still unclear. Some species found in the gut, such as E. coli and Streptococcus, can also be found in the vagina, indicating that proper receptors, nutrients, and oxygen tension, are present for them to grow.

Factors such as hormonal changes (particularly estrogen), vaginal pH, and glycogen content can all affect the ability of lactobacilli to adhere to epithelial cells and colonize the vagina [113]. The menstrual cycle can also cause changes in the vaginal microbiota, with high concentrations of estrogen increasing adherence of lactobacilli to vaginal epithelial cells [114]. With the decrease in estrogen levels, there is also a decrease in lactobacilli present in the vaginal tract as seen in postmenopausal women [109,115-117].

While a vaginal tract dominated by lactobacilli appears to protect the host against some vaginal infections, it does not fully prevent colonization by other species. Pathogens are still able to coexist with these commensal organisms, as shown by Burton and Reid [118], where G. vaginalis, a pathogen associated with BV, was detected in a vaginal sample which also contained a species of Lactobacillus. Interestingly, G.vaginalis was displaced beyond detectable limits for 21 days, following a single intravaginal instillation of probiotic lactobacilli [115].

Pathogenic organisms are able to infect the vagina, with BV, yeast vaginitis, and UTI (urinary tract infections) causing an estimated one billion or more cases per year [119-122]. Lactobacilli are often found in patients with yeast vaginitis, therefore, the induction of infection does not appear to require the yeast displacing or killing off the lactobacilli. Urinary tract infections occur when pathogenic bacteria ascend from the vagina and replicate on, and sometimes within, the bladder urothelium [119,123-124]. In women with no history of UTI, vagina and perineum are most commonly colonized by lactobacilli [125], while in women with recurrent UTI there is an inverse association between lactobacilli and E. coli [126], suggesting that lactobacilli play a role in preventing infection.

The most common urogenital disorder in women of reproductive age is BV. Aerobic vaginitis has also been described in which the vagina is colonized by organisms such as E. coli and enterococci [127]. During pregnancy, BV can increase the risk of preterm labour and low birth weight [128-129]. Other problems associated with BV include pelvic inflammatory disease, UTI, and increased susceptibility to sexually transmitted diseases, including HIV [130-133].The organisms associated with BV form dense biofilms on the vaginal epithelium, and these are associated with increased resistance to lactobacilli-produced lactic acid and hydrogen peroxide (H_2O_2) which are normally antagonistic to planktonic organisms [134]. The bio films are also able to induce host expression of certain inflammatory factors, such as IL-1 and IL-8 [135]. It is not currently known whether the production of H_2O_2 by lactobacilli has a clinically protective role against BV.

As antimicrobial treatment of urogenital infections is not always effective, and problems remain due to bacterial and yeast resistance, recurrent infections [136-137], as well as side effects, it is no surprise that alternative remedies are of interest to patients and their caregivers. It is assumed that recurrences are due to antimicrobials failing to eradicate the pathogens, perhaps because of biofilm resistance, or that the virulent organisms come back from their source (the person's gut, or a sex partner) and attack a host whose defenses are suboptimal. Young girls who suffer from UTI are more likely to have repeated episodes in adulthood, and overall many UTI, BV, and yeast vaginitis patients will have a recurrence [138-139].

Recurrent infection may also be due to the elimination of the commensal organisms in the vagina by the antimicrobial, thereby increasing susceptibility to recolonization by pathogens [140-141]. This is one of the main reasons for considering the use of probiotics, to replenish the commensal microbes as a way to lower the risk of reinfection. The concept of delivering lactobacilli orally to repopulate the vagina was first reported in 2001 [142], and based upon the question "If urogenital pathogens can do this, why cannot lactobacilli"? The organisms were delivered in a milk base and shown to be recovered from the rectum [143]; therefore supporting the concept that ingested strains could pass through the intestine, reach the rectum, and potentially ascend to the vagina. This was confirmed independently by others [144].

The mechanisms whereby lactobacilli function as anti infective defenses are still not fully understood. As discussed above, this may involve production of antimicrobial factors [145], and maintenance of a vaginal pH of ≤4.5. It could also be due to bio surfactants which alter the surrounding surface tension and reduce the ability of a wide range of pathogens to adhere [146-147]. This might explain the relatively sparse coverage of epithelial cells noted in healthy women [112]. In addition, lactobacilli have been shown to bind (coaggregate) some pathogens and this may be a means to block their adhesion, kill them through production of antimicrobials, and prevent their spread to other areas of the vagina and bladder [108]. Among 10 strains of lactobacilli being evaluated for use in a probiotics tablet, Mastromarino et al. [148] found, in vitro, that Lactobacillus gasseri 335 and Lactobacillus salivarius FV2 were able to coaggregate with G.vaginalis. When these strains of lactobacilli were combined with Lactobacillus brevis CD2 in a vaginal tablet, adhesion of G. vaginalis was reduced by 57.7%, and 60.8% of adherent cells were displaced. Boris et al. found that the adherent properties of G. vaginalis were

similarly affected by Lactobacillus acidophilus [149]. It has been known for some time that Lactobacillus produce bacteriocins that can inhibit the growth of pathogens, including some associated with BV, such as G. vaginalis [150]. Only relatively recently has a study shown in animals that bacteriocin production might have an effect *in vivo*. Neri et al. [151] studied 84 women in the first trimester of pregnancy to observe the effects of probiotic-containing yoghurt on BV. The subjects were randomized to one of three treatment groups: inserting a tampon containing 5% acetic acid, a 10 to 15 mL vaginal douche containing > 1.0×10^8 colony-forming units/mL of L. acidophilus, or no treatment. Both active treatments were administered twice a day for one week. Amsel criteria were absent in 88%, 38%, and 15% of subjects who received intra vaginal lactobacilli, acetic acid tampons, and placebo, respectively, after 30 days. There was a significant difference in the cure rate between probiotic and control groups, and lactobacilli and acetic acid groups.

The efficacy of combining probiotics or placebo with oral metronidazole was assessed in 125 women aged 18 to 44 [152]. Oral metronidazole was administered at 500 mg twice daily to all patients for 7 days, and they were randomized to receive twice-daily oral capsules containing either a placebo or L. rhamnosus GR-1 and L. reuteri RC-14 at 1.0×10^9 colony-forming units for a total treatment duration of 30 days. At the end of 30 days, BV was considered absent if the patient had a negative sialidase test and a Nugent score of <3. This was the case in 40% of placebo and 88% of probiotic subjects. If an intermediate Nugent score was regarded as "cure of BV", the cure rate was 100% with metronidazole and probiotics versus 70% with metronidazole and placebo. This study is important as it implies that probiotics can augment the effects of antibiotics in treatment of disease.

Group B Streptococcus (GBS) is the leading cause of neonatal morbidity and mortality [153]. It may be passed from the mother colonized in the genital tract by GBS to their baby during vaginal birth, or by being spread to the amniotic fluid. This vertical transmission can lead to early-onset GBS disease of the newborn (EOGBSD), which manifests in the first 7 days of life, and can be fatal. While approximately 10 to 30% of pregnant people harbour GBS in the vagina or rectum, the incidence of neonatal GBS disease is 1 to 2 infants per 1000 births. The use of intrapartum antibiotics to treat colonized individuals with or without risk factors has led to a 70% decline in the incidence of early-onset GBS sepsis in the past decade [154]. Despite this impressive decline, antibiotic resistance has become a major public health concern. Association between intrapartum antibiotic use and ampicillin resistance in E. coli isolated from neonates has previously been documented [155]. Furthermore, while GBS has remained sensitive to penicillin, 20% are resistant to erythromycin and clindamycin, which are alternate drugs for patients allergic to penicillin. Alternative approaches are therefore needed to reduce the risk of GBS infection.

Earlier researches have been done which include the use of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 (Lactobacillus fermentum RC-14) in the colonization status of GBS in pregnant people [152]. Lactobacilli are part of normal gut and vaginal flora and have been widely used as probiotics to treat various conditions. In particular, these two strains have shown to be beneficial in the treatment of urinary tract infections and bacterial vaginosis [156]. As lactobacilli are part of the human gut flora and have low pathogenicity, no adverse reaction to lactobacilli is usually anticipated, though some patients may experience flatulence.

Bacteria of the lactobacillus sp. are the most common in probiotic capsule preparations. The natural vaginal flora play an important role in dislodging and inhibiting pathogens. The rationale for the use of probiotics then, is the return of the vaginal flora to their healthy, natural state [157]. Indeed, probiotics have been shown to alter the vaginal flora being an effective supplement in the treatment and cure of bacterial vaginosis, and vulvovaginal yeast infections. Probiotic capsules are considered safe for use in pregnancy [158].

The ongoing researches are using 2 capsules (together) of oral Lactobacillus GR-1 and RC-14 once daily for 12 weeks from 24 weeks of pregnancy until their GBS swab test is taken at 35-37 weeks of pregnancy. The studies tend to provide evidence that probiotic prophylaxis is an effective, low-risk strategy that can be offered to patients to reduce their risk of GBS colonization and thus, the need for intrapartum antibiotic prophylaxis and the risks and inconvenience associated with it.

The raised estrogen and growth hormone during pregnancy may increase the activity of HPV molecule and human papilloma virus (HPV) infection. Short-time HPV persistence has been associated with higher risk for cervical intra-epithelial neoplasia and a higher risk of High-Grade Squamous Intraepithelial Lesion (HSIL). Clinical data showed GR-1 and RC-14 can improve the cervical malignancy diagnostics quality for non-pregnant women. The influence of oral probiotics on postpartum diagnosis of cervical pathology remains unknown.

In a study by Hanson et al [159], participants in the probiotic group reported no adverse events or minor side effects; one half reported improved gastrointestinal symptoms. Although two women in each group had positive qualitative prenatal GBS cultures at 36 weeks, the probiotic group participants had lower quantitative GBS colony counts. The eight GBS negative averaged 90% probiotic adherence compared with two GBS positive women who averaged 68%. Yogurt ingestion was inversely related to GBS colonization. It was concluded that prenatal probiotic therapy has the potential to reduce GBS colonization which appears to be linked to its daily adherence.

Reduction in the incidence of Preeclampsia and Preterm delivery

Timely intake of probiotics during pregnancy might help lower the risks of preeclampsia and premature birth, suggests observational research. Probiotics may have an anti-inflammatory effect on lipopoly saccharide inflammatory response in human placental trophoblast cells [160,161]. The anti-inflammatory effect of orally ingested probiotics has also been shown *in vivo* [162-163].

In a study by Nordqvist et al [164], it was revealed that probiotic milk intake during late pregnancy (but not before or in early pregnancy) was associated with reduced risk of preeclampsia, and that

intake during early pregnancy (but not before or in late pregnancy) was associated with reduced risk of preterm delivery.

