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ABSTRACT

The purpose of this integrative review was to identify, critique, and synthesize the maternal and neonatal evidence on the prenatal use of probiotics and prebiotics to inform perinatal health professionals. A comprehensive literature search resulted in 37 studies of prenatal probiotics and 1 on antepartal prebiotics published from 1990 through 2011 that reported maternal, fetal, and/or neonatal

outcomes. The methodologic quality of the studies reviewed was high, although investigators used different probiotic combinations and inconsistently reported perinatal clinical outcomes. The extraction of perinatal outcome variables resulted in identification of 9 maternal and 5 neonatal categories. Prenatal probiotics significantly reduced the incidence of bacterial vaginosis, increased colonization with vaginal Lactobacillus and intestinal Lactobacillus rhamnosus, altered immune markers in serum and breast milk, improved maternal glucose metabolism, and reduced the incidence of gestational diabetes and preeclampsia. Antepartally, probiotics were associated with significantly higher counts of *Bifidobacterium* and *Lactococcus lactis* (healthy intestinal flora) in neonatal stool. Prenatal prebiotics significantly increased maternal intestinal *Bifidobacterium*. No adverse events were reported and there was evidence of safety and tolerance of prenatal probiotics and prebiotics in the scientific investigations reviewed. It is recommended that in future investigations of prenatal probiotics researchers explicitly report maternal and neonatal outcomes.

Key Words

integrative literature review, perinatal, prebiotics, pregnancy, probiotics

Complementary and integrative therapies (CIT) have received a great deal of attention from consumers.[1] Probiotics and prebiotics are considered food[2] and are readily available over the counter to women and families as CITs. A variety of readily available fermented milk products contain live active probiotic bacteria in varying amounts. While numerous commercially available prenatal vitamins now contain prebiotics and probiotics, the scientific evidence supporting these formulations is lacking. Furthermore, some providers are recommending prenatal probiotic supplementation to their clients to reduce *Group B Streptococcus* colonization,[3] although no clinical trials to date support this practice. In addition, numerous infant formulas now contain probiotics and prebiotics, but evidence to support incorporating them is lacking as well.[4] Perinatal nurses and providers need detailed information about the implications of probiotics and/or prebiotics for the woman and neonate so that accurate histories are obtained and providers can offer the best information to women and families who are considering prenatal dietary supplements.[1]

While the scientific information on this topic is available in international journals, it is essentially absent from the perinatal nursing literature. However, it is well documented that prenatal probiotics reduce the incidence and severity of allergic disease in children of mothers who consumed these products.[5] While the pediatric benefits of prenatal probiotics are important, a gap remains in the knowledge about the maternal and neonatal effects and whether these products really impact clinical outcomes.

BACKGROUND

Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.[2] Most commonly available probiotic supplements contain Lactobacillus and/or *Bifidobacterium*, which are part of the normal human microbiome.[6] Probiotics enhance the healthy microbiota of the gastrointestinal and genitourinary tracts in a number of ways.[7,8] They produce lactic, acetic, and other acids that lower the pH in these environments, thus impeding the growth of bacterial pathogens on mucosal surfaces like the intestines and vagina.[8] Probiotics also appear to stimulate the production of numerous substances that work together to improve healthy microflora and displace

harmful bacteria.[8] These substances include vitamins, bacteriocins, enzymes, and biosurfactants that alter the surface tension and reduce pathogen adherence to the mucosa.[8–10] Probiotics are thought to work synergistically with the host immune system to stimulate specific lymphocytes, cytokines, and IgG and IgA antibodies to fight infection.[8]

Prebiotics are not live organisms[11] but are fermented food ingredients that can be used by bacteria to confer health benefits upon the host.[12] Prebiotics serve as food for species of Lactobacillus and/or *Bifidobacterium*, encouraging growth of these beneficial bacteria which in turn may inhibit the growth of pathogenic bacteria where they have colonized.[8]

PURPOSE

An integrative review was chosen as the most robust approach to allow the inclusion of the diverse methods used in the body of scientific literature.[13] The purpose of this integrative review was to identify, critique, and synthesize the perinatal evidence on prenatal probiotics and prebiotics. Maternal and neonatal outcomes derived from the literature are comprehensively detailed in this review. The goal is to review the evidence as it specifically applies to perinatal practice.[13]

METHODS

Medical Literature Analysis and Retrieval System (MEDLINE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library databases were searched using the terms: probiotics, prebiotics, pregnancy, and women's health, for articles published from 1990 through December 2011. Additional hand searches were conducted using reference lists of articles. This process yielded 251 articles that were screened to identify scientific investigations of prenatal probiotics or prebiotics that reported maternal and/or neonatal outcomes. The resulting 38 studies that met criteria, published between 1993 and 2011, were reviewed.

Data were extracted from each article in a systematic manner, using an adaptation of a previously published instrument.[14] During the data evaluation stage, each study was assessed for quality using the Oxford definitions for levels of evidence.[15] The level of evidence ratings for the 36 individual studies are presented in Table 1. Further during the data evaluation process, it was observed that many of the studies could be clustered into research collectives on the basis of specific cross-references, common trial registration numbers, countries in which the research was done, co-authorships, and/or use of the exact same sample. These observations raised concerns about overrepresenting primary data sources.[13] Table 1 is organized by study design, according to identified research collectives (lettered A-H), when applicable. The linkages between studies were not always clear; therefore, the authors indicated in Table 1 which studies made explicit versus vague connections to the parent study. Prenatal probiotic interventions were used in a total of 31 randomized placebo controlled trials,[16–46] while prebiotics were explored in only one.[47] The remaining 4 investigations of probiotics included 1 quasi-experiment,[48] 2 prospective cohort studies,[49,50] and 1 observational study.[51]

