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The case in favour of probiotics before, during and after pregnancy: insights from the first 1,500 days

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REVIEW ARTICLE

Abstract

Successful human reproduction requires microbial homeostasis in the female reproductive tract, and colonisation of the newborn with beneficial microbes. In order to prevent several complications associated with dysbiosis, the administration of probiotics is more often being considered. The objective of the enclosed review was to examine the rationale for probiotic utility before and during pregnancy and in the early phase of infant life. The conclusions emerged from a panel of researchers who met during the International Scientific Association for Probiotics and Prebiotics (ISAPP) workshop held in Washington, DC, USA in 2015. The group concluded based upon the current literature, that a case can be made for the use of a specific sets of probiotic organisms during the first 1,500 days of life, with the goal of a healthy pregnancy to term, and a healthy start to life with lowered risk of infections and inflammatory events. The key to successfully translating these recommendations to practice is that products be made available and affordable to women in developed and developing countries.

Keywords: probiotics, *Lactobacillus*, *Bifidobacterium*, microbiota, C section

1. Introduction

The rapid expansion of the probiotic market has resulted in a growing number of products ostensibly targeting the wellbeing of pregnant women and their newborns. The term ‘ostensibly’ is used as few of these products have actually been tested in humans, based upon a sparsity of evidence published in peer-reviewed journals. Despite this discrepancy, under the International Scientific Association for Probiotics and Prebiotics (ISAPP), we convened a meeting in Washington, DC, USA, of researchers interested in these areas, to determine whether published data provided sufficient reason to consider probiotic supplementation during pregnancy and early life.

The rationale comes from the fact that maternal, foetal and infant morbidity and mortality is often associated with infectious organisms (Lawn *et al.*, 2010; Van Dillen *et al.*, 2010) against which some probiotic strains can act (Deng *et al.*, 2015; Reid *et al.*, 1987). In addition, successful human reproduction has evolved under a close association with beneficial microbes (Aagaard *et al.*, 2014; Barbonetti *et al.*, 2011; Eckert *et al.*, 2003), therefore supplementing the beneficial ones could benefit the host (Figure 1).

The approach we took was to discuss three topics:
- What do we know about nutrition, maternal stress, microbiome and foetal development?
- What would be the basis for microbiota intervention at which stages of gestation?

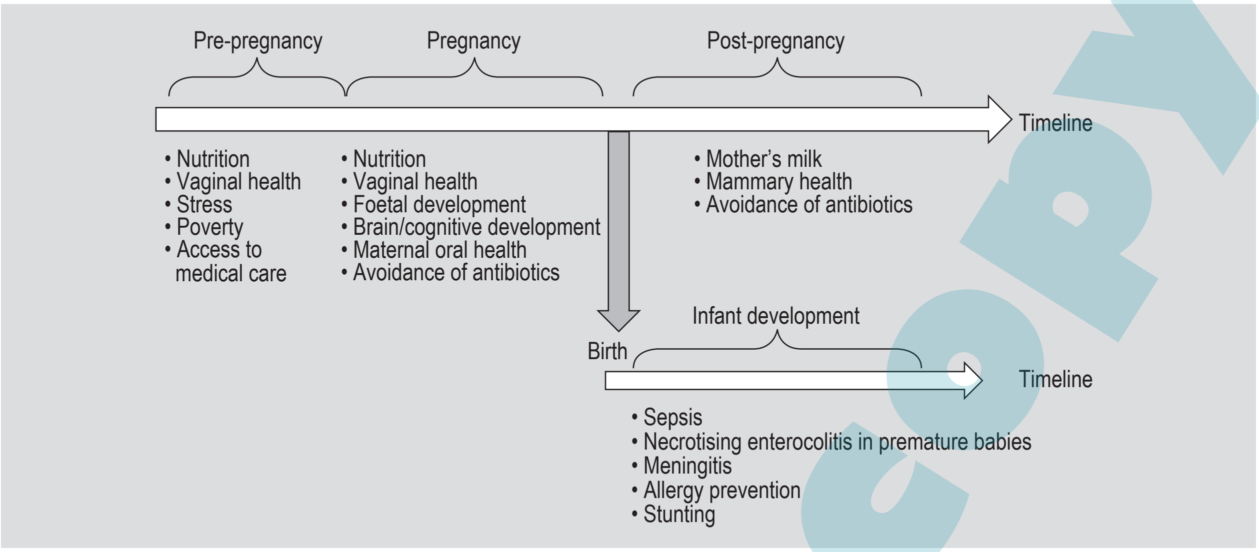

Figure 1. Factors involved in risk of failed pregnancy, and targets for probiotic supplementation from conception to early development.