Two previous studies in the Norwegian Mother and Child Cohort Study (MoBa) showed associations between intake of milk containing probiotics during the first half of pregnancy and reduced risk of preeclampsia and spontaneous preterm delivery [165-166].

The gastrointestinal tract represents the largest immune interface with the environment, probiotics are known to modulate gastrointestinal health through suppression of pathogenic bacteria as stated earlier. Steinborn et al showed that preeclampsia and preterm delivery are characterised by changes in the composition of regulatory T cell, decreasing their suppressive activity [167]. In vitro studies have shown that probiotics (Lactobacillus rhamnosus GR-1 and LGG) may have an anti-inflammatory effect on LPS inflammatory response in human placental trophoblast cells [160,161], potentially a key cell type in preeclampsia. In another large observational study by Brantsaeter et al, it was concluded that there is an independent protective association between intake of probiotic milk products and preeclampsia, especially severe preeclampsia, suggesting that probiotics might specifically "target" and modify the type of inflammation underlying severe preeclampsia [165].

In a randomised, double-blind, placebo-controlled trial which was completed by 29 mother-infant pairs, it was shown that bacterial DNA was detected in all placental samples. Microbial DNA in amniotic fluid and placenta was associated with changes in TLR-related gene expression in the fetal intestine. Maternal probiotic supplementation (10^9 Bifidobacterium lactis alone or in combination with 10^9Lactobacillus rhamnosus GG) significantly modulated the expression of TLR-related genes both in the placenta and in the fetal gut. These findings suggest a link between the maternal gut and that of the developing fetus and that microbial contact at the feto-placental interface may be considered a physiological phenomenon [168].

Probiotics in allergic disease (Controlling inflammation, Stabilizing immune systems)

Probiotics appear not only to modulate T-cells and cytokine profile, but also to help accelerate recovery of barrier function. There is increasing evidence that disturbances in gut microbial composition play a role in the pathophysiology of immune-mediated disorders, such as allergic disease [169]. Gut microbiota are key players in the early development of both local immune maturation and systemic immune programming.

Gut microbiota confer specific immune-protective effects that are probably mediated through complex pathways within (and potentially even beyond) the gut-associated lymphoid tissue (GALT), the largest immune "organ" in humans. These effects include altered local immunoglobulin A (IgA) production and induction of tolerogenic dendritic cells and regulatory T cell populations, with production of immunomodulatory cytokines, such as interleukin (IL) 10 and transforming growth factor (TGF) beta [170]. These mechanisms appear to collectively inhibit local inflammation, improve gut barrier mechanisms, and consequently reduce the risk of inappropriate systemic immune responses.

Early studies reported that low levels of Bifidobacterium and early colonization with potentially pathogenic bacteria, such as Clostridioides (formerly Clostridium) difficile [171,172] and Staphylococcus aureus [171], were more prevalent in children who subsequently developed allergy. Consequently, it has been suggested that a high gut microbial diversity might be more important than the absence or presence of specific genera or species in the context of immune system maturation and subsequent development of immune-mediated disorders. This view is supported by prospective studies that demonstrated reduced gut microbial diversity early in life in infants who later developed allergic manifestations [173-175].

In a double-blind, randomized, placebo-controlled trial, L. rhamnosus GG was given to pregnant women for four weeks prior to delivery, then to newborns at high risk of allergy for six months with the result that there was a significant reduction in early atopic disease [176].The precise mechanisms have not been elucidated, but the premise is based upon the ability of lactobacilli to reverse increased intestinal permeability, enhance gut-specific IgA responses, promote gut barrier function through restoration of normal microbes, and enhance transforming growth factor beta and interleukin 10 production as well as cytokines that promote production of IgE antibodies [176,177].

Production of folate by intestinal bacteria, especially the Bifidobacteria

Folates represent an essential nutrition component in the human diet, being involved in many metabolic pathways. The daily recommended intake of folate is 400 μg/day for adults [178,179] (Table 2).

The gut microbiota has been recognized as a source of vitamins. The microbiota of the human colon is known to produce vitamin K (menaquinones) and most of the water-soluble vitamins of group B, including biotin, nicotinic acid, folates, riboflavin, thiamine, pyridoxine, panthotenic acid, and cobalamin [184]. Unlike dietary vitamins, which are mainly absorbed in the proximal part of the small intestine, the uptake of microbial vitamins predominantly occurs in the colon [185]. Colonocytes appear to be able to absorb biotin, thiamin, folates, riboflavin, panthotenic acid, and menaquinones,

Table 2: Importance of folate in body.

Efficiency of DNA replication, repair and methylation are affected by folate, therefore high amounts of folate are required by fast proliferating cells such as leucocytes, erythrocytes and enterocytes [180]
Prevention of Cancer: folate deficiency is often associated with increased risk of breast cancer and that low folate homeostasis may induce hypomethylation of DNA, thereby promoting cancer on the proliferating cells of the colorectal mucosa that supports rapid and continuous renewal of the epithelium [181-182]
In Inflammatory bowel disease: Increase intake of folate contributes to regulation of rectal cell turnover [183]
Prevention of neural tube defects in fetus
Low folate can lead to poor cognitive performance and coronary heart disease

Table 3: Important actions played by bifidobacteria [188-189]

They produce lactic and acetic acids which acidify the large intestine and restrict putrefactive and potentially pathogenic bacteria
Inhibit the attachment and the growth of transient organisms and pathogens
Repress harmful enzymatic activities within the microbiota
Activate a number of dietary compounds into bioactive healthy molecules
Produce vitamins and amino acids
Participate in the regulation of intestinal homeostasis
Modulate local and systemic immune responses
Play an important role in the protection against cancer and inflammatory diseases

indicating that the microbiota-produced vitamins may contribute to the systemic vitamin levels and especially to the homeostasis of the vitamins in the localized epithelial cells [185,186].

Bifidobacteria - How important they are!

Bifidobacterium are one of the most important health-promoting groups of the colonic microbiota and one of the most important microorganisms to be used as probiotics [187]. Bifidobacterium is a genus of high G + C Gram-positive eubacteria within the phylum of Actinobacteria (Table 3). Among nearly fifty species of bifidobacteria recognized so far [190], the most represented in the gastrointestinal tract of human adults or infants, are Bifidobacterium pseudocatenulatum, B. catenulatum, B. adolescentis, B. longum, B. infantis, B. breve, B. angulatum and B. dentium [191]. In a human trial, the administration of the few strains of bifidobacteria resulted in a significant increase of folate concentration in feces. Even though the effect on plasmatic levels needs further investigation, folate-producing bifidobacteria provide a complementary endogenous source of the vitamin and may contribute to prevent folate deficiency, which is often associated with premalignant changes in the colonic epithelia.

Prevalence of folate deficiency - especially among women of childbearing age- is a growing concern and thereby folate fortification programs should be implemented [192]. Foods can be naturally fortified with folate synthesized by LAB and bifidobacteria during manufacture of fermented foods [193,194].

B. adolescentis and B. dentium are capable of de novo folate production, while B. longum needs to be provided with pABA (para-aminobenzoic acid), and B. animalis requires folate. Several strains of bifidobacteria have been screened for their ability to produce folate in low-folate or folate-free media. Twenty-four strains of B. bifidum, B. infantis, B. breve, B. longum, and B. adolescentis were cultured in a low - folate semi synthetic medium and significant differences in vitamin accumulation were found among the species tested [195]. All B. bifidum and B. infantis strains were classified as high folate accumulators, while B. breve, B. longum, and B. adolescentis produced lower amounts of the vitamin. For all the strains, extracellular folate accounted for most of the accumulated vitamin [196]. In other studies, the highest folate accumulation in reconstituted skim-milk was obtained after incubation with B. breve and B. infantis or B. longum strains [193].

Ability to produce the vitamin in the folate-free medium was found only in 17 strains belonging to nine different species (B. adolescentis, B. breve, B. pseudocatenulatum, B. animalis, B. bifidum, B. catenulatum, B. dentium, B. infantis, and B. longum) [195]. The highest extracellular folate levels (between 41 and 82 ng mL^{-1}) were produced by four strains of B. adolescentis and two of B. pseudocatenulatum. Only one out of 15 B. longum strains grew in folate free-medium. The highest extracellular folate levels (between 41 and 82 ng mL^{-1}) were produced by four strains of B. adolescentis and two of B. pseudocatenulatum. Only one out of 15 B. longum strains grew in folate free-medium. These same strains of B. adolescentis and B. pseudocatenulatum, when given to 23 healthy volunteers in a pilot human study, significantly increased folate concentration in the feces of the subjects [197]. These results corroborate the assumption that the increase of folate levels was markedly due to the effective growth of the folate-producing bifidobacteria. The results from various studies support the evidence that folate-producing probiotic strains may represent an endogenous source of vitamin, preventing its' deficiency in the colon. Localized folate production in the large intestine may provide the proliferating enterocytes with this essential vitamin with potential effects in reducing colonic carcinogenesis [198].

The strains Streptococcus thermophilus CRL803/CRL415 and L. bulgaricus CRL871 were reported to be suitable for the elaboration of yogurt naturally bio-enriched in this vitamin [199]. High folate concentration (up to 150 μg/l) can be reached in yogurt as a result of the ability of S. thermophilus to produce this vitamin [200]. Among bifidobacteria, B. catenulatum ATCC 27539 was shown to produce high levels of folate *in vitro* [201], and B. lactis CSCC5127, B. infantis CSCC5187, and B. breve CSCC5181 strains increased folate concentration during fermentation of reconstituted skim milk [202]. Similarly, L. amylovorus CRL887 can be used for natural folate bio-enrichment of fermented milk [203].

Prevention of depression and anxiety postpartum

Depression and anxiety in pregnancy and after birth affects 10-15 per cent of women, although many are not recognised or treated. There is mounting evidence from animal studies that, the 'microbiome-gut-brain axis' - the biochemical signalling that takes place between the gastrointestinal tract and the central nervous system - may be important for mental health. Maternal depression can produce long-lasting effects on children's cognitive, social-emotional and health outcomes [204,205]. Anxiety often coexists with depression. Despite this, most women with post natal depression are either not recognised as being depressed, are unable to access psychological therapy or are reluctant to take antidepressant medication in pregnancy or while breastfeeding [206]. Furthermore it takes several weeks for the therapeutic effect of antidepressants to appear and there is a 15–30% discontinuation rate [207]. Furthermore, it has been suggested

that fermented foods (prebiotics) alter dietary items before they are ingested, resulting in phytochemical transformation into bioactive chemicals which reduce oxidative stress and inflammation [208].