Two systematic reviews/meta-analyses on prenatal probiotics were included in this integrative review; both were assessed as level 1 evidence. The studies that appeared in the systematic reviews/meta-analyses and that were analyzed in this integrative review are indicated by symbols in Table 1. Dugoua et al[52] included 8 randomized controlled trials (RCTs) of prenatal probiotics and focused on the safety

of Lactobacillus and *Bifidobacterium* species related to 3 specific outcomes: cesarean section, birth weight, and gestational age. Naaktgeboren[53] analyzed 25 RCTs for the outcomes of perinatal probiotics on intestinal microflora, immunity, and maternal and infant nutrient utilization. Then the researcher conducted meta-analyses using 10 of the RCTs focusing on 3 specific pediatric outcomes: (1) atopic dermatitis, (2) skin prick testing, and (3) allergic sensitization. However, neither article incorporated the full range of RCTs, the quasi-experiment, the prospective cohort studies, and the observational investigation included in this integrative review. In addition, neither article fully addressed the maternal and neonatal outcomes.[52,53]

Table 1. **Summary of studies of prenatal probiotics and prebiotics**

Research collective letter	Author reference number and year	Country	Sample size	Trimester when intervention initiated	Blinding	Placebo controlled	Level of evidence[a]
Randomized controlled trials							
A	Kalliomaki[16] 2001[d]	Finland	159	3	DB	Yes	1b
A[b]	Rautava[17] 2000[d,e]	Finland	159	3	DB	Yes	1b
A[b]	Rinne[18] 2005	Finland	96	3	DB	Yes	1b
A[c]	Gueimonde[19] 2007[d]	Finland	53	3	N/A	Yes	1b
A[b]	Kalliomaki[20] 2008[e]	Finland	49	3	DB	Yes	1b
A[b]	Luoto, Kalliomaki[21] 2010	Finland	113	3	DB	Yes	1b
B[c]	Kukkonen[22] 2006[d]	Finland	87	3	DB	Yes	1b
B	Kukkonen[23] 2007[d,e]	Finland	1223	3	DB	Yes	1b
B[b]	Kukkonen[24] 2008	Finland	1223	3	DB	Yes	1b
B[c]	Kuitunen[25] 2009[e]	Finland	891	3	DB	Yes	1b
C	Piirainen[26] 2006	Finland	140	1	DB	Yes	1b
C[b]	Kaplas[27] 2007[d]	Finland	30	1	DB-SB	Yes	1b
C[b]	Huurre[28] 2008[e]	Finland	171	1	DB	Yes	1b
C[b]	Aaltonen[29] 2008	Finland	256	1	DB-SB	Yes	1b
C[b]	Laitinen[30] 2009	Finland	256	1	DB-SB	Yes	1b
C[b]	Luoto, Laitinen[31] 2010	Finland	256	1	DB-SB	Yes	1b
C[b]	Aaltonen[32] 2011	Finland	256	1	DB-SB	Yes	1b
C[b]	Ilmonen[33] 2011	Finland	256	1	DB-SB	Yes	1b
D[b]	Kopp[34] 2007	Germany	105	3	DB	Yes	1b
D	Kopp[35] 2008[e]	Germany	105	3	DB	Yes	1b
E[b]	Boyle[36] 2008	Australia	73	3	DB	Yes	1b
E[b]	Lahtinen[37] 2009	Australia	122	3	DB	Yes	1b
F[c]	Prescott[38] 2008	New Zealand	105	3	DB	Yes	1b
F[b]	Wickens[39] 2008[e]	New Zealand	474	3	DB	Yes	1b
G	Abrahamsson[40] 2007[d,e]	Sweden	232	3	DB	Yes	1b
G[b]	Bottcher[41] 2008[e]	Sweden	109	3	DB	Yes	1b
	Nishijima[42] 2005[d]	Japan	24	N/A	N/A	Yes	3b
	Niers[43] 2009[e]	Netherlands	156	3	DB	Yes	1b
	Dotterud[44] 2010	Norway	415	3	DB	Yes	1b

	Allen[45] 2011	United Kingdom	454	3	DB	Yes	1b
	Asemi[46] 2011	Iran	70	3	SB	Yes	1b
	Shadid[47] 2007	Germany	48	2	DB	Yes	4
Quasi experiment							
	Neri[48] 1993	Israel	84	N/A	N/A	Yes	3b
Prospective cohort studies							
H[b]	Brantsaeter[49] 2011	Norway	33 399	1	N/A	N/A	2b
H[b]	Myhre[50] 2011	Norway	18 888	1	N/A	N/A	2b
Observational study							
	Schultz[51] 2004	Germany	9	3	N/A	N/A	3b

Abbreviations: DB, double blind; N/A, not available; SB, single blinded control group.

[a]Oxford Center for Evidence-based Medicine Levels of Evidence.[15]

[b]Explicit reference to parent study.

[c]Vague reference to parent study.

[d]Included in Dugoua et al[52] systematic review & meta-analyses.

[e]Included in Naaktgeboren[53] meta-analyses.

RESULTS

In this section, an overview of the studies reviewed is provided and participant demographics across the studies are summarized. Probiotic routes, strains, and dosing are explained. Outcome categorization is introduced, and the maternal and neonatal outcomes are described in detail.

