ABSTRACT: Because probiotic foods and supplements are rapidly increasing in popularity, their effects during pregnancy and lactation demand careful attention. This systematic literature review discusses the effects of perinatal probiotic exposure on gut microbiota, the immune system, and nutrient utilization in both the mother and infant. It was found that maternal exposure to probiotics is particularly important in the development of gut microbiota in infants who are delivered by caesarian section or who are formula-fed. Meta-analyses were performed on outcomes related to the immune system. The meta-analyses show that probiotic consumption during pregnancy is associated with a reduced risk of atopic dermatitis in infants. Studies also suggest that maternal probiotic exposure reduces the risk of gestational diabetes and increases the availability of nutrients that the fetus needs for development such as folates and essential fatty acids. Because allergic and metabolic diseases are on the rise and probiotics may be preventative in both of these areas, perinatal exposure to probiotics demands further investigation. The majority of studies suggest that prenatal exposure is more effective than infant exposure. Future research should focus on maternal exposure and should look at dietary sources of probiotics and prebiotics instead of supplements.

KEY WORDS: Bifidobacterium, Breastfeeding, Lactobacillus, Maternal, Prenatal, Probiotics

INTRODUCTION

Maternal nutrition during pregnancy and lactation plays a vital role in infant development. Because the popularity and availability of probiotic foods and supplements is rapidly increasing, it is important to carefully look at the effects of these functional foods and nutraceuticals during the perinatal period. Probiotics are generally considered safe for both the mother and infant (Duguo et al., 2009). However, before maternal consumption of probiotics can be recommended, the hypothesized benefits and long-term effects need to be clear.

Over a century ago, Nobel laureate Ilya Metchnikoff discovered that microbes might have beneficial impacts on human health (Schmalstieg and Goldman, 2008). He observed that people who consumed fermented products lived longer. His hypothesis was that these products provided beneficial bacteria to the gut that helped defend against harmful bacteria and prevent illness.

Probiotics, which means “for life” in Greek, are defined by the World Health Organization as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. Probiotics are naturally found in some foods such as yoghurt, soft cheese, sauerkraut, and pickles and can be added to foods or taken in supplement form. The most common probiotics are from the genera Bifidobacterium and Lactobacillus. Because of the wide diversity of probiotics, each genera and strain needs to be studied individually.

Prebiotics are substances that act as substrates for probiotics. To be classified as a prebiotic, a substance must resist degradation by stomach acid, bile salts, and digestive enzymes, and reach the gut where it stimulates the growth of specific bacteria, resulting in a positive health outcome for the host (Schrezenmeir et al., 2001). Combinations of probiotics and prebiotics are called synbiotics. The majority of research on probiotics has been on use in pathological situations and for people at high risk of allergic diseases (Cani et al., 2009). There is mounting evidence that probiotics may be able to treat various forms of infectious diarrhea and prevent diarrhea caused by radiation or antibiotic use. Probiotics may also be able to prevent and reduce the severity of several allergic diseases (Cani et al., 2009). There is an increasing interest in how probiotics can be used in preventative health in the general population, especially in maternal and child health.

There are many studies and reviews on infant or child exposure
to probiotics, but many of the studies read for this review suggest that maternal exposure is more effective and efficient. Maternal exposure during pregnancy exposes the infant to probiotics at an early stage. Maternal exposure also benefits two people instead of only one. This paper reviews the effects of maternal probiotic exposure on gut microbiota, the immune system, and nutrient utilization.

**METHODS**

**Search Strategy**

PubMed and Cochrane databases were searched in October 2009 for articles in which the exposure was probiotics and the subjects were pregnant or breastfeeding mothers and their infants. Figure 1 depicts the systematic review process. The search strategy required the article to contain a term related to the exposure (probiotics, lactobacillus, or bifidobacterium) as well as a term related to the subjects (breastfeeding, maternal, pregnancy, or prenatal). Because there are many studies on using topical probiotics to prevent and treat vaginal infections, the search was further restricted by requiring that the term vaginal not be found in the title or abstract. This search strategy resulted in 523 papers.

After the abstracts of these 523 papers were read, 484 papers were excluded because they were not related to the topic of interest. The remaining 39 publications were read thoroughly and their references were cross-checked to look for any publications that were missed. Checking the references resulted in six additional papers. In total, 45 papers were read for this review. The main features of the randomized controlled trials were summarized in table format to make it easier to compare them and to see what outcomes they had in common. Meta-analyses were performed when at least three studies looked at the same outcome and the necessary data for the analyses was available in the papers.