In 2005 it was first suggested that probiotics might be an adjuvant therapy for major depression [209]. The study suggests that in depression and similar conditions where depression is a common symptom, lactobacilli levels may be low owing to migration of bacteria from the colon into the small intestine resulting in small intestinal bacterial overgrowth (SIBO). In patients with MDD (major depressive disorder), SIBO is likely to occur because it is often the result of intestinal stasis or low stomach acid secretion. Patients with depression are known to have low levels of stomach acid production and intestinal stasis. Cytokines linked to depressive symptoms, particularly interleukin1-beta (Il-1b) and tumor necrosis factor alpha(TNFa), are capable of inhibiting gastric acid secretion. In addition, physical inactivity, common to depression, is associated with SIBO [209]. Others have also suggested that probiotic enhancement of gut microbiota may improve mood outcomes [210].

The significance of small intestine bacterial over growth in cases of depression can lead to functional abdominal complaints, it can cause malabsorption of fat, carbohydrate, protein, B vitamins and other micronutrients, in turn leading to weakening of host defence against SIBO. Patients with depression are known to have low levels of folic acid, vitamins B_{12}, B_6 and zinc [211-214]. Low levels of vitamin B6 is associated with diminished conversion of alpha linolenic acid into mood regulating eicosapentaenoic acid (EPA). Non-digestible oligosaccharides can increase the availability of nutrients including zinc, effects that are attributed to increased bifidobacterium. It is interesting to note that treatment of SIBO has led to improvements in depression, memory and concentration among CFS patients [215].

A recent systematic review identified 10 clinical trials of the effect of probiotics on symptoms of depression [216]. Seven studies were in healthy subjects, 2 in chronic fatigue syndrome and one in depression. Three of 5 studies reported improved mood with probiotics, and 5 of 7 studies reported improvements in stress and anxiety. A recent study that was published after these reviews reported that obese women treated with a weight-reduction programme and probiotic had reduced symptoms of depression compared with the comparison group, but this effect was not seen in men [217]. There was no effect on anxiety.

In a very recent, first double-blind RCT of probiotics that has evaluated symptoms of depression and anxiety in the postpartum period [206], a significantly lower prevalence of symptoms of depression and anxiety was seen postpartum in women supplemented with the probiotic HN001 during and after pregnancy than in those given a placebo. Furthermore, the number of women reporting clinically significant levels of anxiety on screening was significantly lower in the probiotic group. In this study infant colic was associated with higher depression and anxiety scores. There has been a suggestion in the literature that probiotic supplementation may benefit maternal mood by reducing infant colic. One study reported that direct probiotic supplementation of infants reduced infant colic and this in turn was associated with lower rates of maternal depression [218].

RCT of 40 people with major depressive disorder treated with a combination of three probiotics (Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum) or placebo, also found a significant reduction in symptoms of depression on the Beck Depression Inventory (BDI) in the treatment group [219].

Many Lactobacillus and Bifidobacterium strains have been studied with respect to mental health and these genera seem to show the most beneficial effects [220]. Maternal stress during pregnancy can result in a reduction of both lactobacilli and bifidobacterium in offspring, relative to controls [221].

There is also evidence from human studies indicating that stress can negatively affect microflora [222,223]. Emotional stress can lead to acute and long term reductions in lactobacilli and Bifidobacterium [224]. Bifidobacterium appear to be extremely sensitive to emotional stress. Restraint stress and excess physical demands can also lead to decreases in lactobacilli and bifidobacterium in humans [225].

The gut contains over 100 million neurons; the GI tract is ultimately a meeting place of nerves, microorganisms and immune cells. Microorganisms are responsive to the host's neuroendocrine environment and, conversely, bacteria can influence the neuroendocrine environment by the production of neurochemicals such as gamma amino butyric acid (GABA), serotonin, and various biologically active peptides. Animal studies indicate that GI microorganisms can directly activate neural pathways, even in the absence of an immune response [226,227]. Probiotic bacteria may influence mood by their effect on cytokine production.

Preventing skin disease in newborn

The intestinal microflora in atopic dermatitis has been shown to contain significantly lower levels of bifidobacterium and higher levels of staphylococcus. Percentages of bifidobacteria are significantly lower in patients with severe atopy versus those with mild symptoms [209]. Probiotics should be consumed by pregnant and lactating women and their breastfed infants to prevent the development of atopic dermatitis [228].

A probiotic extract being developed from the human microbiome could offer drug-free topical therapy for patients with atopic dermatitis, and could protect against pathogenic biofilms [229]. The extract has anti-inflammatory effects as well. Staphylococcus aureus biofilms — both methicillin-resistant (MRSA) and methicillin-susceptible (MSSA) — play an important role in patients with moderate and severe atopic dermatitis. The topical extract can disrupt these biofilms and has tremendous potential to not only decrease infection risk, but to improve other aspects of the disease as well, since the bacterial colonization likely contributes to inflammation and skin barrier disruption. The effects are similar to dexamethasone.

In other clinical studies with infants allergic to cow's milk, atopic dermatitis was alleviated by ingestion of probiotic strains L. rhamnosus GG and B. lactis BB-12 [230-232].

The development of the infant microbiome is a key area of study, and its known that there are a variety of contributing factors and situations that impact differences in microbial colonization among infants. Differences in the microbiome have been linked to increased allergy risk. Presently, there is support for the use of probiotics to

prevent eczema. Since eczema is a precursor to a variety of atopic conditions (eg, food allergies and asthma), and because it causes a great deal of suffering, reducing or preventing it, is important. About 10.7% of children younger than 18 have eczema, and about 37% of those with moderate to severe eczema go on to develop food allergies, according to the American College of Allergy, Asthma and Immunology [233,234].While researchers continue to learn about the connection, controlling eczema may be one way to reduce the development of food allergies.

Two separate systematic meta-analyses found a reduction in eczema risk among the offspring of mothers who took probiotic supplements during pregnancy [235,236]. However, these two reviews had some limitations, so they were considered low quality and were not according to the current research [237]. According to the World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics, clinicians should recommend probiotics to women at high risk of having an allergic child, those who breast-feed infants who are at high risk, and to infants who are predisposed to the development of allergy [238]. According to the guidelines, "High risk for allergy in a child is defined as biological parent or sibling with existing or history of allergic rhinitis, asthma, eczema, or food allergy." In addition, the guidelines say that although the quality of the evidence may be low, the possible net effect is worth supplementation, since the risk of negative impact is low.

Probiotics and Infant colic

Babies who cry and fuss for more than 3 h daily have colic. The condition generally starts at 3 weeks of age, occurs on more than 3 days/week, and resolves after 3 months of age (hence the "rule of threes" . The most common description of colic is intense, "paroxysmal" crying that is markedly different from normal fussing and crying. It can also occur as prolonged, unpredictable crying, and the infant is restless and inconsolable. Crying may occur any time of the day without obvious cause but is most common after the evening feeding. The colicky episode is often accompanied by distention of the abdomen and cold feet. Often the baby seems to feel better after passing gas or a stool.

The neonatal microbiota is highly different compared to the adult one, since the first is characterized by rapid changes as mentioned earlier [239]. At birth, the newborn is exposed to a set of bacteria including staphylococci, enterobacteria, and enterococci that immediately colonize the gastrointestinal tract. In the first days of life, the gut is inhabited mainly by Bifidobacterium, Lactobacillus, Clostridium, and Bacteroides. From one to five months of life, the population of the gastrointestinal tract consists of Bifidobacteriales, Lactobacillales, and Clostridiales. At one year of age, the microbiota is similar to the adult one [240,241].

Infant colic previously was felt to be unresponsive to any treatment. Microbial dysbiosis began to be linked to this condition and was confirmed by several groups [242-244], and it was linked to gut inflammation [245]. Therefore, colic might represent a condition for which probiotic treatment would be useful. Several meta-analyses have shown that the probiotic L. reuteri, isolated from a Peruvian mother's breast milk, reduces crying time and irritability in this condition [246-248].

Probiotics and Arthritis

Very recently, dysbiosis have been included in the list of triggers leading to rheumatoid arthritis (RA). Rheumatoid arthritis is a systemic autoimmune disease characterized by autoantibody formation leading to the chronic inflammation of multiple joints. RA is also known to affect other internal organs, including the lungs, heart, and kidneys [249].

People with inflammatory arthritis have been shown to have inflammation of the intestinal tract, which results in increased intestinal permeability. This enables certain bacteria to cross the intestinal barrier, get into the bloodstream and trigger an inflammatory response. Probiotics may be able to help decrease the inflammation associated with increased intestinal permeability. Probiotics appear to have an impact on inflammation, reducing common biomarkers of inflammation, including C-reactive protein. They help to decrease the inflammation associated with increased intestinal permeability.

In a recent study by Zamini et al [250], daily probiotic capsules containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum were given for 8 weeks. Probiotic supplementation group resulted in improved Disease Activity Score of 28 joints (DAS-28). There was a significant decrease in serum insulin levels, homeostatic model assessment-B cell function (HOMA-B) and serum high-sensitivity C-reactive protein (hs-CRP) concentrations.

In a study by Mohammed et al [251], the efficacy of probiotics as an adjuvant therapy for rheumatoid arthritis was studied. The meta-analyses indicated that pro-inflammatory cytokine IL-6 was significantly lower in the probiotics compared with the placebo group but disease activity score could not find any difference.

A study by Chen et al. evaluated the gut microbiota profile in 40 patients with RA and 32 healthy controls. They found decreased gut microbial diversity in RA compared to controls, which additionally correlated with disease duration and with levels of serum rheumatoid factor [252].

Alipour et al. showed that L. casei 01 supplementation decreased serum high-sensitivity C-reactive protein (hs-CRP) levels, reduced tender and swollen joint counts, and improved global health (GH) score. A significant difference was also observed between the two groups with respect to circulating levels of interleukin (IL)-10, IL-12, and tumour necrosis factor (TNF)-α, in favour of the probiotic group [253].

Possible negative effects of probiotics use

Many probiotic products are used on the simple assumption that probiotics can retain health and well being, and potentially reduce long-term risk of diseases of the bowel, kidney, respiratory tract and heart. Multicentre large randomised controlled trials are needed to authenticate such an assumption before making it a regular practice. Study by Tannock et al. [254] mentions an important observation that the ingestion of probiotic strains has not led to measurable long-term colonization and survival in the host. Invariably, the microorganisms

are retained for days or weeks, but no longer. Thus, use of probiotics likely confers more transient than long-term effects, and so continued intake appears to be required. However, in newborn children where a commensally flora has not yet been established, it is assumed that probiotic microorganisms could become primary colonizers that remain long-term, perhaps even for life.

When ingested orally or used vaginally, probiotics are generally considered safe and are well tolerated. One theoretical concern associated with probiotics is the potential for these organisms to cause systemic infections. Although rare, probiotic-related bacteremia and fungemia have been reported [255]. It is estimated that the risk of developing bacteremia from ingested Lactobacillus probiotics is less than 1 per 1 million users [256], and the risk of developing fungemia from Saccharomyces boulardii estimated at 1 per 5.6 million users, and is estimated to be lower in healthy individuals [257]. There have been no reports of bifidobacterium sepsis associated with the use of probiotics in healthy individuals [258]. Risk factors for systemic infections include immune suppression, critical illness, central venous catheters, and impairment of the intestinal epithelial barrier. Probiotics administered orally to combat urogenital infections are not systemically absorbed but rather get to the site of action by passage through the gastrointestinal system and ascending into the vagina [142].