- How would we potentially enhance the gut and/or vaginal microbiota to pass certain microbes to baby at birth, administer probiotics to breast-feeding mother (or enhance infant feeds?) to influence post-natal development?

The following is a summary of the discussions and subsequent review of the literature.

2. Pre-conception and early development

The presence of vaginal lactobacilli appears to be important for fertilisation and sperm motility (Barbonetti *et al.*, 2011). In that study, they showed that soluble factors produced by *Lactobacillus brevis*, *Lactobacillus salivarius*, and *Lactobacillus plantarum*, prevented membrane lipid-peroxidation of *Escherichia coli*-exposed spermatozoa, thus preserving their motility. The use of strains not commonly found in the reproductive tract suggested that this protective effect might be produced across a spectrum of lactobacilli. A study of 96 semen samples that measured semen quality (volume, sperm concentration, motility, Kruger's strict morphology, antisperm antibody (immunoglobulin A – IgA), Atypical, and leukocytes) showed that lactobacilli were associated with healthy quality (Weng *et al.*, 2014). It has been known for some time that lactobacilli are dominant in the vagina and male urethra of healthy individuals (Bowie *et al.*, 1977; Bruce *et al.*, 1973), so it is not surprising to find them in semen. However, their role in actual conception is intriguing.

Nutrients are obviously essential for health, but surprisingly, apart from overall calories, protein, calcium, iron, zinc and folic acid, there is no good understanding of the range of nutrients necessary for the development of different organs, vascular system, skeleton of the foetus, and none on the role of microbes and their metabolites from the mother or at the foetal-maternal interface. Nutrition is important during pregnancy to promote the healthy growth and development of the foetus, and nutrition counselling is clearly beneficial, and along with exercise can reduce the risk of gestational diabetes (Cordero *et al.*, 2015). From the first to third trimester, the maternal gut microbiota become more diverse and the immune system becomes more inflammatory, the latter in a process required for birthing. The supplementation of folic acid to prevent some birth defects preconception; iron to prevent anaemia; calcium and vitamin D for bone development; and perhaps other vitamins and minerals, are all general recommendations made throughout pregnancy. Avoidance of excessive exposure to environmental pollutants such as mercury, and of intake of antibiotics and certain other pharmaceutical agents is also recommended, even if not necessarily practiced (Hassoun-Barhamji *et al.*, 2015; Schoeman *et al.*, 2010).

3. Stress as a confounder

A variety of stresses were discussed that can impact pregnancy. Physical injury from trauma, including military combat, and the subsequent post-traumatic stress disorder, can be detrimental to a sustained healthy pregnancy (Shaw *et al.*, 2014). Partner abuse increases the likelihood of a neonate having an adverse outcome (Alhusen *et al.*, 2014). It is disturbing that partner abuse, especially emotional, is rife in many countries, compounding the disparity of the males being older and more likely addicted to drugs and alcohol partnering with young females with a lower educational level (Bagcchi, 2015; Ibrahim *et al.*, 2015). Personal and social violence are most pervasive and destructive systematic violation of human rights.

A study of two large longitudinal cohorts showed that children of women who experienced severe childhood abuse were more likely to be overweight and smoke in adolescence and early adulthood compared with children of women who reported no abuse (Roberts *et al.*, 2014). In addition, violence against the mother increases the risk of autism spectrum disorder in her offspring (Roberts *et al.*, 2015). This emphasises that adverse health outcomes can occur decades after the traumatic event. It would be foolhardy to suggest that probiotic intake can overcome the severe stress effects of such trauma, but a lowering of anxiety and perhaps aggressive behaviour through gut-vagal nerve mechanisms is worthy of testing (Bailey, 2014), particularly given studies showing probiotics can reduce exam stress (Marcos *et al.*, 2004) and psychological distress measured particularly by the Hopkins Symptom Checklist HSCL-90 scale (global severity index, $P<0.05$; somatisation, $P<0.05$; depression, $P<0.05$; and anger-hostility, $P<0.05$), the Hospital Anxiety and Depression Scale (HADS global score, $P<0.05$; and HADS-anxiety, $P<0.06$), and by the CCL (problem solving, $P<0.05$) and the urinary free cortisol level ($P<0.05$) (Messaoudi *et al.,* 2011).