**RESULTS**

Out of 45 papers, 25 were randomized controlled trials. The remaining articles were primarily reviews or commentaries and there were very few observational studies. The outcomes were grouped into the following categories: gut microflora development, immune system development, and nutrient utilization. The discussion section was structured on these three outcome categories.

The key features of the randomized controlled trials including the number of subjects, probiotic strains studied, time period of exposure, outcomes measured, and results, were compared. There was enough data for small meta-analyses on the following outcomes related to immune system development: atopic dermatitis, positive skin prick test, and sensitization. The results of these meta-analyses can be seen in figures 2, 3 and 4 respectively.

Subjects were very similar across the studies. The majority of studies on probiotic use during pregnancy were on women with a family history of atopic disease. Because much of the research on the effects of probiotics during the perinatal period has been conducted in Scandinavia, most subjects were Caucasian, well-educated, and of a medium to high socio-economic status.

Several different probiotics were studied including Lactobacillus rhamnosus GG (LGG), L. reuteri, L. rhamnosis, L. casei, L. lactis, Bifidobacterium breve, B. lactis, B. animalis, and Propionibacterium freudenreichii. LGG was by far the most commonly studied followed by B. lactis Bb12. Doses of probiotics ranged from 1x10^8 to 2x10^10 colony forming units (cfu) per day.

The studies looked at a variety of time windows of maternal exposure. Exposure start times ranged from the beginning of the second trimester to the beginning of lactation. The end of the exposure periods ranged from the time of delivery to the completion of breastfeeding. Many studies also gave probiotics to the infant. Infant exposure in these studies started at various times ranging from birth to the end of breastfeeding. Because this review only examined the effect of maternal consumption of probiotics, studies in which the infant was also exposed were carefully and creatively examined to see what useful information could be gathered.

**FIGURE 1. Systematic Selection of Studies for Review.**

**Gut Microflora Development**

The human gut contains an estimated 10^{13} bacterial cells, which is ten times more than the number of human cells that make up the body (Hooper et al., 2001). Because gut microbes have various immune and metabolic functions, the composition of gut microbes plays an important role in health. Imbalances of the gut flora have been linked to increased risk of allergic diseases, obesity, type II diabetes, and diarrheal diseases. Probiotic bacteria can alter gut microflora through the following mechanisms: reducing luminal pH, competitive inhibition, secreting bacteriocins and defensins, and by inhibiting bacterial adhesion and translocation (Ng et al., 2009). While many of these activities are defenses targeted against pathogenic bacteria, they also affect the composition of normal gut flora.

Studies have shown that consumption of probiotics in adult subjects results in temporary colonization. Long term colonization may also be possible if a probiotic is taken for a long period of time. Only one study has looked at whether probiotics can temporarily colonize the gut of pregnant women. Lahtinen et al., (2009) showed that after four weeks of administration of LGG to pregnant women, 67% of the mothers in the probiotic group were colonized with LGG compared with 12% of the mothers in the placebo group (prevalence ratio=5.67; 95% CI, 2.2-14.6; p-value < .001). The results of this study make it reasonable to assume that probiotics can temporarily...
colonize the gut of pregnant women. No studies have looked at how probiotics influence maternal gut microflora in the long-term.

It has not been determined whether maternal consumption of a probiotic results in colonization of the infant gut with that same probiotic. An observational study in which LGG was consumed by six women during late pregnancy found temporary colonization of the gastrointestinal tract in five out of six exposed newborns (Schultz et al., 2004). LGG was not detected in any of the three control newborns. This study indicated that probiotics administered to the mother may be able to temporarily colonize the infant gut, but because this was a small observational study, no causal claims should be made. A randomized controlled trial of 122 mother-infant pairs showed contradictory results to this observational study (Lahtinen et al., 2009). No difference was detected in the prevalence of LGG at 90 days in infants whose mothers took LGG versus infants of mothers who received placebos (12.7% vs. 8.8%; prevalence ratio, 1.45; 95% CI, 0.49-4.30). These two studies suggest, but by no means prove, that maternal probiotic consumption may result in temporary, but not long-term, colonization of the infant with that same strain.