Annually, over one billion doses of probiotics are administered worldwide, and those administered for urogenital health have been well tolerated [115,152,256,259-261]. In addition, the mouth, gastrointestinal tract, and female genitourinary tract are inhabited by Lactobacillus [256]. Yet, endocarditis and bacteremia caused by lactobacilli are extremely rare. Most cases occur in patients with chronic diseases or debilitating conditions that provide direct access to the bloodstream from a leaky gut. Only 1.7% of 241 cases of bacteremia, endocarditis, and localized infections associated with Lactobacillus that were investigated by Cannon et al. were considered to have a possible link with heavy consumption of dairy products [262]. Only one case had a Lactobacillus isolate that was indistinguishable from a probiotic strain. There was no connection between the species of Lactobacillus isolated and the type of infection or mortality. A recent study that directly instilled a six-strain bacterial product into the intestine of patients with severe, potentially fatal pancreatitis portrayed probiotics as being dangerous [262]. However, the product had never been proven to be probiotic, it was administered as a drug unlike 99.9% of probiotics, the randomization process led to patients with multiorgan failure being given large doses of live bacteria, and the authors failed to provide a rationale for the study in an appropriate animal model. All this led to warranted adverse publicity for the field of probiotics [263].

Probiotics do not appear to pose any safety concerns for pregnant and lactating women. Systemic absorption is rare when probiotics are used by healthy individuals [264].

Future Researches

One of the studies to watch for is the Probiotics in Pregnancy (PiP) Study, a multicentre, multinational study that has recruited pregnant women to research the effect of L rhamnosus HN001 in early pregnancy through breast-feeding. Researchers expect administration to reduce the rate of infant eczema and atopic sensitization at 12 months. Researchers also are studying the impact of supplementation on GDM, bacterial vaginosis, and group B streptococcal vaginal colonization before birth, and depression and anxiety postpartum [265].

Another study to keep an eye on is The Environmental Determinants of Diabetes in the Young (TEDDY), also a multicentre, multinational study. The TEDDY study is exploring the causes of type 1 diabetes mellitus to understand what interventions could help reduce the risk of it's development. These researchers are exploring the interaction between genes and environmental contributors. The study is ongoing, but in 2015, researchers presented early data that showed a reduction of 33% in autoimmunity, based on the development of auto antibodies after infant supplementation with probiotics starting in the first month of life. Although promising, more research is needed to confirm these findings [266].

Probiotic foods are a safe way for pregnant women to introduce and consume healthful microbes during pregnancy and may provide other positive nutritional benefits. These may include foods such as fermented sauerkraut (a source of fibre), and yogurt and kefir (providing calcium and vitamin D). Pregnant patients should avoid unpasteurized milk and juice products because of the risk of foodborne illness. Pregnant women who fall into the high-risk category are good candidates for probiotic supplements. In fact, regular consumption of safe, whole, fermented, and probiotic foods may benefit all patients. Finally, research on the benefits of probiotics is growing and dietitians should continue to follow the research in this area to provide the best evidence-based guidelines to use in practice.

References

1. Hillman ET, Yao HLT, Nakatsu CH (2017) Microbial Ecology along the Gastrointestinal Tract. Microbes Environ 32: 300-313.
2. O'HaraA M, Shanahan F (2006) The gut flora as a forgotten organ. EMBO Rep 7: 688-693.
3. Johnson CL, Versalovic J (2012) The human microbiome and its potential importance to paediatrics. Pediatrics 129: 950-60.
4. Baldassarre ME, Palladino V, Amoruso A (2018) Rationale of Probiotic Supplementation during Pregnancy and Neonatal Period. Nutrients 10: 1693.
5. Lay C, Sutren M, Rochet V, Saunier K, Doré J, et al. (2005) Design and validation of 16S rRNA probes to enumerate members of the Clostridium leptum subgroup in human faecal microbiota. Environ Microbiol 7: 933-946.
6. Pickard JM, Zeng MY, Caruso R, Núñez G (2017) Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunol. Rev 279: 70-89.
7. Sohn K, Underwood MA (2017) Prenatal and postnatal administration of prebiotics and probiotics. AJOG 22: 284-289.
8. Gibson GR, Hutkins R, Sanders ME, Susan PL, Reimeret RA et al (2017) Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14:491.
9. Armstrong C (2011) AAP Reports on Use of Probiotics and Prebiotics in Children. Am Fam Physician. 83: 849-852.
10. Monash University. Dietary Fibre and natural prebiotics for gut health: FAQs. Monash University.

11. Lennard L.B (2011) New and Emerging Developments in Food Production. In: Wahlqvist, M.L, editor. Food and Nutrition: Food and Health Systems in Australia and New Zealand. 3rd ed. Crows Nest: Allen and Unwin 183-189.

12. Boehm G, Lidestri M, Casetta P, Jelinek J, Negretti F, et al. (2002) Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. Arch Dis Child Fetal Neonatal Ed 86: F178.

13. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, et al. (2006) A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. Arch Dis Child 91: 814-819.

14. Vandenplas Y, De Greef E, Veereman G (2004) Prebiotics in infant formula. Gut Microbes 5: 681–687.

15. Maslowski KM, Vieira AT, Ng A, Kranich J, et al. (2009) Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature 461: 1282.

16. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJA et al. (2006) Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 40: 235-243.

17. Schouten B, van Esch BC, Hofman GA, et al. (2009) Cow milk allergy symptoms are reduced in mice fed dietary synbiotics during oral sensitization with whey. J Nutr 139: 1398-1403.

18. Scholtens PA, Alliet P, Raes M, Alles MS, Kroes H, et al. (2008) Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. J Nutr 138: 1141- 1147.

19. van Hoffen E, Ruiter B, Faber J, Rabet LM, Knol EF, et al. (2009) A specific mixture of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. Allergy 64: 484.

20. Guarner F, Schaafsma GJ (1998) Probiotics. Int J Food Microbiol 39: 237-238.

21. World health Organization (2006) Food and Agriculture Organization of the United Nations. Probiotics in food. Health and nutritional properties and guidelines for evaluation. FAO Food and nutrition paper 85. FAO and WHO.

22. Metchnikoff E (1907) The prolongation of life: Optimistic studies. London: W. Heinemann; 1907. Lactic acid as inhibiting intestinal putrefaction; 161-83.

23. Tissier H (1906) Traitement des infections intestinales par la méthode de la flore bactérienne de l'intestin. CR.Soc Biol 60: 359-361.

24. Tannock GW (1999) Analysis of the intestinal microflora: A renaissance. Antonie van Leenwenhoek 76: 265-278.

25. Mitsuoka T (1992) Intestinal flora and ageing. Nutr Rev 50: 438-446.

26. Gasbarrini G, Bonvicini F, Gramenzi A (2015) Probiotics history. J Clin Gastroenterol. 2016 Nov/Dec; 50 Suppl 2, Proceedings from the 8th Probiotics, Prebiotics & New Foods for Microbiota and Human Health meeting held in Rome, Italy on September 13-15, S116-S119.

27. Holzapel WH, Haberer P, Snel J, Schillinger U, Hu in't Veld JH (1998) Overview of gut flora and probiotics. Intl J Food Microbiol 41: 85-101.

28. Klein G, Pack A, Bonnaparte C, Reuter G (1998) Taxonomy and physiology of lactic acid bacteria. Int J Food Microbiol 41: 103-125.

29. Tamime AY, Saarela M, Korslund Sødergaard A, Mistry VV, Shah NP (2005). "Production and maintenance of viability of probiotic micro-organisms in dairy products," in Probiotic Dairy Products, ed. A. Y. Tamime (Oxford: Blackwell Publishing Ltd) 39-72.

30. Castro JM, Tornadijo ME, Fresno JM, Sandoval H, et al. (2015) Biocheese: a food probiotic carrier. Biomed. Res. Int 723056.

31. Linares DM, Ross P, Stanton C, et al (2016) Beneficial microbes: the pharmacy in the gut. Bioengineered 7: 11-20.

32. Vanderhoof JA, Young RJ (1998) Use of probiotics in childhood gastrointestinal disorders. J. Pediatr. Gastroenterol. Nutr 27: 323-332.

33. EFSA (2011). Scientific Opinion on the substantiation of a health claim related to "Lactobacillus plantarum TENSIATM in the semihard Edam-type "heart cheese"of HarmonyTM" and maintenance of normal blood pressure pursuant to Article 13(5) of Regulation (EC) No 1924/20061. EFSA panel on dietetic products,nutrition and allergies (NDA). EFSA J. 9, 1981.

34. Jones ML, Martoni CJ, Parent M, Prakash S (2012) Cholesterollowering efficacy of a microencapsulated bile salt hydrolase-active Lactobacillus reuteri NCIMB 30242 yoghurt formulation in hypercholesterolaemic adults. Br J Nutr 107: 1505-1513.

35. Aragon F, Carino S, Perdigón G, de Moreno de LeBlanc A, et al (2014) The administration of milk fermented by the probiotic Lactobacillus casei CRL 431exerts an immunomodulatory effect against a breast tumour in a mouse model. Immunobiology 219: 457-464.

36. Harmsen HJ, Wildeboer-Veloo AC, Raangs GC, Wagendorp AA, Klijn N et al. (2000) Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. J Pediatr Gastroenterol Nutr 30: 61-67.

37. Cullen G, O'Donoghue D (2007) Constipation and pregnancy. Best Pract Res Clin Gastroenterol 21: 807.

38. Mirghafourvand M, Homayouni RA, Alizadeh Charandabi SM, Fardiazar Z, KShokri K(2016) The effect of probiotic yogurt on constipation in pregnant women: a randomized controlled clinical trial. Iranian Red Crescent Med 18: e39870.

39. Khalif IL, Quigley EM, Konovitch EA, I D Maximova et al (2005) Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. Dig Liver Dis 37: 838-849.

40. Zoppi G, Cinquetti M, Luciano A,A Benini A, Muner A, et al (1998) The intestinal ecosystem in chronic functional constipation. Acta Paediatr 87: 836-841.

41. Ait-Belgnaoui A, Han W, Lamine F, Eutamene H, HFioramontiet J, et al (2006) Lactobacillus farciminis treatment suppresses stress induced visceral hypersensitivity: a possible action through interaction with epithelial cell cytoskeleton contraction. Gut 55: 1090-1094.

42. Rousseaux C, Thuru X, Gelot A, Barnich N, Neutet C al (2007) Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. Nat Med 13: 35-37.