4. Chronic malnutrition

Nutrition is a fundamental asset of human capital. Malnutrition disempowers individuals by aggravating infection and illness, lowering educational attainment and diminishing livelihood skills and family savings. Globally 165 million children are stunted and 80% of those live in 14 countries including Bangladesh (Black *et al.,* 2013; UNICEF, 2013). Under-nutrition underlies about 3.1 million deaths of children aged less than 5 years annually (Bhutta *et al.,* 2013; UNICEF, 2013). In Bangladesh, the prevalence of malnutrition is very high and many women and children suffer from one or more forms of wasting, stunting, underweight, vitamin A deficiency, iodine deficiency disorders and anaemia. Though the country has made good progress in the last decade, 41% of children aged under five years still suffer from moderate to severe stunting, an indicator for chronic malnutrition. There is clearly a role for probiotic food in alleviating malnutrition. A yoghurt not supplemented with probiotic, but that provides 30% required daily intake of iron, zinc, iodine and vitamin A has been introduced in Bangladesh with resultant improvements in height gain after one year (Sazawal *et al.,* 2013). A study from India showed the potential to alleviate stunting by improving gut-barrier function, nutrient uptake and lowering diarrhoeal rates (Saran *et al.,* 2002) (Table 1). The widely available, nutrient-rich *Moringa oleifera* provides another means to supplement probiotic fermented milk in developing countries (Van Tienen *et al.,* 2011), including for pregnant women (Bisanz *et al.,* 2015).

5. Foetal brain development

The foetal brain develops early in gestation and matures post-birth. Its composition is mostly fat cells. Malnutrition is well known to diminish cognitive function. Long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) improve neural development in humans resulting in improved cognition

Table 1. Probiotic strains for use before and during pregnancy and for early life of the newborn.

Strains	Timing of administration	Objective
Lactobacillus brevi cd2, *Lactobacillus salivarius* fv2, and *Lactobacillus plantarum* fv9	pre-conception	reduce risk of sperm lipid peroxidation and aid sperm motility and viability
Lactobacillus rhamnosus GR-1 and *Lactobacillus reuteri* RC-14	pre-conception and during 1st to 3rd trimester	reduce recurrence of bacterial vaginosis and heavy metal uptake
L. rhamnosus GG and *Bifidobacterium lactis* Bb-12	first trimester	reduce risk of gestational diabetes
L. rhamnosus LPR and *Bifidobacterium longum* BL999 or *Lactobacillus paracasei* ST11 and *B. longum* BL999	for the last two months of pregnancy and first two months of breastfeeding	reduce the risk of atopic eczema
Lactobacillus fermentum CECT5716 or *L. salivarius* CECT5713 or *Bifidobacterium infantis*	for three weeks before delivery	to reduce risk of mastitis and improve infant health through it being in breast milk
B. lactis Bb-12 and *L. rhamnosus* GG	from week 20 of pregnancy to term then to newborn for first 6 months	reduce the risk of allergic disease
Bifidobacterium breve, *Bifidobacterium bifidum*, *B. longum*, *B. infantis*, and *L. rhamnosus* HA-111	first day of life of premature baby until discharge	to prevent NEC
L. reuteri ATCC 55730	2-5 years of age	for oral health to reduce plaque and caries
50 ml curd containing *Lactobacillus acidophilus*	2-5 years of age	reduce stunting

and sensorimotor integration (Janssen and Kiliaan, 2014). A study has shown that supplementation of the maternal diet with cod liver oil containing 1,183 mg/10 ml DHA, 803 mg/10 ml EPA and a total of 2,494 mg/10 ml summation operator n-3 polyunsaturated fatty acids correlated with improved mental processing scores of the children at four years of age (Helland *et al.,* 2003). It is feasible that maternal ingestion of probiotic strains producing compounds such as alpha linoleic acid (Yang *et al.,* 2014), could also improve foetal brain development and subsequent childhood cognition. The ability of *Bifidobacterium breve* to produce alpha linolenic acid (Rosberg-Cody *et al.,* 2004), raises the concept of administering it as a probiotic in the 3rd trimester for foetal neural development. As this species is generally regarded as safe, it could be tested, although how success would be measured is difficult to define. Another potential mechanism is the production by the probiotics of neurochemicals that can influence cognition (Lyte and Cryan, 2014).