Overview of studies reviewed

Data from studies conducted in 11 countries in which women were given probiotics during pregnancy were synthesized. A representative sample size was estimated from the 7 research collectives that conducted RCTs; together these totaled nearly 2000 pregnant women who were likely exposed to probiotics. Moreover, 2 prospective cohort studies (research collective H) included more than 33 000 women with varying amounts of ingested probiotics in their diets.[49,50] Twenty-four pregnant women were exposed to prebiotics in 1 study reviewed.[47]

Demographic characteristics of prenatal participants

Participant characteristics were underreported in the articles reviewed. Investigators in 4 studies performed in Scandinavia and Northern Europe reported the sample race as Caucasian.[30–32,35] While researchers from New Zealand provided details of their diverse sample,[39] those from Japan and Iran did not report the race(s) of their study subjects.[42,46] Of the investigations that included the percent of participants who were college educated,[25,26,29–33,45] the median percent who attended college was 70.6% for the probiotic and prebiotic groups and 68.1% for controls. Among those who reported mean ages,[25–27,29–36,38,41,43–48] the results were 30.4 years for probiotic and prebiotic group study subjects and 31.3 years for women in the control groups. Overall, from the partial information available, the participants appeared to include mature, highly educated adults from primarily homogeneous groups.

Although all the studies reviewed included healthy pregnant women, investigators in 19 had selected samples of women specifically with a risk of atopy (a predisposition toward developing allergic hypersensitivity reactions)[54] to examine whether prenatal probiotics or prebiotics would reduce subsequent development of allergic disease in offspring.[16,17,21–25,28,35–41,43–45,47] This risk was defined by the researchers as having at least 1 first degree relative with atopic dermatitis or eczema, allergic rhinitis, and/or asthma. The purposeful sampling of women with atopic risk suggests that the outcomes of prenatal probiotics and prebiotics could be different in women without this risk. Furthermore, studies that preferentially included women with atopic risk also tended to measure long-term pediatric outcomes, beyond the neonatal period, and thus exceeded the time parameter established for this integrative review.

Routes, strains, and doses of study interventions

Because probiotics are live cultured microbial food supplements,[55] the dose is measured by colony forming units (CFUs) per milliliter, calculated by dividing the number of colonies, multiplied by the dilution on a Petri dish, by the volume of the culture on the same plate.[56] In the 35 individual probiotic studies reviewed, doses ranged from 1 × 107 to 2 × 1010 CFUs (see Table 2). Most of the probiotic studies used 1 or more strains of *Lactobacillus*, and several added at least 1 *Bifidobacterium*. These products are available over the counter.

In 27 of the studies, probiotics were administered as capsules and 2 others used oil dilutions.[40,41] In the remaining 6 studies, shown in Table 3, probiotic interventions were in the form of milk or yogurt products. In addition, one researcher studied a water-soluble prebiotic supplement containing both galacto-oligosaccharides and long-chain fructo-oligosaccharides derived from cow's milk.[47] Investigators did not provide rationale to explain their choices of probiotic or prebiotic in any of the studies reviewed. Most of the investigators began the intervention during the third trimester and continued at least until birth. Six reports were unclear concerning treatment duration,[26,27,42,48–50] and a seventh study only gave probiotics between 28 and 37 weeks' gestation.[46]

Table 2. **Probiotic species and doses in studies reviewed**

Lactobacillus (CFUs)	Bifidobacterium (CFUs)	Other species (CFUs)	Reference numbers
L. rhamnosus $(2.0 \times 10^9 - 2.0 \times 10^{10})$			16, 17, 18, 19, 20, 21, 34, 35, 36, 37, 51
L. reuteri (1.0×10^8)			40, 41
L. rhamnosus (6.0×10^9)	*B. animalis* (9.0×10^9)		38, 39
L. rhamnosus $(1.0 \times 10^9 - 1.0 \times 10^{10})$	*B. animalis subsp lactis* $(1.0 \times 10 - 1.0 \times 10^{10})$		26, 27, 28, 29, 30, 31, 32, 33
L. rhamnosus (1.0 × 1010)	*B. breve* (2.0 × 108 bid)	*Propionibacterium freudenreichii subsp shermanii* (2.0 × 109 bid)	22, 23, 24, 25
L. salivarius (6.25×10^9) *L. paracasei* (1.25×10^9)	*B. animalis* (1.25×10^9) *B. bifidum* (1.25×10^9)		45
[No *Lactobacillus*]	*B. animalis* (1×10^9) *B. bifidum* (1×10^9)	*Lactococcus lactis* (1×10^9)	43

Abbreviations: B, Bifidobacterium; bid, twice daily; CFUs, colony forming units; L, Lactobacillus; subsp, subspecies.

Table 3. **Yogurts and fermented milk probiotic products studied**

Country	Brand name	Product	Route	Dose	pH	Lactobacillus (CFUs)	Bifidobacterium (CFUs)	Reference numbers
Israel	N/A	Yogurt	Vaginal	10-15 mL	<4.5	*L. acidophilus* $(> 1 \times 10^8/\mathrm{mL})$		48
Japan	Nestlé	Fermented Milk	Oral	120 g per day	N/A	*L. johnsonii* $(1.0 \times 10^9/\mathrm{mL})$		42
Norway	Biola	Milk	Oral	No-zero low = 13 mL per day high = 85 mL per day	N/A	*L. acidophilus* (1.0×10^8)/mL *L. rhamnosus* (1.0×10^8)/mL	*B. lactis* (5.0×10^9)	44, 49, 50
Norway	Cultura	Milk	Oral	No-zero low = 13 mL per day high = 85 mL per day	N/A	*L. acidophilus* (1×10^8)/mL	*B. lactis* (5.0×10^9)	49, 50
Iran	N/A	Yogurt	Oral	200 g per day	4.3-4.5	*L. acidophilus* (1.0×10^7)/ 200g	*B. animalis* (1.0×10^7)	46

Abbreviations: B, Bifidobacterium; CFUs, colony forming units; L, Lactobacillus; N/A, not available; subsp, subspecies.