43. Bueno L, de Ponti F, Fried M, Kullak-Ublick GA, Kwiateket MA et al (2007) Serotonergic and non-serotonergic targets in the pharmacotherapy of visceral hypersensitivity. Neurogastroenterol Motil 19: 189-119.

44. Quigley EM (2007) Bacteria: a new player in gastrointestinal motility disorders–infections, bacterial overgrowth, and probiotics. Gastroenterol Clin North Am 36: 735-748.

45. Waller PA, Gopal PK, Leyer GJ, Ouwehand AC, Reiferet C et al. (2011) Dose-response effect of Bifidobacterium lactis HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. Scand J Gastroenterol 46: 1057-1064.

46. Salminen S, Salminen E (1997) Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. Scand J Gastroenterol Suppl 222: 45-48.

47. Dimidi E, Christodoulides S, Fragkos KC, Scott SM, Whelan K et al. (2014) The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. The American Journal of Clinical Nutrition 100: 1075-1084.

48. Miller LE, Ouwehand AC (2013) Probiotic supplementation decreases intestinal transit time: meta-analysis of randomized controlled trials. World J Gastroenterol 19: 4718-4725.

49. Saad RJ, Rao SS, Koch KL, Kuo B, Parkman HP, et al.(2010) Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. Am JGastroenterol 105: 403-411.

50. Connell AM, Hilton C, Irvine G, Lennard-Jones JE, Misiewiczet JJ, et al. (1965) Variation of bowel habit in two population samples. BMJ 2: 1095-1099.

51. Heaton KW, Radvan J, Cripps H, Mountford RA, Braddon FE, et al. (1992) Defecation frequency and timing, and stool form in the general population: a prospective study. Gut 33: 818-824.

52. Saavedra JM, Bauman NA, Oung I, Perman JA, Yolken RH, et al. (1994) Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhea and shedding of rotavirus. Lancet 344: 1046-1049.

53. Szajewska H, Kotowska M, Mrukowicz JZ, Armańska M, Mikołajczyk W, et al. (2001) Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr 138: 361-365.

54. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T, et al.(1991) A human Lactobacillus strain (Lactobacillus casei sp. strain GG) promotes recovery from acute diarrhea in children. Pediatrics 88: 90-97.

55. Guarino A, Berni Canani R, Spagnuolo MI, Albano F, Benedettoa LDi et al. (1997) Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. J Pediatr Gastroenterol Nutr 25: 516-519.

56. Majamaa H, Isolauri E, Saxelin M, Vesikari T et al. (1995) Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. J Pediatr Gastroent Nutr 20: 333-338.

57. Shornikova AV, Isolauri E, Burkanova L, Lukovnikova S, Vesikari T, et al.(1997) A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhea. Acta Paediatr 86: 460-465.

58. Perdone CA, Bernabeu AO, Postaire ER, Bouley CF, Reinert P (1999) The effect of supplementation by Lactobacillus casei (strain DN-114 001) on accute diarrhea in children attending day care centers. Int J Clin Pract 53: 179-184.

59. Allen SJ, Okoko B, Martinez E, Gregorio G, Danset LF (2004) Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev CD003048.

60. Huang JS, Bousvaros A,Lee JW, Diaz A, Davidson EJ, et al. (2002) Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. Dig Dis Sci 47: 2625-2634.

61. Gaon D, Garcia H, Winter L, Rodríguez N, Quintáset R et al.(2003) Effect of Lactobacillus strains and Saccharomyces boulardii on persistent diarrhea in children. Medicina (B Aires) 63: 293-298.

62. Basu S, Chatterjee M, Ganguly S, Chandra PK et al. (2007) Effect of Lactobacillus rhamnosus GG in persistent diarrhea in Indian children: a randomized controlled trial. J Clin Gastroenterol 41: 756-760.

63. Oberhelman RA,Gilman RH, Sheen P, Taylor DN, Black RE, et al. (1999) A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. J Pediatr 134: 15-20.

64. Sur D, Manna B, Niyogi SK, Ramamurthy T, A Palit A, et al. (2011) Role of probiotic in preventing acute diarrhoea in children: a community-based, randomized, double-blind placebo-controlled field trial in an urban slum. Epidemiol Infect 139: 919-26.

65. Szajewska H, Ruszczynski M, Radzikowski A (2006) Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. J Pediatr 149: 367-72.

66. Corrêa NB, Péret Filho LA, Penna FJ, Lima FMLS, Nicoli JR et al. (2005) A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. J Clin Gastroenterol 39: 385-389.

67. Hawrelak JA, Whitten DL, Myers SP (2005) Is Lactobacillus rhamnosus GG effective in preventing the onset of antibiotic-associated diarrhoea: a systematic review. Digestion. 72: 51-56.

68. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ, et al. (2002) Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ 324:1361.

69. Kale-Pradhan PB, Jassal HK, Wilhelm SM (2010) Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. Pharmacotherapy 30: 119-126.

70. Presti I, D'Orazio G, Labra M, La Ferla B, Mezzasalma V, et al. (2015) Evaluation of the probiotic properties of new Lactobacillus and Bifidobacterium strains and there in vitro effect. Appl. Microbiol. Biotech 99: 5613-5626.

71. Turkova K, Mavric A, Narat M, Rittich B, Spanová A, et al. (2013) Evaluation of Lactobacillus strains for selected probiotic properties. Folia Microbiol 58: 261-267.

72. Lievin-Le Moal V, Servin AL (2014) Anti-infective activities of lactobacillus strains in the human intestinal microbiota: From probiotics to gastrointestinal anti-infectious biotherapeutic agents. Clin. Microbiol. Rev 27: 167-199.

73. Chen YH, Tsai WH, Wu HY, Chen CY, Ling Yeh W, et al. (2019) Probiotic Lactobacillus spp. act Against Helicobacter pylori-induced Inflammation. J Clin Med 8: 90.

74. Martinez RC, Bedani R, Saad SM (2015) Scientific evidence for health effects attributed to the consumption of probiotics and prebiotics: An update for current perspectives and future challenges. Br. J. Nutr 114: 1993-2015.

75. Polk DB, Peek RM Jr (2010) Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer 10: 403-414.

76. Espinoza JL, Matsumoto A, Tanaka H, Matsumura I, et al. (2018) Gastric microbiota: An emerging player in Helicobacter pylori-induced gastric malignancies. Cancer Lett 414:147-152.

77. London LE, Kumar AH, Wall R, Casey PG, O'Sullivan O et al. (2014) Exopolysaccharide-producing probiotic Lactobacilli reduce serum cholesterol and modify enteric microbiota in ApoE-deficient mice. J Nutr 144: 1956-1962.

78. Michael DR, Davies TS, Moss JWE, Calvente DL , Ramji DP, et al. (2017) The anti-cholesterolaemic effect of a consortium of probiotics: An acute study in C57BL/6J mice. Sci Rep 7: 2883.

79. Lin HJ, Hsu FY, Chen WW, Lee CH, Lin YJ et al. (2016) Helicobacter pylori Activates HMGB1 Expression and Recruits RAGE into Lipid Rafts to Promote Inflammation in Gastric Epithelial Cells. Front Immunol 7:341.

80. Lai CH, Huang JC, Cheng HH, Wu MC, Huang MZ, et al. (2018) Helicobacter pylori cholesterol glucosylation modulates autophagy for increasing intracellular survival in macrophages. Cell Microbiol 20: e12947.

81. Hadar E, Oats J, Hod M (2009) Towards new diagnostic criteriafor diagnosing GDM: the HAPO study.Journal of PerinatalMedicine 37: 447-449.

82. Shah BR, Retnakaran R, Booth GL (2008) Increased risk of cardiovascular disease in young women following gestationaldiabetes mellitus.Diabetes Care 31: 1668-1669.

83. Vohr BR, Boney CM (2008) Gestational diabetes: the fore runner for the development of maternal and childhood obesity and metabolic syndrome? Journal of Maternal-Fetal Medicine 2: 149-157.

84. Laitinen K, Poussa T, Isolauri E (2009) Probiotics and dietary counselling contribute to glucose regulation during andafter pregnancy: a randomised controlled trial. Br J Nutr 101: 1679-1687.

85. Andreasen AS, Larsen N, Pedersen-Skovsgaard T, Berg RMG, Møller K, et al. (2010) Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr 104: 1831-1838.

86. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, et al. (2012) Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition 28: 539-543.

87. Flint HJ (2012) The impact of nutrition on the human microbiome. Nutrition Reviews 1: 10-13.

88. Nieuwdorp M, Gilijamse PW, Pai N, et al. (2014) Role of the microbiome in energy regulation and metabolism. Gastroenterology 146: 1525-1533.

89. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 444: 1027-1031.

90. Kadooka Y, Sato M, Ogawa A, Miyoshi M, Uenishi H et al. (2013) Effect of Lactobacillus gasseri SBT2055 in fermented milk on abdominal adiposity in adults in a randomised controlled trial. Br J Nutr 110: 1696-1703.

91. Barreto FM, Colado Simão AN, Morimoto HK, Lozovoy MA, Dichi I et al. (2014) Beneficial effects of Lactobacillus plantarum on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. Nutrition 30: 939-942.

92. Ruan Y, Sun J, He J, Chen F, Chen R, et al. (2015) Effect of Probiotics on Glycemic Control: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. PLoS One 10: e0132121.

93. Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29: 415-445.

94. Sekirov I, Russell SL, Antunes LC, Finlay BB, et al. Gut microbiota in health and disease. Physiol Rev 90: 859-904.

95. Asemi Z, Samimi M, Tabassi Z, Rad MN, Foroushani AR, et al.(2013) Effect of daily consumption of probiotic yoghurt on insulin resistance in pregnant women: a randomized controlled trial. Eur J Clin Nutr 67: 71-74.

96. Barrett HL, Dekker Nitert M, Conwell LS, Callaway LK (2014) Probiotics for preventing gestational diabetes.Cochrane Database of Systematic Reviews CD009951.

97. Poolsup N, Suksomboon N, Amin M (2014) Effect of treatment of gestational diabetes mellitus: a systematic review and meta-analysis. PLOS One 3: e92485.

98. Wickens KL, Barthow CA, Murphy R, Abels PR, Maude RM, et al. (2017) Early pregnancy probiotic supplementation with Lactobacillus rhamnosus HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial. Br J Nutr 117: 804-813.

99. Lindsay KL, Kennelly M, Culliton M, Smith T, Maguireet OC et al (2014) Probiotics in obese pregnancy do not reduce maternal fasting glucose: a double-blind, placebo-controlled, randomized trial (Probiotics in Pregnancy Study). Am J Clin Nutr 99: 1432-1439.

100. Callaway LK, McIntyre HD, Barrett HL, Katie Foxcroft, Anne Tremellen et al. (2019) Probiotics for the Prevention of Gestational Diabetes Mellitus in Overweight and Obese Women: Findings From the SPRING Double-Blind Randomized Controlled Trial. Diabetes Care 42: 364-371.