Progress in the development of modern imaging techniques to assess brain size and function and track auditory and organ development in the foetus (Girardi, 2015; Lagercrantz, 2014) has made it possible to study the brain before and after maternal probiotic intervention. However, this invariably require a period of stillness that is not easy to acquire and is expensive due to time on the imaging system. We look forward to seeing functional data that correlates improvements in the foetal and infant brain following probiotic use.

6. The basis for probiotic use before and during pregnancy

As stated, there is a basis for examining probiotic use during pregnancy. The following section will list probiotic strains that could be considered to improve reproductive outcomes. No claim is made that these strains are conclusively proven to safely and effectively confer these benefits, but there is merit to further studies.

Oral health

Oral diseases remain a factor in poor pregnancy outcomes, with studies suggesting that periodontal bacteria can directly infect the uteroplacenta and the foetus, and systemic inflammation can activate preterm labour at the maternal-foetal interface (Cetin *et al.,* 2012). Recent work has demonstrated that probiotic bacteria can decrease oral pathogen levels and also influence salivary and gingival levels of caries related factors, including *Streptococcus mutans* (Saha *et al.,* 2014). There appears to be a good rationale for using probiotics during the prenatal period for supplementation of dental hygiene. However, these studies have focused on infants, and thus there is insufficient level of evidence to provide specific recommendations for treating pregnant women.

On the other hand, various studies support the use of probiotics for infants. Early administration of *Lactobacillus reuteri* ATCC 55730 from birth and during the first year of life is associated with reduced caries prevalence and gingivitis score in the primary dentition at 9 years of age (Stensson *et al.,* 2014). This conclusion was based upon clinical and radiographic examination of the primary dentition and carious lesions, plaque and gingivitis, and determination of mutans streptococci, lactobacilli and salivary secretory IgA. In another study, the failure to reduce *S. mutans* colonisation using *Bifidobacterium lactis*, xylitol or sorbitol twice daily for an average of 14 months via novel slow-release pacifier or a spoon (daily dose of 10^{10} cfu and polyol 200-600 mg) emphasises that not all probiotic strains work (Taipale *et al.,* 2012).

In a randomised, controlled, double-blind trial healthy young volunteers used lozenges containing a combination of *Lactobacillus rhamnosus* GG and *B. lactis* Bb-12 or lozenges without added probiotics (control group, n=31) for 4 weeks (Toiviainen *et al.,* 2015). At baseline and at the end of the test period, the plaque index (PI) and gingival index (GI) were determined, and stimulated saliva was collected. The probiotic lozenge decreased both PI and GI ($P<0.05$) while no changes were observed in the control group. However, no probiotic-induced changes were found in the microbial compositions of saliva in either group. The probiotic lozenge improved the periodontal status without affecting the oral microbiota. Short-term probiotic consumption decreased the amount of plaque which was associated with a clinical impact: a decrease in gingival inflammation.

Reproductive health

Bacterial vaginosis (BV) diminishes the ability to conceive and increases the risk of preterm delivery (Li *et al.,* 2012), perhaps mediated by specific strains of *Leptotrichia/Sneathia*, BVAB1 and *Mobiluncus* (Nelson *et al.,* 2014). The case has been made for replenishing and maintaining lactobacilli before and during pregnancy. Intervention studies have been undertaken to prove efficacy of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 taken orally, but the control group rate for preterm labour was too low to make definitive conclusions despite some evidence of an effect (A.D. Bocking, unpublished data; Krauss-Silva *et al.,* 2011). Nevertheless, the safe use of the *L. rhamnosus* GR-1 and *L. reuteri* RC-14 combination orally per day in humans, plus supportive *in vitro* and animal studies (Yang *et al.,* 2014), and anti-BV effects (Hummelen *et al.,* 2010; Macklaim *et al.,* 2015, Reid *et al.,* 2001) supports their use in pregnancy. Furthermore, the ability of *L. rhamnosus* GR-1 to reduce uptake of mercury and arsenic in pregnancy (Bisanz *et al.*, 2014) could be extremely important as excessive levels of heavy metals exist in women (Schoeman *et al.*, 2010), and these can have detrimental effects on foetal neurodevelopment. The latter probiotic action has clinical significance particularly in the developing world.