Categorizing outcomes

All discrete outcomes reported in the scientific investigations were extracted. First, the outcomes were broadly classified as maternal or neonatal. During the data reduction process for this integrative review,[13] the first 2 authors conducted a content analysis to identify each discrete perinatal study outcome. Commonalities between studies were identified and combined into categories. These logical categories provided meaningful descriptions of the major maternal and neonatal outcomes. The third author confirmed that the categories accurately reflected the data. This inclusive and comprehensive process resulted in a total of 14 categories. The 9 maternal outcome categories identified were mode of birth, vaginal flora composition preterm labor, blood pressures and preeclampsia prevention, glucose metabolism, body mass index (BMI) and weight gain, gastrointestinal outcomes, breast milk composition, and maternal immunomarkers. The neonatal findings are detailed in 5 categories: gestational age at birth, fetal cord blood, Apgar scores, anthropometric measures, and gastrointestinal outcomes. All findings were reported according to these 14 outcome categories and are identified according to article reference numbers in Table 4.

In the following sections, the statistically significant and clinically relevant perinatal outcomes are presented according to the categories. Although most maternal and neonatal outcomes were statistically nonsignificant, a comprehensive presentation is provided in adherence to the principles of the integrative review process.[13] Furthermore, some nonsignificant findings have clinical relevance for perinatal health professionals as the findings may suggest the safety of the intervention and facilitate complete disclosure of information by providers to women and their families.

Maternal outcomes

In the following sections, the 9 statistically significant and clinically relevant maternal outcomes are described. For ease of reference, all the outcome categories are summarized in Table 4. This includes those studies with nonsignificant findings.

Mode of birth

In most of the 20 investigations that reported cesarean rates in the study and control groups, between-group differences were not statistically analyzed. However, according to one meta-analysis,[52] there was no significant difference in mode of birth in the probiotic groups when compared with controls (OR = 0.88; 95% CI: 0.65-1.19; *P* = 4). Therefore, based on current limited evidence prenatal probiotics do not appear to impact the mode of birth.

Vaginal flora and pH

One of the mechanisms of action of probiotics is the acidification of mucosal surfaces like the vagina, thus inhibiting the growth of pathogens. Vaginal flora or pH were explored in only 3 studies; 2 of which reported statistically significant findings. Neri et al[48] conducted a 3-group comparison of an intravaginal yogurt intervention for treating bacterial vaginosis, compared to vaginal acetic acid (tampon soaked in 10-15 mL of 5% acetic acid), and a nontreatment control group. All 32 women in the yogurt group reported symptom relief after 2 days of treatment. At both 1 and 2 months posttreatment, women in the yogurt group had a significantly higher bacterial vaginosis cure rate than those in the acetic acid (*P* = .04) and the control (*P* < .0005) groups. Nishijima et al[42] studied the impact of probiotics on the vaginal flora of pregnant women and found that probiotic treatment (*n* = 32)

significantly increased vaginal *Lactobacillus* colonization (*P* = .025) and eliminated pathogenic bacteria (*Gardnerella* and *Corynebacterium*) (no *P* value provided). Overall, the results suggest that probiotics reduced the symptoms and presence of bacterial vaginosis and other pathogens within 1 month of administration. Vaginal flora findings beyond the presence of bacterial vaginosis were not explored in any of the investigations reviewed.

Table 4. **Summary of findings according to outcome category and reference numbers[a] of studies Reviewed**

Outcome Category	Any significant findings	Exclusively nonsignificant findings
Maternal outcomes		
Mode of birth (cesarean sections rates)	N/A	17, 19, 20, 21, 22, 23, 24, 25, 30, 31, 34, 35, 36, 37, 38, 39, 40, 43, 47, 52
Vaginal flora and pH	42, 48	47
Preterm labor	42 and 48[b], 50	N/A
Blood pressures and preeclampsia prevention	49	26, 29
Glucose metabolism	30, 31, 32	N/A
Body mass index and weight gain	49, 50	26, 27, 29, 30, 32, 33, 46
Gastrointestinal measures	37, 47	19, 30, 51
Breast milk composition	17, 38, 41	18, 28, 37
Maternal immunomarkers	36, 46	N/A
Neonatal Outcomes		
Gestational age at birth	N/A	16, 17, 18, 20, 21, 23, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 38, 41, 43, 44, 47, 52
Fetal cord blood and pH	38	16, 17, 27, 34, 36, 44, 47
Apgar scores (5 and/or 10 min)	N/A	22, 29, 30, 31, 32
Anthropometric measures (birth weight, length, and/or head circumference)	28	16, 17, 20, 21, 22, 23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 38, 39, 40, 43, 44, 47, 52
Fecal microflora samples	19, 43	23, 47, 51

Abbreviation: N/A, not available.

[a]Each number represents a study reviewed and its location in the reference list.

[b]The data from these 2 studies reviewed were pooled by Othman et al[57] in a Cochrane review to determine statistical significance.

Preterm labor

Because there is an association between bacterial vaginosis and preterm labor, probiotics have a potential role in prevention.[57] In a Cochrane review of prenatal probiotics to prevent preterm labor,[57] the results of Nishijima et al[42] and Neri et al[48] were pooled and it was found that probiotics reduced the risk of genital infection (particularly bacterial vaginosis) by 81% (OR: 0.19; 95% CI: 0.08-0.48, *P* = not reported). However, the authors concluded that there was not enough evidence to determine if probiotics reduced the incidence of preterm labor.

More recently, Myhre et al[50] evaluated the intake of probiotics and the risk of preterm labor in a large prospective cohort study. In addition to completing other questionnaires, women were asked to specify the quantity of probiotic milk products consumed (Table 3). Using logistic regression, the researchers found that women who reported a high intake of probiotic containing foods had a significantly lower risk of preterm labor (OR = 0.82; 95% CI: 0.681-0.986; *P* = .035). This study was limited by the use of recall questionnaires and a lack of clarity in reporting outcomes, but the authors concluded that probiotics may function by lowering the number of colonies of pathogenic bacteria and improving vaginal health, thereby limiting systemic inflammation that may play a role in the cascade of events that lead to preterm labor.[57] Current data are insufficient to determine whether or not probiotics have a role in the prevention of preterm labor.