101. Baral M (2010) Probiotics and Pregnant Women. Natural medicine journal 2.

102. Ley RE, Turnbaugh PJ, Klein S, Gordonet JI (2006) Microbial ecology: human gut microbes associated with obesity. Nature 444: 1022-1023.

103. Laitinen K, Hoppu U, Ha¨ma¨la¨inen M, Linderborg K, Moilanenet E et al (2006) Breast milk fatty acids may link innate and adaptive immune response regulation: analysis of soluble CD14, prostaglandin E2, and fatty acids. Pediatr Res 59: 723-727.

104. Shore SA (2008) Obesity and asthma: possible mechanisms. J Allergy Clin Immunol 121: 1087-1093.

105. Redondo-Lopez V, Cook RL, Sobel JD (1990) Emerging role of lactobacilli in the control and maintenance of the vaginal bacterial microflora. Reviews of Infectious Diseases 12: 856-872.

106. Anukam KC, Osazuwa EO, Ahonkhai I, Reid G et al. (2005) 16S rRNA gene sequence and phylogenetic tree of Lactobacillusm species from the vagina of healthy Nigerian women. African Journal of Biotechnology 4: 1222-1227.

107. Oakley BB, Fiedler TL, Marrazzo JM, Fredricks DN et al. (2008) Diversity of human vaginal bacterial communities and associations with clinically defined bacterial vaginosis. Appl Environ Microbiol 74: 4898-4909.

108. Reid G, McGroarty JA, Domingue PAG,. Chow AW, Bruce AW et al. (190) Coaggregation of urogenital bacteria in vitro and in vivo. Current Microbiology 20: 47-52.

109. Heinemann C, Reid G (2005) Vaginal microbial diversity among postmenopausal women with and without hormone replacement therapy. Canadian Journal of Microbiology 51: 777-781.

110. Swidsinski A, Mendling W, Loening-Baucke V, Ladhoff A, Swidsinski S, et al. (2005) Adherent biofilms in bacterial vaginosis," Obstetrics & Gynecology 106: 1013-1023.

111. Saunders SG, Bocking A, Challis J, Reid G, et al. (2007) Effect of Lactobacillus challenge on Gardnerella vaginalis biofilms. Colloids and Surfaces B 55: 138-142

112. Nugent RP, Krohn MA, Hillier SL (1991) Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol 29: 297-301.

113. Galask RP (1988) Vaginal colonization by bacteria and yeast. American Journal of Obstetrics & Gynecology 158: 993-995.

114. Chan RCY, Bruce AW, Reid G (1984) Adherence of cervical, vaginal and distal urethral normal microbial flora to human uroepithelial cells and the inhibition of adherence of gram-negative uropathogens by competitive exclusion. The Journal of Urology 131: 596-601.

115. Burton JP, Cadieux PA, Reid G (2003) Improved understanding of the bacterial vaginal microbiota of women before and after probiotic instillation. Applied and Environmental Microbiology 69: 97-101.

116. Devillard E, Burton JP, Hammond JA, Lam D, Reid G, et al. (2004) Novel insight into the vaginal microflora in postmenopausal women under hormone replacement therapy as analyzed by PCR-denaturing gradient gel electrophoresis. Eur J Obstet Gynecol Reprod Biol 117: 76-81.

117. Raz R, Colodner R, Rohana Y Rottensterich E, Wasseret I, et al.(2003) Effectiveness of estriolcontaining vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in postmenopausal women. Clinical Infectious Diseases 36: 1362-1368.

118. Burton JP, Reid G (2002) Evaluation of the bacterial vaginal flora of 20 postmenopausal women by direct (Nugent score) and molecular (polymerase chain reaction and denaturing gradient gel electrophoresis) techniques. J Infect Dis 186: 1770-1780.

119. Reid G, Bruce AW (2006) Probiotics to prevent urinary tract infections: the rationale and evidence. World J Urol 24: 28-32.

120. Foxman B,Barlow R, D'Arcy H, Gillespie B, Sobel JD et al (2000) Urinary tract infection: self-reported incidence and associated costs. Annals of Epidemiology 10: 509-515.

121. Allsworth JE, Peipert JF (2007) Prevalence of bacterial vaginosis: 2001–2004 National Health and Nutrition Examination Survey data. Obstetrics & Gynecology 10: 114-120.

122. Sobel JD (2007) Vulvovaginal candidosis. The Lancet 369: 1961–1971.

123. Hooton TM, Scholes D, Hughes JP, Winter C, Robertset PL et al. (1996) A prospective study of risk factors for symptomatic urinary tract infection in young women. The New England Journal of Medicine 335: 468-474.

124. Imirzalioglu C, Hain T, Chakraborty T, Domann E, et al. (2008) Hidden pathogens uncovered: metagenomic analysis of urinary tract infections. Andrologia 40: 66-71.

125. Bruce AW, Chadwick P, Hassan A, VanCott GF, et al. (1973) Recurrent urethritis in women. Canadian Medical Association Journal 108: 973-976.

126. Gupta K, Stapleton AE, Hooton TM, Roberts PL, Fennell CL, et al.(1998) Inverse association of H2O2-producing lactobacilli and vaginal Escherichia coli colonization in women with recurrent urinary tract infections. The Journal of Infectious Diseases 178: 446-450.

127. Donders GG, Vereecken A, Bosmans E, Dekeersmaecker A, Salembier G, et al. (2002) Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. An International Journal of Obstetrics & Gynaecology 109: 34-43.

128. Gravett MG, Hummel D, Eschenbach DA, Holmes KK (1986) Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis. Obstet Gynecol 67: 229-237.

129. Jacobsson B, Pernevi P, Chidekel L, et al. (2002) Bacterial vaginosis in early

pregnancy may predispose for preterm birth and postpartum endometritis. Acta Obstetricia et Gynecologica Scandinavica 81:1006-1010.

130. Sewankambo N, Gray RH, Wawer MJ, Paxton L, McNaim D, et al. (1997) HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. The Lancet 350: 546-550.

131. Cherpes TT, Meyn LA, Krohn MA, et al. Risk factors for infection with herpes simplex virus type 2: role of smoking, douching, uncircumcised males, and vaginal flora. Sexually Transmitted Diseases 2003;30(5):405–410.

132. Sharami SH, Afrakhteh M, Shakiba M (2007) Urinary tract infections in pregnant women with bacterial vaginosis. J Obstet Gynaecol 27: 252-254.

133. Gallo MF, Warner L, Macaluso M, Stone KM, Brill I, et al. (2008) Risk factors for incident herpes simplex type 2 virus infection among women attending a sexually transmitted disease clinic. Sex Transm Dis 35: 679-685.

134. Patterson JL, Girerd PH, Karjane NW, Jefferson KK (2007) Effect of biofilm phenotype on resistance of Gardnerella vaginalis to hydrogen peroxide and lactic acid. Am Journal Obstet Gynecol 197: 170.e1-7.

135. Simhan HN, Caritis SN, Krohn MA, Hiller SL (2005) The vaginal inflammatory milieu and the risk of early premature preterm rupture of membranes. Am J Obstet Gynecol 192: 213-218.

136. Schmitt C, Sobel JD, Meriwether C (1992) Bacterial vaginosis: treatment with clindamycin cream versus oral metronidazole. Obstet Gynecol 79: 1020-1023.

137. Reid G, Seidenfeld A (1997) Drug resistance amongst uropathogens isolated from women in a suburban population:laboratory findings over 7 years. Can J Urol 4: 432-437.

138. Reid G (2001) Probiotic agents to protect the urogenital tract against infection. Am J Clin Nutr 73: 437S-443S.

139. Stamm WE, Raz R (1999) Factors contributing to susceptibility of postmenopausal women to recurrent urinary tract infections. Clin Infect Dis 28: 723-725.

140. Reid G, Bruce AW, Cook RL, Llano M (1990) Effect on the urogenital flora of antibiotic therapy for urinary tract infection. Scand J Infect Dis 22: 43-47.

141. Hooton TM, Hillier S, Johnson C, Roberts PI, Stamm WE (1991) Escherichia coli bacteriuria and contraceptive method. JAMA 265: 64-69.

142. Reid G, Bruce AW, Fraser N, Heinemann C, Owen J et al. (2001) Oral probiotics can resolve urogenital infections. FEMS Immunol Med Microbiol 30: 49-52.

143. Gardiner GE, Heinemann C, Baroja ML, Bruce AW, Beuerman D et al. (2002) Oral administration of the probiotic combination *Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 for human intestinal applications. Int Dairy J 12: 191-196.

144. Morelli L, Zonenenschain D, Del Piano M, Cognein P (2004) Utilization of the intestinal tract as a delivery system for urogenital probiotics. J Clin Gastroenterol 38: S107-S110.

145. Aroutcheva A, Gariti D, Simon M, Shott S, Faro J, et al. (2001) Defense factors of vaginal lactobacilli. Am J Obstet Gynecol 185: 375-379.

146. Velraeds MM, van der Mei HC, Reid G, Busscher HJ (1996) Inhibition of initial adhesion of uropathogenic Enterococcus faecalis by biosurfactants from Lactobacillus isolates. Appl Environ Microbiol 62: 1958-1963.

147. Velraeds MMC, van der Belt B, van der Mei HC, Reid G, Busscher HJ (1998) Interference in initial adhesion of uropathogenic bacteria and yeasts silicone rubber by a Lactobacillus acidophilus biosurfactant. J Med Microbiol 49: 790-794.

148. Mastromarino P, Brigidi P, Macchia S, Maggi L, Pirovano F, et al. (2002) Characterization and selection of vaginal Lactobacillus strains for the preparation of vaginal tablets. J Appl Microbiol 93 : 884-893.

149. Boris S, Suarez JE, V ´ azquez F, Barbes C (1998) Adherence of human vaginal lactobacilli to vaginal epithelial cells and interaction with uropathogens. Infect Immun 66: 1985-1989.

150. Simoes JA, Aroutcheva A,Heimler I, Shott S, Faro S (2001) Bacteriocin susceptibility of Gardnerella vaginalis and its relationship to biotype, genotype, and metronidazole susceptibility. Am J Obstet Gynecol 185: 1186-1190.

151. Neri A, Sabah G, Samra Z (1993) Bacterial vaginosis in pregnancy treated with yoghurt. Acta Obstet Gynecol Scand 72: 17-19.

152. Anukam K, Osazuwa E, Ahonkhai I, Ngwu M, Osemene G, et al. (2006) Augmentation of antimicrobial metronidazole therapy of bacterial vaginosis with oral probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14: randomized, double-blind, placebo controlled trial. Microbes Infect 8: 1450-1454.

153. Stoll BJ, Hansen NI, Sánchez PJ, Faix GR, Poindexter BB, et al. (2011) Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics 127: 817-826.