The use of probiotics to prevent preterm labour by reducing the risk of BV has a good clinical rational and is supported by a series of *in vitro* and animal studies (Yang *et al.*, 2015). However, in Brazilian and Canadian clinical trials using these strains, treatment has been short in duration therapy (A.D. Bocking, unpublished data; Krauss-Silva *et al.*, 2011). Given that BV recurrence can occur at any time, it makes better sense to administer the GR-1/RC-14 probiotics orally each day from the second trimester to term. With no apparent safety concerns, such treatment may also reduce urinary tract infection rates (Beerepoot *et al.*, 2012) and improve gut function.

Given the increased incidence of obesity and diabetes, we explored the potential to apply probiotics over and above nutrition counselling and exercise (Van Poppel *et al.*, 2014). The recently discovered association between gut microbiota composition and host metabolism and obesity (reviewed in Cani *et al.*, 2014) has created research interest in gut microecology during pregnancy. Significant changes in gut microbiota composition associated with weight, weight gain and cholesterol levels have been reported to occur during pregnancy (Koren *et al.*, 2012; Santacruz *et al.*, 2010). Moreover, the pregnancy-induced changes in gut microbiota composition have been shown to lead to obesity in experimental animals (Koren *et al.*, 2012). Based on these observations, it has been hypothesised that modulating the maternal microbial environment by certain probiotics during pregnancy might reduce the risk of excessive weight gain and gestational diabetes (GDM). In line with this notion, supplementation with the probiotics *L. rhamnosus* GG and *B. lactis* Bb-12 together with dietary counselling starting from the first trimester of pregnancy reduced the risk of GDM from 36 to 13% and resulted in lower blood glucose and insulin concentrations and improved glucose tolerance in a randomised, controlled trial of 256 pregnant women from Finland while dietary counselling alone had no impact on GDM risk (Laitinen *et al.*, 2009). These promising results warrant confirmation in larger clinical trials.

The potential to influence newborn health via the mother's milk, has been raised by the finding that probiotic *Lactobacillus fermentum* CECT5716 or *L. salivarius* CECT5713 reach the mammary ducts after three weeks oral administration in women with mastitis (Arroyo *et al.*, 2010). Thus, presumably if a woman took these strains in the third trimester, they could be passed on to the newborn through breast feeding, as well as helping to prevent mastitis. To recommend this for newborn health, studies would be required, and strains such as *Bifidobacterium longum* subsp. *infantis* of potential more importance to the newborn (Underwood *et al.*, 2013, 2015; Zivkovic *et al.*, 2011) should be tested. Such approaches may be of interest in women intending to have an elective caesarean (C) section, a procedure that is highly common practice in developed countries.

7. Elective Caesarean section issues

The rising rates of C section (both elective and emergency after labour) in developed countries, approaching 31% in the USA (Neu and Rushing, 2011) is a significant issue with important implications for the 'adequacy and diversity' of the initial infant microbiome (Mueller *et al.*, 2015). The process of vaginal birth enables the mother's reproductive tract microbiome to serve as the 'starter culture' for the infant microbiome (Domininguez-Bello *et al.*, 2010). With no maternal vaginal/intestinal microbiome transfer to the infant occurring with C section, the infant microbiome is less diverse (Azad *et al.*, 2013). Adverse effects for infants reported to be associated with C section include higher risk of allergy and infection in the short term (Neu and Rushing, 2011), autoimmune and coeliac disease in the medium term (Decker *et al.*, 2010) and obesity and metabolic syndrome in the longer term (Mueller *et al.*, 2005).

Strategies to overcome this apparent disadvantage in caesarean born infants could include administration of a 'designer' evidence-based probiotic via the mother prebirth, or to the infant after birth; or using personalised transfer of the mother's own vaginal microbiome to the baby's mouth and/or wiped over skin surfaces at birth. These are in addition to the passage of microbes that occur from breast milk/skin surfaces. The administration of a probiotic supplement raises questions as the timing, composition (species, different strains for different targeted conditions), dose and safety. This will be discussed in a later section.