Even if maternal consumption of probiotics does not result in colonization of the infant, maternal exposure to probiotics during pregnancy and/or during breastfeeding may still help develop a healthier balance of gut flora in the infants. A randomized controlled trial of 53 women who took LGG during both pregnancy and lactation examined the fecal samples of their three-week-old infants (Gueimonde et al., 2006). The infants whose mothers received the probiotic tended (although the p-value was not <.05) to have more Bifidobacterium species present than those whose mother received the placebo (number of species: 1.22 [0.80-1.44] vs. 0.81 [0.51-1.15], p-value= .134). An increase in diversity of the exposed infants gut microflora was seen by a lower similarity index of mother and infant when the infant was three weeks old (probiotic,

**FIGURE 2.** Meta-analysis results for the exposure of probiotics on infant atopic dermatitis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahamson et al 2007</td>
<td>12</td>
<td>34</td>
<td>11</td>
<td>1.20 [0.38, 2.87]</td>
</tr>
<tr>
<td>Kalliomaki et al 2008</td>
<td>15</td>
<td>64</td>
<td>31</td>
<td>0.37 [0.17, 0.77]</td>
</tr>
<tr>
<td>Kopp et al 2008</td>
<td>14</td>
<td>50</td>
<td>12</td>
<td>2.56 [0.42, 1.57]</td>
</tr>
<tr>
<td>Kallonen et al 2009</td>
<td>175</td>
<td>445</td>
<td>193</td>
<td>0.85 [0.65, 1.11]</td>
</tr>
<tr>
<td>Kukkonen et al 2007</td>
<td>120</td>
<td>461</td>
<td>150</td>
<td>0.74 [0.55, 0.98]</td>
</tr>
<tr>
<td>Niers et al 2009</td>
<td>27</td>
<td>50</td>
<td>33</td>
<td>4.33 [0.25, 1.22]</td>
</tr>
<tr>
<td>Wickens et al 2009</td>
<td>61</td>
<td>315</td>
<td>43</td>
<td>0.65 [0.41, 1.01]</td>
</tr>
</tbody>
</table>

Total events 424 473
Heterogeneity: Chi² = 6.34, df = 6 (P = 0.39); I² = 5%
Test for overall effect: Z = 3.52 (P = 0.0004)

**FIGURE 3.** Meta-analysis results for the exposure of probiotics on positive skin prick test results in infants.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahamson et al 2007</td>
<td>17</td>
<td>95</td>
<td>27</td>
<td>0.53 [0.27, 1.06]</td>
</tr>
<tr>
<td>Kalliomaki et al 2008</td>
<td>11</td>
<td>61</td>
<td>9</td>
<td>1.37 [0.52, 3.57]</td>
</tr>
<tr>
<td>Kallonen et al 2009</td>
<td>165</td>
<td>443</td>
<td>164</td>
<td>0.92 [0.77, 1.14]</td>
</tr>
<tr>
<td>Niers et al 2009</td>
<td>4</td>
<td>46</td>
<td>4</td>
<td>1.62 [0.24, 4.36]</td>
</tr>
<tr>
<td>Wickens et al 2008</td>
<td>65</td>
<td>350</td>
<td>42</td>
<td>0.72 [0.46, 1.12]</td>
</tr>
</tbody>
</table>

Total events 262 246
Heterogeneity: Chi² = 4.73, df = 4 (P = 0.31); I² = 16%
Test for overall effect: Z = 1.69 (P = 0.32)
85±15%; control, 66±20; p-value=.008). In addition, a microflora composition characteristic of people at a lower allergy risk was found at five days after birth. This composition is a lower prevalence of *B. adolescentis* (30% vs. 0%; p-value<.05) and higher prevalence of *B. breve* (27.3% vs. 0%; p-value <.05).

The study by Lahtinen et al. had similar findings to Gueimonde et al.’s. At 90 days, the infants of exposed mothers had a higher prevalence of *B. longum* species (prevalence ratio 1.35; 95% CI 1.06-1.72; p-value=.01) and exhibited a trend towards a higher prevalence of total *Bifidobacterium* (prevalence ratio 1.06, 95% CI .99-1.12; p-value=.08). A study in which infants were also exposed produced similar results (Niers et al., 2009). Because a diverse gut flora with a high prevalence of *Bifidobacterium* is considered healthy, the results of these three studies suggest that maternal consumption of probiotics may help develop healthy infant gut microflora.

There is a high correlation between the gut microbes in mothers and their offspring (Gueimonde et al., 2006). The following routes of bacterial transfer from mother to child have been proposed: transplacental, during delivery (either by exposure to vaginal or fecal bacteria), fecal-oral, and through breastfeeding. A better understanding of these mechanisms of transfer will help determine the windows of time in which exposure makes the most difference.