154. Verani JR, McGee L, Schrag SJ (2010) Prevention of perinatal group B streptococcal disease--revised guidelines from CDC. MMWR Recomm Rep 59(RR-10): 1-36.

155. Money DM, Dobson S. Canadian Paediatric Society, Infectious Diseases Commitee (2004) The prevention of early-onset neonatal group B streptococcal disease. J Obstet Gynaecol Can 26: 826-840.

156. Martinez RC, Franceschini SA, Patta MC, Quintana SM, Gomes BC, et al. (2009) Improved cure of bacterial vaginosis with single dose of tinidazole (2 g), Lactobacillus rhamnosus GR-1, and Lactobacillus reuteri RC-14: a randomized, double-blind, placebo-controlled trial. Can J Microbiol 55: 133-138.

157. Martinez RCR, Franceschini SA, Patta MC, Quintana SM, Candido RC, et al. (2009) Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14. Lett Appl Microbiol 48: 269-274.

158. Reid G, Dols J, Miller W (2009) Targeting the vaginal microbiota with probiotics as a means to counteract infections. Curr Opin Clin Nutr Metab Care 12: 583-587.

159. Hanson L, Vandevusse L, Duster M, Warrack S, Safdar N (2014) Feasibility of oral prenatal probiotics against maternal group B Streptococcus vaginal and rectal colonization. J Obstet Gynecol Neonatal Nurs 43: 294-304.

160. Yeganegi M, Watson CS, Martins A, Kim SO, Reid G, et al. (2009) Effect of Lactobacillus rhamnosus GR-1 supernatant and fetal sex on lipopolysaccharide induced cytokine and prostaglandin-regulating enzymes in human placental trophoblast cells: implications for treatment of bacterial vaginosis and prevention of preterm labor. Am J Obstet Gynecol 200: 532. e1-8.

161. Bloise E, Torricelli M, Novembri R, Borges LE, Carrarelli P, et al. (2010) Heat-killed Lactobacillus rhamnosus GG modulates urocortin and cytokine release in primary trophoblast cells. Placenta 31: 867-872.

162. van Baarlen P, Troost F, van der Meer C, Hooiveld G, Boekschoten M, et al. (2011) Human mucosal in vivo transcriptome responses to three lactobacilli indicate how probiotics may modulate human cellular pathways. Proc Natl Acad Sci U S A Suppl 1(Suppl 1): 4562-4569.

163. Lorea Baroja M, Kirjavainen PV, Hekmat S, Reid G (2007) Anti-inflammatory effects of probiotic yogurt in inflammatory bowel disease patients. Clin Exp Immunol 149: 470-479.

164. Nordqvist M, Jacobsson B, Brantsæter A-L, Myhre R, Nilsson S, et al. (2018) Timing of probiotic milk consumption during pregnancy and effects on the incidence of preeclampsia and preterm delivery: a prospective observational cohort study in Norway. BMJ Open 8: e018021.

165. Brantsaeter AL, Myhre R, Haugen M, Myking S, Sengpiel V, et al. (2011) Intake of probiotic food and risk of preeclampsia in primiparous women: the Norwegian Mother and Child Cohort Study. Am J Epidemiol 174: 807-815.

166. Myhre R, Brantsæter AL, Myking S, Gjessing HK, Sengpiel V, et al. (2011)

Intake of probiotic food and risk of spontaneous preterm delivery. Am J Clin Nutr 93: 151-157.

167. Steinborn A, Schmitt E, Kisielewicz A, Rechenberg S, Seissler N, et al. (2012) Pregnancy-associated diseases are characterized by the composition of the systemic regulatory T cell (Treg) pool with distinct subsets of Tregs. Clin Exp Immunol 167: 84-98.

168. Rautava S, Collado MC, Salminen S, Isolauri E (2012) Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial. Neonatology 102: 178-184.

169. West CE, Renz H, Jenmalm MC, Kozyrskyj AL, Allen KJ, et al. (2015) The gut microbiota and inflammatory noncommunicable diseases: associations and potentials for gut microbiota therapies. J Allergy Clin Immunol 135: 3-13.

170. Prescott SL, Björkstén B (2007) Probiotics for the prevention or treatment of allergic diseases. J Allergy Clin Immunol 120: 255-262.

171. Björkstén B, Sepp E, Julge K, Mikelsaar M (2001) Allergy development and the intestinal microflora during the first year of life. J Allergy Clin Immunol 108: 516-520.

172. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, et al. (2001) Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol 107: 129-134.

173. Wang M, Karlsson C, Olsson C, Adlerberth I, Wold AE, et al. (2008) Reduced diversity in the early fecal microbiota of infants with atopic eczema. J Allergy Clin Immunol 121: 129-134.

174. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, et al. (2012) Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol 129: 434-440.

175. Bisgaard H, Li N, Bonnelykke K, Chawes BLK, Skov T, et al. (2011) Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol 128: 646-652.

176. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, et al. (2001) Probiotics in primary prevention of atopic disease: A randomised placebo-controlled trial. Lancet 357: 1076-1079.

177. Isolauri E. Probiotics in prevention and treatment of allergic disease. Pediatr Allergy Immunol 2001;12(S14): 56-59.

178. FAO/WHO. Folate and folic acid. In Human Vitamin and Mineral Requirements: Report of a Joint FAO/WHO Expert Consultation. Bangkok, Thailand; FAO: Rome, Italy, 2001; Chapter 4,pp. 53-63.

179. IOM. Folate. In Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline; The National Academies Press: Washington,DC, USA, 1998; Chapter 8, pp. 196-305.

180. Fuchs CS, Willett WC, Colditz GA, Hunter DJ, Stampfer MJ, et al. (2002) The influence of folate and multivitamin use on the familial risk of colon cancer in women. Cancer Epidemiol. Biomarkers Prev 11: 227-234.

181. Sellers TA, Kushi LH, Cerhan JR, Vierkant RA, Gapstur SM, et al. (2001) Dietary folate intake, alcohol, and risk of breast cancer in a prospective study of postmenopausal women. Epidemiology 12: 420-428.

182. TerryP, Jain M, Miller AB, Howe GR, Rohan TE (2002) Dietary intake of folic acid and colorectal cancer risk in a cohort of women. Int. J. Cancer 97: 864-867.

183. Birn, H (2006) The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins. Am J Physiol Renal Physiol 291: F22-F36.

184. Hill MJ (1997) Intestinal flora and endogenous vitamin synthesis. Eur J Cancer Prev 6: S43-S45.

185. Said HM, Mohammed ZM (2006) Intestinal absorption of water-soluble vitamins: an update. Curr Opin Gastroenterol 22: 140-146.

186. Ichihashi T, Takagishi Y, Uchida K, Yamada H (1992) Colonic absorption of menaquinone-4 and menaquinone-9 in rats. J Nutr 122: 506-512.

187. Rossi M, Amaretti A, Raimondi S (2011) Folate Production by Probiotic Bacteria. Nutrients 3:118-134.

188. Mach T (2006) Clinical usefulness of probiotics in inflammatory bowel diseases. J Physiol Pharmacol.57: 23-33.

189. Rossi M, Amaretti A (2010) Probiotic Properties of Bifidobacteria. In Bifidobacteria: Genomics andMolecular Aspects; van Synderen, D, Mayo, B., Eds.; Caister Academic Press: Norfolk, 6: 97-123.

190. LPSN List of Prokaryotic names with Standing in Nomenclature.

191. Biavati B, Mattarelli P (2006) The Family Bifidobacteriaceae. In The Prokaryotes, 3rd ed.; Dworkin, M., Falkow, S., Rosenberg, E., Schleifer, K.H., Stackebrandt, E., Eds.; Springer: New York, NY, USA, 3: 322-382.

192. Linares DM, Gómez C, Renes E, Fresno JM, Tornadijo ME, et al. (2017) Lactic Acid Bacteria and Bifidobacteria with Potential to Design Natural Biofunctional Health-Promoting Dairy Foods. Front Microbiol 8: 846.

193. Lin MY, Young CM (2000) Folate levels in cultures of lactic acid bacteria. Int Dairy J 10: 409-413.

194. Saubade F, Hemery YM, Guyot JP, Humblot C (2017) Lactic acid fermentation as a tool for increasing the folate content of foods. Crit Rev Food Sci Nutr 57: 3894-3910.

195. Pompei A,Cordisco L, Amaretti A, Zanoni S, Matteuzzi D (2007) Folate production by bifidobacteria as a potential probiotic property. Appl Environ Microbiol 73: 179-185.

196. Deguchi Y, Morishita T, Mutai M (1985) Comparative studies on synthesis of water-soluble vitamins among human species of bifidobacteria. Agric Biol Chem 49: 13-19.

197. Strozzi GP, Mogna L (2008) Quantification of folic acid in human feces after administration of Bifidobacterium probiotic strains. J Clin Gastroenterol 42: S179-184.

198. Choi SW,Mason JB (2002) Folate status: effects on pathways of colorectal carcinogenesis. J Nutr 132: 2413S-2418S.

199. Laiño JE, Juarez del Valle M, Savoy de Giori G, JosephLeBlanc JG (2013) Development of a high folate concentration yogurt naturally bio-enriched using selected lactic acid bacteria. LWT Food Sci Technol 54: 1-5.

200. Hugenholtz J, Hunik J, Santos H, Smid E (2002) Nutraceutical production by propionibacteria.82: 103-112.

201. D'Aimmo MR, Mattarelli P, Biavati B, Carlsson NG, Andlid T (2012) The potential of bifidobacteria as a source of natural folate. J Appl Microbiol 112: 975-984.

202. Crittenden RG, Martinez NR, Playne MJ (2003) Synthesis and utilisation of folate by yoghurt starter cultures and probiotic bacteria. Int J Food Microbiol 80: 217-222.

203. Laiño JE, Juarez del Valle M, Savoy de Giori G, LeBlanc JGJ (2014) Applicability of a Lactobacillus amylovorus strain as co-culture for natural folate bio-enrichment of fermented milk. Int J Food Microbiol 19: 10-16.

204. Tronick E, Reck C (2009) Infants of depressed mothers. Harvard Rev Psychiatry 17: 147-156.

205. Grace SL, Evindar A, Stewart DE (2003) The effect of postpartum depression on child cognitive development and behavior: a review and critical analysis of the literature. Arch Women's Ment Health 6: 263-274.

206. Slykerman RF, Hood F, Wickens K, Thompson JMD, Barthow C, et al. (2017) Effect of Lactobacillus rhamnosus HN001 in Pregnancy on Postpartum Symptoms of Depression and Anxiety: A Randomised Double-blind Placebo-controlled Trial. EBioMedicine 24: 159-165.

207. Gartlehner G, Hansen RA, Carey TS, Lohr KN, Gaynes BN, et al. (2005) Discontinuation rates for selective serotonin reuptake inhibitors and other second-generation antidepressants in outpatients with major depressive

disorder: a systematic review and meta-analysis. Int Cli Psychopharmacol 20: 59-69.