The transfer of mother's vaginal organisms using a gauze swab that is administered to the baby requires consideration of risk/benefit. At risk is the potential that maternal pathogens including Group B streptococci may be transferred, despite the mother receiving antibiotics. When repeat C section is planned, screening for pathogens (including sexually transmitted viruses and bacteria), should be undertaken in advance and subject to the health regulatory processes including ethics and study in a controlled fashion where follow-up is mandated. One trial is underway by M.G. Dominguez-Bello (personal communication) with no outcomes as yet available. In their method after screening: (1) a gauze is placed in mother's vagina for 1 h and extracted before C section; (2) the newborn is exposed to the vaginal gauze (mouth first, then face, then rest of body). In addition to the concerns over pathogens, it is also unclear to what extent the mother's faecal microbiota, which contacts the newborn via vaginal birthing, affects infant microbiome development, as no exposure to faeces occurs with C section.

8. Probiotics in early life

Breastfeeding is associated with reduced risk of a wide range of infectious, inflammatory, immune-mediated and metabolic disorders (reviewed in Rautava and Walker, 2009). These beneficial effects are in part mediated by direct passive immune-protection provided by factors including immunoglobulins, defensins, Toll-like receptors and oligosaccharides in breast milk. In addition, human milk contains a variety of active immunomodulatory molecules such as hormones, cytokines and growth factors. The nutrient and microbial contents of human milk are clearly critical for the health of the recipient, not just for the intestine (reviewed in Collado *et al.*, 2015). Our understanding of the role and significance of microbes and immune factors in human milk for child health is currently rudimentary. Recovering *L. reuteri* in the milk after oral intake and presumably internal transfer from the gut has been reported (Abrahamsson *et al.*, 2009). We would like to see this or another probiotic strain added to pasteurised donor milk, to assess whether nutrition, immunological and microbiological benefits are accrued, since rates of breastfeeding have been declining in the developed world.

In addition to potentially delivering probiotics via the mother's milk, the newborn may receive probiotics via direct administration. The consumption of *B. lactis* Bb12 and *L. rhamnosus* GG from week 20 of gestation to the first 6 months of the baby's life as a supplement to human milk, has the potential to reduce the risk of allergic disease, and uptake of environmental toxins. The latter has been discussed for *L. rhamnosus* GR-1, but the GG strain also binds to heavy metals (Bisanz *et al.*, 2014) and to potent aflatoxins that can induce illness (Gratz *et al.*, 2007).

The basis for early administration of probiotics to reduce the risk of childhood atopic disease is based upon aberrant early gut colonisation patterns preceding the development of atopic manifestations (Abrahamsson *et al.*, 2012; Kalliomäki *et al.*, 2001). Further corroboration for the role of early microbial contact in the development of atopic disorders has been obtained from experimental animal models (Stefka *et al.*, 2014). Several randomised clinical trials in which probiotic intervention has been used in an attempt to prevent atopic disease in the infant have been published and the results have been promising but also conflicting. The discrepancies in the efficacy of probiotic intervention may be due to differences in the probiotic strains, matrix and dosage used, the target population or the timing and route of probiotic intervention (Isolauri *et al.*, 2012). A recent systematic review and meta-analysis of clinical trials suggests that the probiotic intervention should be commenced antenatally through the pregnant mother and continued after birth in order to be effective (Panduru *et al.*, 2015). Consistently with this interpretation, maternal supplementation with the probiotic combinations of *L. rhamnosus* LPR and *B. longum* BL999 or *Lactobacillus paracasei* ST11 and *B. longum* BL999 for the last two months of pregnancy and the first two months of breastfeeding significantly reduced the risk of atopic eczema at the age of two years in high-risk infants in a double-blind, placebo controlled clinical trial (Rautava *et al.*, 2012). For high-risk birth cohorts, supplementation with *L. rhamnosus* HN001 (6×10^9 cfu/day) from 35 weeks gestation until 6 months of breastfeeding plus infant supplementation from birth until 2 years halved the cumulative prevalence of eczema at 2 and 4 years (Wickens *et al.*, 2013).