Blood pressures and preeclampsia prevention

The development and severity of preeclampsia appears to be related to both the maternal immune system and infections.[58] Prenatal probiotics may reduce the placental and systemic inflammatory processes in ways that modify the maternal immune system to prevent preeclampsia.[49] Maternal blood pressure was measured in 3 studies, among which 1 reported significant findings. Brantsaeter et al[49] explored the relationship between probiotics and the risk of preeclampsia in primiparous women enrolled in a prospective cohort study. Although this study was limited by the use of dietary recall, the researchers found that daily probiotic intake significantly reduced the risk of preeclampsia (OR = 0.80; 95% CI: 0.66-0.96; *P* = not reported). The risk of severe preeclampsia was significantly reduced by weekly (OR = 0.75; 95% CI: 0.57-0.98; *P* = not reported) or daily (OR = 0.61; 95% CI: 0.43-0.89; *P* = not reported) probiotic intake. These findings suggest that regular probiotics consumption during pregnancy may play a role in preeclampsia prevention.

Glucose metabolism

In an RCT conducted in Finland healthy pregnant nondiabetic women in the first trimester of pregnancy (*N* = 256) were randomized to 1 of 3 groups: (1) dietary counseling and probiotics, (2) dietary counseling and placebo, and (3) control and placebo. Dietary counseling included intensive instructions provided by a nutritionist to follow the recommended Nordic prenatal diet[32] with special attention to sources of dietary fat and fiber, but no assessment of the subjects' preintervention diets were reported. Laitinen et al[30] found that women in the experimental group had a significantly lower mean plasma glucose level (OR = 0.31; 95% CI: 0.12-0.78; *P* = .013); the lowest insulin levels (adjusted means 7.55, 7.32, and 7.27 mU/L; *P* = .032); and, during the last trimester, the highest index of insulin sensitivity obtained from a fasting sample (adjusted means 0.37, 0.35, and 0.35; *P* = .028). Luoto et al31 reported a significantly lower risk of gestational diabetes, 13% in the probiotics/diet group compared with a combined average of 35% across the placebo groups (*P* = .003). Aaltonen et al[32] also reported a significantly lower incidence of gestational diabetes, 0% in the probiotics/diet group compared with a combined average of 10.8% in the placebo groups (*P* = .033). These studies were all limited by the use of participants' dietary recall, yet these findings suggested that dietary counseling combined with probiotics could be used to both prevent and partially treat glucose disorders of pregnancy but more prospective study is needed.

Body mass index and weight gain

Because probiotics are considered food, the inclusion of weight gain as an outcome seems logical. While seven RCTs included body mass index (BMI) and/or pregnancy weight gain as study variables, only 2 prospective cohort studies from a single research collective reported statistically significant findings.[49,50] Myhre et al[50] found that women who consumed high levels of probiotic containing foods also had significantly lower prepregnant BMIs ($P < .001$) than those who consumed lesser amounts. Brantsaeter et al[49] found that for women of normal prepregnant weight, there was no evidence that probiotics significantly altered overall maternal weight gain. More consistent inclusion of maternal prenatal and postpartum weight measurements in probiotics and prebiotics research is needed to guide clinicians.

Gastrointestinal measures

Because probiotics and prebiotics act on the mucosal surface of the gut, rectal swabs and fecal samples were used to assess changes in maternal intestinal colonization in 3 studies. While Lahtinen et al[37] found no difference in *Bifidobacterium* counts, the probiotic group had a significantly greater colonization of *Lactobacillus rhamnosus* (66.7%) than the placebo group (11.8%) (OR = 5.67; 95% CI: 2.19-14.64; $P < .001$). By detecting the intervention probiotic in the maternal gastrointestinal tract, the researchers demonstrated that it survived the digestive processes of the upper tract and can benefit the mucosal surfaces of the colon. In the study by Schultz et al,[51] *L. rhamnosus* was not detectible in rectal swabs done at 1 month postpartum in 3 of 6 women who took prenatal probiotics. Shadid et al[47] demonstrated a significant increase in the proportion of intestinal *Bifidobacterium* colony counts in women who took prebiotics compared with women in a placebo group (21% and 12.4%, respectively, $P = .026$). Because intestinal colonization with healthy bacteria has implications for both maternal and neonatal health, a more rigorous assessment of gastrointestinal measures would better inform clinical practice.

Prenatal progesterone levels lead to a physiologic slowing of the maternal gastrointestinal tract. Probiotics are often used to improve gastrointestinal symptoms. Laitinen et al[30] found pregnant women in both study groups reported minor gastrointestinal discomforts, such as flatulence, loose stools, or constipation at study initiation. Specifically 7% of the diet/probiotic, 8% in the diet/placebo, and 3% in the control/placebo groups reported these symptoms. Subsequently, because of the relative rarity of the symptoms, the researchers reported a combined prevalence of gastrointestinal symptoms, which were reduced to 2% in the second trimester and 0.5% in the third. This finding is clinically significant, because probiotic intake was not associated with any increase in the incidence of minor gastrointestinal discomforts in pregnant women, Gastrointestinal outcomes were not reported in most of the scientific investigations reviewed, representing a missed opportunity to attempt to address this important aspect of symptom management and quality of life during pregnancy. More investigation is needed to identify the impact of prenatal probiotics on the physiologic changes of pregnancy, such as constipation.