Because the fetus is generally considered to be microbiologically sterile, it is traditionally thought that first inoculum of bacteria takes place during birth. However, recent research has shown that the placenta may be colonized by bacteria in non-pathogenic situations and that the first stool, called meconium, of healthy neonates is not sterile as once thought (Pettker et al., 2007; Jimenez et al., 2008). It has also been observed that oral administration of a bacterial strain in pregnant mice results in the presence of that particular strain in the meconium (Jimenez et al., 2008). These findings support the hypothesis that there is prenatal transfer of bacteria from mother to fetus through the placenta. Gut microflora development likely begins before birth.

The primary route of bacterial transfer between mother and infant is considered to be fecal-oral. The infant is exposed to microbes during delivery and in the first few days after birth from close contact with the mother. Because there is a difference in the microbiota of infants who are born vaginally versus those who are delivered by caesarian section, it is thought that exposure to bacteria in the birth canal (as well as to fecal bacteria) during delivery is important for gut microflora development (Isolauri et al., 2001; Bjorksten et al., 2001). Kuittinen et al. (2009) studied whether a combination of prenatal and postnatal probiotic exposure was preventative against IgE-associated allergic diseases at age five. The results of the randomized control trial showed that probiotics are protective against IgE-associated allergic disease in caesarian delivered children, but not in vaginally delivered children (24.3% vs. 40%; OR, 0.47; 95% CI. .23 to .96; p-value=.035).

Infants delivered vaginally may not have benefited from probiotics in this study because the good bacteria that they were exposed to during birth already protected them. Kuittinen et al’s study supports the hypothesis that exposure bacteria during delivery may help prevent allergic disease. Provided that this hypothesis is true, more research should be done to find out whether probiotics could be used as a substitute for the maternal bacteria that an infant is not exposed to when they are delivered by cesarean. If this hypothesis is true, mothers with planned cesarean sections should consume probiotics to protect their children from allergic disease.

Feeding is also major determinant of intestinal colonization of the neonate (Lara-Villoslada et al., 2007). Breast milk is a symbiont that contains the probiotics and prebiotics necessary for the development of a healthy gut. Many infant formulas now contain probiotics. For example, Nestlé’s Good Start Natural Cultures contains *B. lactis*. The probiotic strains most common in the gut of a healthy infant, *Bifidobacterium* and *Lactobacillus*, have both been found in breast milk (Satokari et al., 2009). Perhaps it is not

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**FIGURE 4. Meta-analysis results for the exposure of probiotics on infant sensitization (defined as both a positive skin prick test and high levels of circulating IgE.)**
only the presence of probiotics, but also the fact that they kill off pathogenic bacteria that is responsible for breast milk’s protective effects. It is estimated that breast milk contains $10^{4.64}$ CFU/ml of Bifidobacterium (95% CI, $10^{1.95}$–$10^{7.07}$). Assuming that infants consume around 700 ml of milk per day, they receive around $10^{5}$ CFU per day from breast milk (Butte et al., 1984). This is much less than the average $10^7$ or $10^{10}$ CFU per day that is administered to infants in randomized controlled trials.

There is wide variation in the composition of infant gut flora. The microbiota of healthy breast-fed infants consists of about 90% Bifidobacterium and Lactobacillus, while in formula-fed newborns these two genera only account for about 50% (Harmsen et al., 2000). Rinne et al. found that fecal Bifidobacterium as well as counts of combined Lactobacillus and Enterococcus were higher in breast-fed than formula-fed infants at six months (p-value <.0001 and p-value = .01, respectively). The differences in gut microbiota between formula-fed and breast-fed infants may help explain the protection that breastfeeding offers against infections and allergies. Perhaps it is not only the presence of probiotics, but also the fact that they kill off pathogenic bacteria that is responsible for breast milk’s protective effects.

If probiotics are able to make gut flora of formula-fed infants more like that of breast-fed infants, probiotics may be able to produce similar health benefits to those gained from breastfeeding. Infant formulas should be developed with the goal of developing a gut microflora identical to that of breast-fed infants. However, it is important to remember that there will never be a perfect substitute for a mother’s milk and that breastfeeding should always be promoted when possible.

Maternal exposure to probiotics may alter the bacteria present in breast milk. A randomized controlled trial in which L. reuteri was administered during the last four weeks of pregnancy showed that a higher percentage of mothers in the treatment arm of the trial had L. reuteri in their colostrum (12% vs. 2%; P=.02) (Abrahamsson et al., 2009). Another study was unable to detect a difference in the number of Bifidobacterial species found in the breast milk of 13 mothers taking probiotic preparations versus seven (Abrahamsson et al., 2009). This study examined the link between farm exposure, which is highly correlated to microbial exposure, and altered immune responses. The PARSIFAL study gathered information on maternal exposure to a farm during pregnancy as well as lactation so that the time period in which exposure acted could be determined. Outcomes that were investigated included diagnosis of asthma and atopic sensitization, which was measured by presence of allergen specific IgE for several allergens in serum.