208. Selhub EM., Logan AC, Bested AC (2014) Fermented foods, microbiota, and mental health: ancient practice meets nutritional psychiatry. J Physiol Anthropol 33: 2.

209. Logana AC, Katzman M (20015) Major depressive disorder: probiotics may be an adjuvant therapy. Med J Hypotheses 64: 533-538.

210. Dinan TG, Cryan JF (2016) Mood by microbes: towards clinical translation. Genome Med 6: 36.

211. Morris MS, Fava M, Jacques PF, Selhub J, Rosenberg IH (2003) Depression and folate status in the US population. Psychother Psychosom 72: 80-87.

212. Tiemeier H, van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, et al. (2002) Vitamin B12, folate, and homocysteine in depression: the Rotterdam study. Am J Psychiatry 159: 2099-2101.

213. Stewart JW, Harrison W, Quitkin F, Baker H (1984) Low B6 levels in depressed outpatients. Biol Psychiatry 19: 613-616.

214. Nowak G, Siwek M, Dudek D, Zieba A, Pilc A (2003) Effect of zinc supplementation on antidepressant therapy in unipolar depression: a preliminary placebo-controlled study. Pol J Pharmacol 55: 1143-1147.

215. Pimentel M, Hallegua D, Chow EJ, et al (2000) Eradication of small intestinal bacterial overgrowth decreases symptoms in chronic fatigue syndrome: a double blind, randomized study. Gastroenterology 118: A414.

216. Wallace CJK, Milev R (2017) The effects of probiotics on depressive symptoms in humans: a systematic review. Ann General Psychiatry 16: 14.

217. Sanchez M, Darimont C, Panahi S, Drapeau V, Marette A, et al. (2017) Effects of a diet-based weight-reducing program with probiotic supplementation on satiety efficie,ncy, eating behaviour traits, and psychosocial behaviours in obese individuals. Nutrients 9: 284.

218. Mi G, Zhao L, Qiao D, Kang WQ, Tang MQ, et al. (2015) Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. Antonie Van Leeuwenhoek 107: 154-155.

219. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, et al. (2016) Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. Nutrition32: 315-320.

220. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K (2014) Gut microbes and the brain: paradigm shift in neuroscience. J Neurosci 34: 15490-15496.

221. Bailey MT, Lubach GR, Coe CL (2004) Prenatal stress alters bacterial colonization of the gut in infant monkeys. J Pediatr Gastroenterol Nutr 38: 414-421.

222. Moore WE, Cato EP, Holdeman LV (1978) Some current concepts in intestinal bacteriology. Am J Clin Nutr (10 Suppl): S33-42.

223. Holdeman LV, Good IJ, Moore WE (1976) Human fecal flora:variation in bacterial composition within individuals and a possible effect of emotional stress. Appl Environ Microbiol 31: 359-375.

224. Lizko NN (1987) Stress and intestinal microflora. Nahrung 31: 443-447.

225. Lizko NN (1991) Problems of microbial ecology in man space missions. Acta Astronaut 23: 163-169.

226. Lyte M, Varcoe JJ, Bailey MT (1998) Anxiogenic effect of subclinical bacterial infection in mice in the absence of overt immune activation. Physiol Behav 65: 63-68.

227. Gaykema RP, Goehler LE, Lyte M (2004) Brain response to cecal infection with Campylobacter jejune: analysis with Fos immunohistochemistry. Brain Behav Immun 18: 238-245.

228. Johnson K (2014) Probiotics in Pregnancy, Lactation Reduce Dermatitis. American College of Allergy, Asthma & Immunology (ACAAI).

229. Johnson K (2014) Probiotic 'Promising' to Prevent and Treat Atopic Dermatitis. American College of Allergy, Asthma & Immunology (ACAAI).

230. Majamaa H, Isolauri E (1996) Evaluation of the gut mucosal barrier: Evidence for increased antigen transfer in children with atopic eczema. J Allergy Clin Immunol 97: 985-990.

231. Majamaa H, Isolauri E (1997) Probiotics: A novel approach in the management of food allergy. J Allergy Clin Immunol 99: 179-185.

232. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S (2000) Probiotics in the management of atopic eczema. Clin Exp Allergy 30: 1604-1610.

233. Shaw TE, Currie GP, Koudelka CW, Simpson EL (2011) Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol 131: 67-73.

234. Eczema and children (2017) American College of Allergy, Asthma and Immunology.

235. Cuello-Garcia C, Brozek J, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, et al. (2015) Probiotics for the prevention of allergy: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol 136: 952-961.

236. Zuccotti G, Mariapia F, Meneghin F, Barone G, Callegari ML, et al. (2015) Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy 70: 1356-1371.

237. Szajewska H, Shair R, Turck D, van Goudoever JB, Mihatsch WA, et al. (2015) Recommendations on probiotics in allergy prevention should not be based on pooling data from different strains. J Allergy Clin Immunol 136: 1422.

238. Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, et al. (2015) World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): probiotics. World Allergy Organ J 8: 4.

239. Pickard JM, Zeng MY, Caruso R, Núñez G (2017) Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunol. Rev 279: 70-89.

240. Indrio F,Riezzo G, Raimondi F, Di Mauro A, Francavilla R (2013) Microbiota Involvement in the Gut-Brain Axis. JPGN 57: S11-S15.

241. Baldassarre ME, Bellantuono L, Mastromarino P, Miccheli A, Fanelli M, et al. (2014) Gut and Breast Milk Microbiota and Their Role in the Development of the Immune Function. Curr Pediatr Rep 2: 218-226.

242. de Weerth C, Fuentes S, Puylaert P, de Vos WM (2013) Intestinal microbiota of infants with colic: development and specific signatures. Pediatrics 131: e550-558.

243. Rhoads JM, Fatheree NY, Norori J, Liu Y, Lucke JF, et al. (2009) Altered fecal microflora and increased fecal calprotectin in infants with colic.J Pediatr 155: 823-828.e1.

244. Savino F, Cordisco L, Tarasco V, Calabrese R, Palumeri E, et al. (2009) Molecular identification of coliform bacteria from colicky breastfed infants. Acta Paediatr 98: 1582-1588.

245. Rhoads JM, Collins J, Fatheree NY, Hashmi SS, Taylor CM, et al. (2018) Infant Colic Represents Gut Inflammation and Dysbiosis. J Pediatr 203: 55-61.e3.

246. Harb T, Matsuyama M, David M, Hill RJ (2016) Infant Colic-What works: A Systematic Review of Interventions for Breast-fed Infants. J Pediatr Gastroenterol Nutr 62: 668-686.

247. Sung V, D'Amico F, Cabana MD, Chau K, Koren G, et al. (2018) *Lactobacillus reuteri* to Treat Infant Colic: A Meta-analysis. Pediatrics 141: e20171811.

248. Xu M, Wang J, Wang N, Sun F, Wang L, et al. (2015) The Efficacy and Safety of the Probiotic Bacterium Lactobacillus reuteri DSM 17938 for Infantile Colic: A Meta-Analysis of Randomized Controlled Trials. PLoS ONE 10: e0141445.

249. de Oliveira GLV, Leite AZ, Higuchi BS, Gonzaga MI, Mariano VS (2017)

Intestinal dysbiosis and probiotic applications in autoimmune diseases. Immunology 152: 1-12.

250. Zamani B, Golkar HR, Farshbaf S, Emadi-Baygi M, Tajabadi-Ebrahimi M, et al. (2016) Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Int J Rheum Dis 19: 869-879.

251. Mohammed AT, Khattab M, Ahmed AM, Turk T , Sakr N, et al. (2017) The therapeutic effect of probiotics on rheumatoid arthritis: a systematic review and meta-analysis of randomized control trials. Clin Rheumatol 36: 2697-2707.

252. Chen J, Wright K, Davis JM, Jeraldo P, Marietta EV, et al. (2016) An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. Genome Med 8: 43.

253. Alipour B, Homayouni-Rad A, Vaghef-Mehrabany E, Sharif SK, Vaghef-Mehrabany L, et al. (2014) Effects of Lactobacillus casei supplementation on disease activity and inflammatory cytokines in rheumatoid arthritis patients: a randomized double-blind clinical trial. Int J Rheum Dis 17: 519-527.

254. Tannock GW, Munro K, Harmsen HJ, Welling GW, Smart J, et al. (2000) Analysis of fecal microflora of human subjects subjects consuming a probiotic product containing Lactobacillus rhamnosus DR20. Appl Environ Microbiol 66: 2578-2588.

255. Snydman DR (2008) The safety of probiotics. Clin Infect Dis 46: S104-111.

256. Borriello SP, Hammes WP, Holzapfel W, Marteau P, Schrezenmeir J, et al. (2003) Safety of probiotics that contain lactobacilli or bifidobacteria. Clin Infect Dis 36: 775-780.

257. Karpa KD (2007) Probiotics for Clostridium difficile diarrhea: putting it into perspective. Ann Pharmacother 41: 1284-1287.

258. Boyle RJ, Robins-Browne RM, Tang M (2006) Probiotic use in clinical practice: what are the risks? Am J Clin Nutr 83: 1256-1264.

259. Cadieux P, Burton J, Gardiner G, Braunstein I, Bruce AW, et al. (2002) Lactobacillus strains and vaginal ecology. JAMA 287: 1940-1941.

260. Anukam KC, Osazuwa E, Osemene GI, Ehigiagbe F, Bruce AW, et al. (2006) Clinical study comparing probiotic Lactobacillus GR-1 and RC-14 with metronidazole vaginal gel to treat symptomatic bacterial vaginosis. Microbes Infect 8: 2772-2776.

261. Marrazzo JM, Cook RL, Wiesenfeld HC, Murray PJ, Busse B, et al. (2006) Women's satisfaction with an intravaginal Lactobacillus capsule for the treatment of bacterial vaginosis. J Women's Health(Larchmt) 15: 1053-1060.

262. Cannon JP, Lee TA,Bolanos JT, Danziger LH (2005) Pathogenic relevance of Lactobacillus: a retrospective review of over 200 cases. Eur J Clin Microbiol Infect Dis 24: 31-40.

263. Reid G, Gibson G, Sanders ME, et al. (2009) Concerns over the Utrecht pancreatitis study. The Lancet 372:112-113.

264. Elias J, Bozzo P, Einarson A (2011) Are probiotics safe for use during pregnancy and lactation? Can Fam Phys 57: 299-301.

265. Barthow C, Wickens K, Stanley T, Mitchell EA, Maude R, et al. (2015) The Probiotics in Pregnancy Study (PiP): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy. BMC Pregnancy Childbirth 16: 133.

266. Uusitalo U, Liu X, Yang J, Aronsson CA, Hummel S, et al. (2016) Association of early exposure of probiotics and islet autoimmunity in the TEDDY study. JAMA Pediatr 170: 20-28.