Another study followed a similar process of administering a probiotic (*B. bifidum* W23, *B. lactis* W52 and *Lactococcus lactis* W58) to pregnant women (6 weeks before delivery) and to the newborn (for one year), with the result of an altered microbiota at two year follow-up in atopic children (Rutten *et al.*, 2015).

There is a magnitude of evidence to indicate that probiotics can prevent necrotising enterocolitis (NEC) in premature babies (Lau and Chamberlain, 2015), yet few intensive care units employ this approach. This is all the more baffling in countries like Canada, where there is supposed to be universal health care. A number of formulations have been used successfully, but none compared with each other, so it is not easy to recommend one specific product over another. The advantage to the one used in some Canadian sites, containing *B. breve, B. bifidum, B. longum, B. infantis,* and *L. rhamnosus* HA-111 is the latter two species have been shown to be important in infant health (Janvier *et al.*, 2014). In clinical trials in preterm infants who were predominantly caesarean-born, NEC incidence was reduced by administration of *B. infantis* BB 02 96579, *B. lactis* Bb12 and *S. thermophilus* Th-4 15957 DMSZ in a total dose of 10^9 with reduced sepsis by half in the subgroup ≥28 weeks (Jacobs *et al.*, 2013).

There are some similarities between NEC and neonatal sepsis, in terms of symptomatic presentation and timing, but for the most part probiotics have not yet been proven to prevent sepsis. This is perhaps surprising, if the rationale for preventing infection is to increase the proportion of beneficial bacteria in the host, which appears to work effectively to prevent NEC. Potentially, *Bifidobacterium* strains lack factors, such as hydrogen peroxide and other antimicrobial substances present in lactobacilli that are needed to inhibit pathogen colonisation. But a study of 585 newborns <33 weeks or birthweight <1,500 g randomised to receive standard milk feed supplemented with *L. rhamnosus* GG once a day until discharge, starting with the first feed or placebo, showed no effect on sepsis (Dani *et al.*, 2002), thereby countering that argument. The recent finding that a strain of *L. plantarum* included in a food matrix could reduce the incidence of early onset neonatal sepsis in newborns in India (Panagrahi, unpublished data), suggests that strain selection is critical.

Interestingly, a study of 94 preterm infants found a significantly lower incidence of rhinovirus respiratory tract infections with prebiotics galacto-oligosaccharide and polydextrose mixture, or probiotic *L. rhamnosus* GG from days 3 to 60 of life, compared to placebo (Luoto *et al.*, 2014). This again illustrates distant site effects following oral administration.

In developing countries, vaginal birthing and exclusive breastfeeding continue at high rates, but issues remain with maternal and infant morbidity and mortality. Ironically, despite studies showing that certain probiotic products can benefit women and infants in developing countries, the products are either not made available or are too expensive for the majority of the population. Apart from being almost unethical, it means that potentially life-saving interventions are not reaching people who already face challenges of poor access to effective health care, lack of finances, and poor nutrition. The creation of community kitchens where probiotic yogurt is affordably produced and made available, has the potential to help millions of people (Reid, 2010; Sybesma *et al.*, 2015).

9. Conclusions and recommendations

For the most critical part of human life – conception to early development – surprisingly little research has been done to understand the key nutrients and microbes that support optimal health. The rationale for probiotic administration has some substance – human evolution with fermented foods, microbes associated with many health benefits – but the mechanisms by which strains actually confer health still remain elemental. The optimal time to administer probiotics to improve cognitive function, reduce atopic and infectious disease, and prevent premature birth, requires more study, along with dose and duration. In this review, a case is made to include probiotic supplementation as part of a healthy pregnancy and with breast feeding for early infant health (Table 1). The field would be helped if every company selling products ostensibly for maternal and infant health, funded independent studies that examine these factors. In addition, the vast investments in the first 1,500 days projects around the world from governments and NGO's risk failing if significant investment in the microbial contribution to resolution is not included in parallel. In this way, it is reasonable to expect that the extent to which microbial intervention can improve the health and well-being of mother and infant, can be determined, and evidence-based advocacy passed on to people around the world. The fact that there are some probiotic products that can help before, during and after therapy, leads to us recommending them for consideration (Table 1).

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