The strongest protective effect in the PARSIFAL study was prenatal exposure working in a stable on atopic sensitization (OR, 0.58: 95% CI, 0.39-0.86; P=.007). A subset of the cohort was examined for gene expression of innate immune receptors TLR2, TLR4, and CD14. It was found that the more animals the mothers were exposed to during pregnancy, the higher the gene expression these innate immune receptors were in their offspring. The effects on the immune system were stronger as a result of exposure during pregnancy rather than during breastfeeding. This suggests that more attention needs to be given to prenatal exposures. The results of the PARSIFAL study strongly support the “hygiene hypothesis” that exposure to an environment rich in microbes during pregnancy prevents allergic diseases. If exposure to probiotics is a good substitute for a microbial rich environment, exposure to probiotics during pregnancy will also be preventative against allergic diseases.

Immune System Development

The prevalence of immune disorders, particularly atopic diseases such as asthma, food allergies, and aeroallergies, has increased rapidly in the past few decades (Isolauri et al., 2004). It is now estimated that these atopic diseases affect 20-30% of Western populations. The “hygiene hypothesis” blames the epidemic on the increasingly sterile environment. The sterile environment may alter gut microflora in a way that makes the immune system more responsive to certain allergens. Atopic diseases begin early in life and are one of the most common chronic childhood health issues. Eczema commonly develops during infancy and asthma often develops before the age of two. Since exposure must precede disease, it is important to consider exposures even before conception.

The prenatal environment strongly influences the immune system of infants. For example, it is well known that certain viruses cross the placenta and that vaccinations during pregnancy may also result in immunity in the infant. A recent study showed that prenatal exposure to an environment rich in microbial compounds might alter the immune system of the child.

The Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style Study (PARSIFAL) is a large cross-sectional study of more than 8,000 school-aged children in five European countries (Ege et al., 2009). This study examined the link between farm exposure, which is highly correlated to microbial exposure, and altered immune responses. The PARSIFAL study gathered information on maternal exposure to a farm during pregnancy as well as lactation so that the time period in which exposure acted could be determined. Outcomes that were investigated included diagnosis of asthma and atopic sensitization, which was measured by presence of allergen specific IgE for several allergens in serum.

The studies described above emphasize the importance of breast feeding and vaginal birth in the development of healthy gut flora in infants. It is important to remember that there is no perfect substitute for nature. However, it is also important that research continues on how maternal probiotic exposure influences the development of gut flora in infants who are delivered by caesarian section or are formula-fed.
There are many studies on childhood exposure to probiotics in preventing allergic diseases, but only handfuls have looked at maternal exposures. Enough studies were found in this systematic review to do small meta-analyses on maternal exposure to probiotics on the following allergic outcomes: atopic dermatitis, positive skin prick tests, and sensitization. Out of ten studies, only three did not directly expose the infant (Böttcher et al., 2008; Huure et al., 2008; and Rautuva et al., 2008). Although the studies did not expose the subjects to the same probiotics or use the same outcome measurements, the results of the meta-analyses are still of interest.

The meta-analysis of atopic dermatitis (Figure 2) suggests that a combined maternal and infant exposure is protective for the infant (OR=0.74; 95% CI .63-.88; p-value=.0004). A similar protective effect may also be gained from maternal exposure alone. The odds ratio when only the mothers were exposed was very similar to when the infants were also exposed (OR=0.6; 95% CI .33-1.1; p-value=0.11). While the p-value is less than .05, this odds ratio should be taken seriously as the location is very similar to the prior odds when both the mother and the infant were exposed. A larger sample size would most likely show with a p-value of less than .05 that maternal exposure alone is protective.

The meta-analyses of probiotics for the prevention of positive skin prick tests in infants did not show any statistically significant results. All of the summary 95% confidence intervals spanned the null (Figure 3). A study with a larger sample size would likely find a significantly significant protective effect. However, if a protective effect exists, it is likely to be small. The meta-analyses results for sensitization were similar to those for the skin prick test (Figure 4). Because these studies defined sensitization as both a positive skin prick test and high circulating levels of IgE, it was not surprising that this meta-analysis did not differ much from the one only on skin prick tests.

To better understand whether maternal exposure to probiotics can prevent disease, we must understand the mechanisms by which probiotics alter the immune system. Perinatal consumption of probiotics may affect the infant’s immune system through the following hypothesized routes: transplacental immune stimulation, gut microbiota development, altered breast milk composition, and epigenetic modification.