Breast milk composition

There is a suggestion in the literature that intestinal microflora play a role in breast milk composition.[41] Because there is a correlation between intestinal production of Transforming Growth Factor-beta (TGF-*β*) (a cytokine associated with allergic sensitization) and the newborn's ability to make Immunoglobulin

A (IgA) antibodies and avoid allergies,[17] these components in breast milk were evaluated in 6 studies. Three of the articles reported significant differences between groups. Rautava et al[17] examined breast milk at 3 months postpartum while the mother was just finishing the probiotic or placebo treatment. The researchers found that the concentration of TGF-*β*2 was higher in the breast milk of probiotic group mothers than in that of controls (*P* = .018). In Bottcher et al,[41] probiotics were administered only until the time of birth. There was no significant difference in breast milk IgA between groups, although significantly lower levels of TGF-*β*2 were identified in the breast milk of women who had the probiotic intervention (*L. reuteri*) found in their feces, compared with controls (*P* = .04). Probiotic treated women also had higher Interleukin 10 (IL-10) (an anti-inflammatory cytokine) in colostrum than controls (*P* = .046). However, neither difference was sustained in breast milk samples taken at 1 month postpartum. While the TGF-*β*2 findings of Bottcher et al[41] contradicted those of Rautava et al,[17] both described their results as protective against atopic disease development.

In a 3-group RCT, Prescott et al[38] studied women ingesting 2 different probiotics compared with a placebo and measured breast milk immune markers. The breastfeeding women continued the probiotic or placebo through 6 months postpartum. Prenatal *Bifidobacterium lactis* ingestion resulted in significantly higher TGF-*β*1 levels in early (1 week) breast milk (*P* = .028). At 1 week, women in both probiotic groups also had significantly higher levels of IgA in breast milk (*B. lactis*, *P* = .008; *L. rhamnosus*, *P* = .011). At 3 months, only women in the *B. lactis* group had significantly higher levels of breast milk IgA (*P* = .027). It appears that probiotic supplementation during breastfeeding may result in at least some important immunologic benefits for the neonate, but to sustain these changes, continued probiotic ingestion may be needed. Because most of the studies were conducted in Northern Europe, where breastfeeding rates are high, it may be a missed opportunity that only a few studies examined breast milk composition.

Maternal immunomarkers

Significant findings related to maternal immunomarkers following probiotic administration were found in 2 RCTs. Boyle et al[36] found that prenatal administration of *L. rhamnosus* significantly decreased human interferon *γ* **(**IFN-*γ*) (a protein released as part of the immune response to pathogens) (*P* = .02). Asemi et al46 found that *Lactobacillus acidophilus* and *Bifidobacterium animali*s administration during pregnancy significantly decreased the serum level of highly sensitive C-reactive protein (a marker for inflammation) (*P* = .001). Proinflammatory factors are increased during pregnancy and these factors are associated with insulin resistance and pregnancy complications such as gestational diabetes, premature birth, and preeclampsia.[46] These factors need to be included as outcomes in future investigations to better elucidate probiotic mechanisms of action.

Neonatal outcomes

In Table 4, all of the neonatal outcome categories are summarized with relevant references. Throughout this integrative review, details of statistically significant findings are presented. Although examination of neonatal outcomes revealed numerous statistically nonsignificant findings, a number of these outcomes are clinically relevant and therefore important to providers and their clients. It is possible that the absence of significant differences between groups may underscore the safety of prenatal probiotic exposure for the offspring.

Gestational age at birth

Variations in the timing of probiotic initiation reported among the studies limited the examination of the impact of prenatal probiotics on preterm birth prevention. However, gestational age at birth was included as a neonatal outcome in more than one-half of the studies and no significant differences were found between probiotic and control groups. In one metaanalysis,[52] a nonsignificant increase in gestational age of 0.4 weeks in the infants of women in the probiotic versus control groups ($P = .336$) was found. Current evidence does not suggest an association between antenatal probiotics and clinically relevant differences in gestational age.

Fetal cord blood and pH

Researchers in 8 of the studies reviewed attempted to examine the prenatal use of probiotics or prebiotics for reducing the expression of immunoglobulin E antibodies associated with the development of atopic disease in children. However, as previously described, the long-term measures extended beyond the neonatal period and the parameters established for this integrative review. Only Prescott et al[38] reported significant between-group differences in cord blood markers of allergic response. There was significantly less soluble cluster of differentiation 14 (a cell marker of atopic disease) in *B. lactis* group neonates ($P = .045$) and higher levels of interferon-*γ* cytokine in *L. rhamnosus* group neonates ($P = .030$) compared with the placebo group. The authors concluded that probiotics may modify cytokines and other parameters that play a role in neonatal immune responses. Only in the investigation of prebiotics did the researchers[47] measured cord pH; no differences were found between prebiotic and control group neonates. The lack of consistent markers and the inclusion of women at risk for atopic disease limits the generalizability and utility of these findings.

Apgar scores

Apgar scoring is a universal neonatal measure that indicates the need for immediate newborn resuscitation.[59] Investigators in only 6 of the studies reviewed explored 5- and/or 10-minute Apgar scores and reported no significant differences. With so little attention given to Apgar scores, there is insufficient evidence to draw conclusions about this outcome.

Anthropometric measures

Investigators in 24 of the studies reviewed included at least 1 newborn anthropometric measure (birth weight, length, and/or head circumference), and all but 2 reported no significant differences between groups. Huurre et al[28] reported a significant difference in birth weight and length, with probiotic group infants averaging 170 g lighter ($P < .05$) and 0.6 cm shorter ($P < .05$). The weight difference (approximately 6 ounces) might be clinically significant for some dyads, while the shorter length (0.2 in) is unlikely to have an impact. A contradictory finding was reported in a meta-analysis,[52] in which there was a nonsignificant trend toward larger birth weights (45 g increase or 1.6 ounces) in probiotic infants than in controls ($P = .699$).