A recent experimental study found that the placenta of healthy neonates is colonized by the commonly consumed probiotic species Bifidobacteria as well as by L. rhamnosus (Satokari et al., 2009). While they were unable to cultivate either of these species (possibly because cultivation of these species is difficult), DNA from Bifidobacteria and L. rhamnosus was detected in most of the 34 samples. While it is possible that the placentas were contaminated during delivery, nine of the deliveries were at a low risk of contamination as they were cesarean.

The presence of bacterial DNA in the placenta may trigger immune responses in the fetus. It is thought that the CpG oligodeoxynucleotides, which are present in particularly high quantity in the DNA of Bifidobacterium and other probiotics, activate TL9 receptors, which in turn trigger a Th-1-type immune response (Kreig et al., 2002). An increased Th-1 type immune response helps reduce allergic diseases by counter-balancing a high Th-2 type immune response. A randomized controlled trial in which LGG was administered prenatally in 73 women failed to detect transplacental immune effects in the parameters under study. These parameters included T-cell proliferation, FoxP3 expression, DC phenotype, and cytokine production (Boyle et al., 2008). The authors suggested that the protective effect that probiotics have against allergic disease is not likely to be transplacental. However, transplacental effects should definitely not be ruled out because this study was not exhaustive. The study only looked at cord blood, exposure to one probiotic strain, and did not measure all immune parameters. Transplacental immune stimulation by probiotics is likely and demands further study.

Breastfeeding is the “gold standard” for allergy prevention. Breast milk’s anti-allergenic properties are in part due to its immune components. A study showed that two different strains of Lactobacillus that were isolated from the breast milk of healthy women caused different and opposing immune responses in in vivo and in vitro murine models (Diaz-Ropero et al., 2007). L. fermentum was found to be immunostimulatory while L. salivarius was found to be anti-inflammatory. This experiment stresses the importance of testing the strain-specific effect of each probiotic. It also suggests that a variety of bacterial strains in the gut are necessary for the fine-tuning of the immune responses. Consuming probiotics may improve the balance of bacterial strains in breast milk, but it could also upset an existing healthy balance.

Four studies found that exposure to probiotics during pregnancy and lactation resulted in significantly altered levels of breast milk immunomodulatory factors (Böttcher et al., 2007; Huure et al., 2008; Prescott et al., 2008; and Rautuva et al., 2002). Both Böttcher and Rautuva showed that supplementation with probiotics during late pregnancy reduces levels of TGF-ß2 (p=.02 and p=.018, respectively). Böttcher additionally showed that a low level of TGF-ß2 is associated with decreased infant sensitization (AOR=0.3; 95% CI 0.1-0.9). While these results may seem convincing, Huure’s results suggested that the opposite is true: that probiotics increase the levels of TGF-ß2 (probiotic/placebo ratio=1.5, p=0.073). There is a significant need for studies on how consumption of probiotics modifies breast milk and how these changes in breast milk affect the infant.

Epigenetics means “above the gene” and is the study of inherited changes in gene expression caused by mechanisms other than changes to the DNA sequence. Recent data suggests that prenatal probiotic exposure may alter DNA methylation processes, a key element of epigenetic inheritance. A mouse model showed that prenatal exposure to a specific strain of Acinetobacter was found to decrease the level of inflammatory cytokine IFNγ in newborns (Teich et al., 2009). The decreased production of IFNγ was inversely correlated with DNA methylation of the IFNγ promoter. This experiment was the first to demonstrate that epigenetic regulation may be a mechanism by which the allegro-protective effects of prenatal exposure to probiotics are transferred from mother to offspring. The study of interaction between probiotics and epigenetic is in its infancy and has great potential.

Looked at as a whole, these studies point to maternal, and not
child, probiotic exposure as a possible solution for preventing allergic diseases. Because allergic diseases are one of the most common childhood chronic health problems, this topic requires further study. Future research should examine how probiotics transplacentally stimulate the fetus's immune system, how they alter breast milk composition, and how they alter epigenetic inheritance.

**Nutrient Utilization**

Maternal nutrition impacts the long-term health of both the infant and the mother. Two major nutritional problems during pregnancy are micronutrient deficiencies and overnutrition. During pregnancy there is an increased need for micronutrients to help the fetus develop. An example of a micronutrient deficiency particularly harmful during pregnancy is folic acid, which causes neural tube defects. Overnutrition during pregnancy leads to excess weight gain by both the mother and the fetus. Excessive weight gain can result in problems ranging from a difficult delivery due to the large size of the infant to metabolic problems later in life such as type II diabetes. There is strong evidence that suggests that maternal consumption of probiotics may prevent micronutrient deficiencies and help regulate metabolism.

*In vitro* studies indicate that probiotic bacteria are capable of generating many water-soluble vitamins, particularly B vitamins and folate. Probiotics may be able to provide their host with a good source of these micronutrients (Pompei et al., 2007). A study on yoghurt cultures reported that fermentation of skim milk using a combination of *Bifidobacterium animalis* and *S. thermophilus* resulted in a six-fold increase in folate concentration (Crittenden et al., 2003). It has been demonstrated that folate may be synthesized and secreted by probiotics in the human intestine and subsequently absorbed and used by the host (Strozzi et al., 2008). In this study, three groups of subjects were each administered a different species of *Bifidobacterium*. Folate concentrations in the feces were measured before and after exposure. Folate concentrations increased by about 50% in each group that consumed a probiotic (p-value<.05 for all groups). If probiotics produce a constant source of folates, consuming them before conception and during the first few months of pregnancy would help prevent development defects caused by folate deficiency.

Essential fatty acids such as omega-3 and omega-6 must be obtained from the diet are found in foods such as fish, leafy vegetables, and some seeds. Maternal consumption of essential fatty acids has important consequences on infant health as they are needed for neurological and visual development. It has been shown that prenatal probiotic supplements combined with dietary modifications may change the fatty acid composition of the placenta (Kaplak et al., 2007). The placentas of women who were in the diet/probiotic arm of the trial had significantly higher levels of eicosapentaenoic acid, eicosatetraenoic acid, and arachidonic acid than those in the control/placebo arm (p-value <.05). It was also found that the placentas in the diet/probiotic arm had significantly higher levels of linoleic acid than those in the diet/placebo arm (p-value <.05). In this study, dietary changes alone resulted in a higher polyunsaturated fatty acid concentration, but probiotic supplementation added to this effect. The mechanism behind the interaction between probiotic supplementation and fatty acid makeup in the placenta is poorly understood and should be a high priority for further research.

Maternal nutrition may initiate metabolic and immunoinflammatory conditions that affect the fetus later in life. Glucose levels naturally rise over the course of pregnancy to provide the fetus with an increasing amount of energy for development. If blood glucose levels are too high and the mother develops impaired insulin tolerance, she may suffer from gestational diabetes. The fetus may then in turn suffer from macrosomia and decreased glucose tolerance. An experiment by Laitinen et al. (2009) showed that probiotics might mediate glucose levels in healthy pregnant women. This randomized controlled trial had three groups of pregnant women: diet/probiotic (a mix of LGG and *Bifidobacteria lactis* Bb12), diet/placebo, and control/placebo. During the third trimester, the diet/probiotic group had a lower risk of elevated glucose concentrations (>4.8mmol/l) compared to the control/placebo group (OR=0.31, 95% CI 0.12-0.78, p-value=0.013), but the diet/placebo group did not (OR=1.26, 95% CI 0.59-2.69, p-value=.55). This research shows that a particular diet combined with probiotic consumption may lower the glucose concentrations. Because many mothers and infants suffer from gestational diabetes, more research is needed on whether probiotic exposure helps prevent it.

Deviations from normal microbiota have recently been associated with obesity, but it is not known whether the altered microbiota causes obesity or visa versa (Ley et al., 2005; Kalliomäki et al., 2008). There are two proposed mechanisms by which bacteria may cause obesity. One theory is that certain strains of harmful bacteria may be able to increase energy harvest and storage (Turnbaugh et al., 2006). Another idea is that since some microbiota have inflammatory properties while others have anti-inflammatory properties, an imbalance of gut microbiota may lead to low grade systemic inflammation, which is associated with obesity (Collado et al., 2008). If probiotics can restore a healthy balance of gut microbiota, they could prove to be a useful weapon in combating the obesity epidemic.

One study examined the difference in gut microbiotic composition between normal weight and overweight women over the course of their pregnancy (Collado et al., 2008). Gut microbiota composition was found to differ between the two groups in that overweight women had higher concentrations of *Bacteroides* and Staphylococcus. In addition, excessive weight gain in pregnancy (defined as >16.0 kg for normal-weight and >11.5 kg for overweight women) was found to be associated with a high concentration of *Bacteroides* (r=0.30, p-value=0.14). Because overweight women supply more energy to the fetus, there is an increased risk of high birth weight infant. It has been suggested that high birth weight is a risk factor for adult obesity. However, this hypothesis has been hard to prove as there are many confounding genetic and environmental factors. Establishing proper balance of gut microbiota in the developing infant as well as in the mother may have the potential to help combat the obesity epidemic.