Without consistent information provided about birth weights in the studies reviewed, it is impossible to determine whether the incidence of low-birth-weight infants is impacted by probiotics or prebiotics.[52] Only limited information on birth weight ranges was reported in one-half of the studies reviewed. The incidence of low birth weight was not reported by any investigators. Therefore, information is insufficient to draw conclusions about the impact of prenatal probiotics and prebiotics on low birth weight, although analysis of this aspect would be important to include in future work.[52]

Luoto et al[31] investigated prenatal and postnatal infant growth using maternal antepartal dietary modifications and probiotics in women with gestational diabetes. When analyzed by neonatal birth weight and length, significantly more infants of control group mothers with gestational diabetes were, on average, both heavier (426 g) and longer (1.7 cm) (P = .001) than probiotic exposed infants. This difference is also clinically significant as it amounts to nearly a pound lighter for probiotic group infants of diabetic mothers. Therefore, among women with gestational diabetes, findings suggest a possible protective effect against macrosomia. Because neonatal anthropometrics often play a role in birth outcomes, inclusion of these measures in sufficient detail in future interventional studies of prenatal probiotics and prebiotics would be simple yet meaningful.

Fecal microflora samples

Enhancement of neonatal gut microflora is one goal of prenatal probiotic ingestion. In 5 investigations reviewed, neonatal fecal samples were tested for the presence of probiotic bacteria. The investigators were attempting to identify if the probiotic bacteria ingested by the mother prenatally could be retrieved from neonatal fecal samples. Authors of 2 of the studies found significant between-group differences in fecal bacteria. Gueimonde et al[19] analyzed neonatal fecal samples at 5 days of age and found significantly more *B*. *breve* in probiotic group neonates than in controls (P = .044), while *B. adolescentis* was significantly higher in placebo group neonates (P = .043). These differences were not significant in the 3-week stool samples (P = .069), but the researchers found that the intestinal microflora of neonates whose mothers took probiotics were more complex and less similar to their mothers. Niers et al[43] examined neonatal stools weekly during the first month of life and found that colonization with *Lactococcus lactis* was significantly increased in the feces of probiotic group neonates at 2 weeks (P < .01), and at 3 to 4 weeks of life (P < .001). However, there were no significant differences in *Bifidobacterium* counts between groups in this study. While *Bifidobacteium* predominates in a healthy gut, it takes several months to fully develop during infancy.[60]

Because the bacterial flora of the neonatal gut is markedly affected by mode of birth, environmental exposures, and feeding methods, interpretation of gastrointestinal outcomes of probiotic and prebiotic use must be examined within those contexts.[61] The presence of *Bifidobacterium* and overall bacterial complexity and diversity are important indicators of a healthy neonatal intestinal microbiota.[19] These measures were omitted in most of the studies reviewed; more in depth, long-term study is needed.

Adverse effects of probiotics and prebiotics

No adverse effects attributable to the use of prenatal probiotics or prebiotics were reported by investigators in any of the studies reviewed. In 1 article, neonatal morbidities such as jaundice, hypoglycemia, infection, the need for supplemental oxygen administration, and other more rare complications were not significantly different between probiotic and control group neonates.[24] Allen et al[45] focused on adverse events as the primary study outcome tracked using World Health Organization International Statistical Classification of Disease Criteria and questionnaires completed by mothers and providers. Adverse events such as infections and diseases of the nervous, respiratory, and digestive systems were reported by 15 women (6.8%) in the probiotic group compared with 21 (9.0%) in the placebo group, but these differences were not statistically significant. Overall, no negative sequelae were attributed to prenatal probiotics or prebiotics.[45]

In healthy individuals, probiotics are not thought to be systemically absorbed.[62] Although probiotic bacteria such as *Lactobacillus* are "generally regarded as safe,"[2,63] and were included in nearly all of the study probiotic interventions, some concerns persist. For example, there are theoretical risks of probiotics for pregnant women and neonates due to their slightly compromised immune responses.[53] The development of serious infections in immune-compromised patients exposed to probiotics is considered possible.[53] Prebiotic use would not introduce strains of new bacteria and therefore should pose no potential risk.[53] In summary, no evidence of adverse effects of prenatal probiotics or prebiotics were documented in this review.

DISCUSSION

More than one-half of the prenatal probiotic studies reviewed were conducted for the purpose of reducing atopic disease in children. Prenatal probiotics have a well-established record of significantly reducing the incidence and severity of atopic disease in offspring.[5] Unfortunately, many maternal and neonatal outcomes were largely ignored in the research studies reviewed, highlighting missed opportunities to build a strong body of perinatal evidence about the intervention.

Summary of statistically significant findings

Overall, few statistically significant maternal and neonatal outcomes associated with prenatal probiotic use were reported among the studies reviewed. However, the statistically significant maternal outcomes of prenatal probiotic ingestion are detailed as follows: reduced rates of bacterial vaginosis,[48,57] increased vaginal bacterial colony counts of *Lactobacillus*,[42] increased intestinal colonization with *L. rhamnosus*,[37] lowered the incidence of preeclampsia,[49] lowered the incidence of gestational diabetes,[31,32] improved glucose metabolism,[30] altered immune markers in serum,[36,46] and those in breast milk[17,38,41] and, when taken in high amounts, according to one prospective cohort[50] study and a Cochrane review,[57] may reduce the risk preterm labor. Prebiotics significantly increased maternal *Bifidobacterium* in the intestines.[47]

Similarly for the neonate, prenatal probiotics were associated with significantly higher intestinal colonization with *Bifidobacterium*[19] and *Lc. Lactis.*[43] Prenatal probiotics also modified several cord blood[38] immunomarkers, placental cytokines, and other protective and/or growth promoting factors.[27]

Limitations

This integrative review has several limitations. First, it was difficult to determine with precision how the investigators analyzed specific measures and variables. A number of the studies reviewed did not contain clear reporting of statistics and/or between-group differences on maternal and neonatal outcomes. Despite careful consideration of the research collectives, some of the perinatal outcomes may have been overrepresented due to the inclusion of secondary analyses. Furthermore, even when authors did clearly indicate that they were using a subsample of a larger, earlier study, the number of women who were exposed to probiotics during pregnancy may be overestimated. The use of atopy as an eligibility criterion in more than one-half of the studies reviewed threatens the generalizability of the findings. In addition, the investigators used a variety of probiotics. There is emerging evidence that the effect of probiotics is strain specific and the findings from the use of one probiotic may not be attributable to another.[8] Finally, given that there was only 1 study of prebiotics, conclusions about perinatal outcomes of prebiotic administration are limited.

Clinical implications

Most of the probiotic interventions were initiated in the third trimester and included once daily oral dosing with a probiotic containing *Lactobacillus*, and several added at least 1 *Bifidobacterium*. There was no evidence that taking probiotics beginning in the first trimester would be harmful. On the basis of the 2 prospective cohort studies, the use of live cultured milk products may be considered as a nutritional intervention valuable to all pregnant women. For example, the consumption of approximately 3 ounces of a cultured milk product daily was associated with a significant decrease in the risk of spontaneous preterm birth.[50] The lowest risk of severe preeclampsia was associated with the consumption of approximately 7 ounces of cultured milk product daily.[49] While these specific products may not be available in the United States, this review and the details provided could be used to select similar products that could meet the needs of pregnant women. When compared with the CFU dosing in most of the probiotic capsule supplements in the studies reviewed, substituting cultured milk products would require the consumption of large amounts to achieve a similar dosage. Because of the diversity of the studies reviewed, there is no single probiotic supplement that could be recommended universally to all pregnant women.

Pregnancy is an opportune time for probiotic use because of the potential positive effects for the health of the woman and her neonate. Probiotics appear to hold promise for clinicians as nonpharmacologic, readily available, well-tolerated, low-risk therapies for women with minor complaints and may play a role in preventing major pregnancy complications. However, the maximal and immediate benefits for pregnant women appear to exist primarily during active probiotic ingestion, although the immunologic benefits for the infant exposed prenatally may persist for months or years.[21] The outcomes of postpartum ingestion have not been clearly addressed in the scientific literature because several investigators continued probiotic ingestion for infants and sometimes for the mother during breastfeeding. On the basis of this review, prenatal probiotic and/or prebiotic use appears to be low risk and may lead to a variety of potential short- and long-term benefits for healthy women.

The long-term safety for children born after probiotic use in pregnancy was evaluated by Luoto et al[21] at intervals up to 10 years of age. There were no adverse events or perinatal deaths in any women or infants involved in the study. While 26% of the study children exposed to probiotics during pregnancy were lost to follow-up and many of the outcomes were beyond the parameters for this review, the researchers concluded that probiotics did not significantly alter the duration of pregnancy, the mode of birth, prenatal or postnatal growth, rates of sepsis, Apgar scores, or the duration of breastfeeding.

Research implications

Detailed information about the effect of prenatal probiotics and prebiotics is vital for researchers, clinicians, and parents. There is emerging evidence that probiotics inhibit pathogens in the human microbiome.[7,8] For example, an *in vitro* study showed that a probiotic composed of *Lactobacillus* and *Bifidobacterium* inhibited *Group B Streptococcus* growth[64]; this finding needs *in vivo* testing.

Future research with a focus on more clarity and inclusion of consistent maternal and neonatal outcomes and measures is needed to enhance the clinical utility of the findings. Apgar scoring, newborn weight ranges (with incidence of preterm birth and low birth weight) could readily be

included. Explicit reporting of sample demographics and outcomes, such as vaginal flora and pH, intestinal microbiota, immune markers, and the incidence of minor adverse effects would better contribute to the body of knowledge. The heterogeneity in outcome measures in this body of literature limits researchers' abilities to conduct systematic reviews. Furthermore, analysis of between-group differences would facilitate replication and the conduct of meaningful meta-analyses.

The omission of race as a demographic variable in all but 5 studies may be due to the fact that most were conducted in countries that have homogeneous populations. Because colonization with microbiota varies by race/ethnicity[65] and geographic location,[66] more research that explores the outcomes of prenatal probiotic use in diverse women from countries with heterogeneous populations is warranted. In addition, future investigations could be strengthened by including rationale for the choice of probiotics or prebiotics, the dose chosen, and the mode of administration.

Well-controlled double blind trials of larger populations of healthy women (including those not at risk of atopic disease) are needed. Important clinical issues urgently need to be addressed, such as preterm labor prevention and promoting the establishment of healthy neonatal intestinal flora. The latter investigation requires controlling for mode of birth and type of infant feeding. The interactions between maternal and neonatal physiology were explored in only 11 studies.[17–19,27,28,34,36,38,41,46,47] Most of the research in this integrative review focused on long-term infant and pediatric outcomes. Critical measures during the transition from pregnancy through the first month of life, such as comparisons of maternal and neonatal intestinal flora,[19] breast milk cytokines,[17,18,28,41] other immunomarkers[34,36,38,46,47] and placental fatty acids,[27] were largely ignored.

CONCLUSION

In this integrative review, findings are presented on the clinical application of prenatal probiotics during pregnancy. Evidence was noted for the safety and tolerance of probiotics used during pregnancy, which is an opportune time to positively affect the long-term health of the developing fetus and child. Prenatal probiotics are associated with a decrease in atopic disease and may also have demonstrated impacts on other perinatal outcomes, although inconsistencies in measuring and reporting the outcomes limited the utility and generalizability of these findings. Only 1 study of prebiotics was found. Well designed and controlled clinical trials of diverse healthy women using well-characterized strains of probiotics with rigorous assessment of the impact on intestinal and vaginal microbiota are needed to better determine clinically relevant perinatal outcomes.

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