Taken as a whole, these studies suggest that maternal exposure to probiotics plays an important role in nutrition and metabolism.
There is a need for studies that look at only one time period maternal probiotic as opposed to infant supplementation? How, then, is it possible to distinguish the effects of complications during pregnancy? Many studies also gave supplements to infants. How, then, is it possible to distinguish the effects of mechanisms by which maternal probiotic exposure affects infant development? Because allergic and metabolic diseases are on the rise, probiotic exposure during the perinatal period must be further investigated.

There is much left to learn about probiotics before supplements are recommended to all pregnant and lactating mothers. The mechanisms by which maternal probiotic exposure affects infant health are poorly understood. There is also very little information on effective dosages and the difference between strains. Another problem with probiotic supplementation is the inability of the fed strain to colonize the gut permanently and become an integral part of the community. This means that to get the health benefits of probiotics, large doses need to be administered repeatedly. Research needs to be done on probiotics, rather than infant, exposure and should look at dietary sources of probiotics and prebiotics instead of supplements.

Almost all studies of probiotics are intervention studies. Researchers choose randomized controlled trials for studying probiotics so that exposure can be clearly defined and accurately classified. Assigning exposure makes it possible for subjects to receive a known dosage of a certain probiotic strain at specified time intervals. However, in the real world, exposure is more varied. Now that there is scientific evidence from randomized controlled trials that probiotics confer health benefits, there is a need for observational studies in which normal exposure to probiotics in the diet is studied.

Observational studies will provide greater access to a large and more diverse group of patients. Observational studies will also allow for studying probiotic exposure as part of a diet rather than as a supplement. Foods containing probiotics, either naturally or by fortification, are more accessible to the public than supplements. In addition, probiotics need to be taken in context of the health benefits and harms of the foods in which they are contained. The major problem with observational studies for probiotics is classifying exposure. It is not known to what extent nutritional epidemiological tools such as food frequency questionnaires, 24-hour diet recalls, and diet journals can say something about probiotic exposure. Nutritional epidemiologists need to develop a tool to assess probiotic exposure in the diet. For probiotics to make a large impact on population health, the focus should be on promoting a diet rich in probiotics, rather than probiotic supplements.

Existing birth cohorts may provide further insight into the effects of probiotics. Cohorts are good for looking at long-term exposures and diseases with a long induction period. Nested case controls may also be a good option if there is information on the birth cohorts’ diets and supplements and the researcher has access to medical records that contain information on outcomes of interest such as allergic and metabolic diseases.

Despite all the possible benefits of probiotic supplementation during the perinatal period, researchers should be aware that there are still some safety concerns (Shafai 2009, Duguoa 2009). While probiotics are generally assumed to be safe, there have been several reports that some strains have caused serious infections in immunocompromised patients (Liong 2008). Because mothers have slightly compromised immune systems during pregnancy and the immune systems of newborns are not completely developed, both mothers and infants are likely to be at higher risk than the average person for an infection caused by probiotics. Because of the possible health risks of introducing new strains of bacteria, probiotics, which nurture existing healthy gut flora, are a safer alternative and should be given more attention.

Maternal exposure to probiotics plays an important role in healthy gut microbiota development, the prevention of allergic diseases, and nutritional status of the infant. It was found that maternal exposure to probiotics is particularly important in the development of gut microbiota in infants who are delivered by caesarian section or who are formula-fed. The meta-analyses on outcomes related to the immune system showed that probiotic consumption during pregnancy is associated with a reduced risk of atopic dermatitis in infants. Studies suggest that maternal probiotic exposure reduces the risk of gestational diabetes and increases the availability of nutrients, such as folates and essential fatty acids, which the fetus needs for development. Because allergic and metabolic diseases are on the rise, probiotic exposure during the perinatal period must be further investigated.

There is much left to learn about probiotics before supplements are recommended to all pregnant and lactating mothers. The mechanisms by which maternal probiotic exposure affects infant health are poorly understood. There is also very little information on effective dosages and the difference between strains. Another problem with probiotic supplementation is the inability of the fed strain to colonize the gut permanently and become an integral part of the community. This means that to get the health benefits of probiotics, large doses need to be administered repeatedly. Research needs to be done on probiotics, rather than infant, exposure and should look at dietary sources of probiotics and prebiotics instead of supplements.
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