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# Prenatal and postnatal administration of prebiotics and probiotics

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## SUMMARY

Colonization of the neonatal gut by beneficial bacteria is important for the establishment and maintenance of the mucosal barrier, thus protecting the neonate from enteric pathogens and local and systemic inflammation. The neonatal microbiome is influenced by infant diet, environment, and the maternal microbiome. Dysbiosis in pregnancy increases the risk of pre-eclampsia, diabetes, infection, preterm labor, and later childhood atopy. Dysbiosis of the neonatal gut plays an important role in colic in the term infant, in the disease processes which plague preterm infants, including necrotizing enterocolitis and sepsis, and in the long-term outcomes of neonates. Administration of enteral prebiotics, probiotics, and synbiotics during pregnancy, lactation, and postnatal life appears to be a safe and feasible method to alter the maternal and neonatal microbiome, thus improving pregnancy and neonatal outcomes.

### Keywords

Pregnancy; Microbiota; Prematurity; Necrotizing enterocolitis; Atopic dermatitis; Allergic rhinitis; Metabolic syndrome; Diabetes mellitus

## 1. Introduction

Novel approaches to analysis of microbial communities have provided evidence that changes in maternal, fetal, and neonatal microbes impact both short- and long-term outcomes. As this field is still in its infancy, we begin with some definitions. The term microbiota is used to describe the microbial community of a given anatomic or environmental niche; microbiome is widely used both as a synonym for microbiota and for the genetic material of the microbiota. We use the term dysbiosis to refer to alterations in the microbiota associated with disease, probiotic to mean a dietary supplement or drug containing live micro-

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organisms administered with the intent to improve health, prebiotic to mean a dietary supplement that is not digestible by the host and stimulates the growth of desirable or commensal microbes, and synbiotic to mean a dietary supplement that contains both probiotic microbes and prebiotic components. Micro-organisms can modify the human microbiota by reducing luminal pH, competing for nutrients, secreting antimicrobial compounds, preventing bacterial adhesion, and inducing antimicrobial production by the host. Table 1 presents many of the bacteria that discussed below, classified by their phylum, class, order, family, genus, and species.

## 2. The maternal microbiome: changes during normal pregnancy

### 2.1. The vaginal microbiome

This changes from the first to the third trimester of pregnancy, with an overall decrease in microbial diversity and a shift toward predominance of *Lactobacillus* spp., followed by Clostridiales, Bacteroidales, and Actinomycetales [1,2]. Lactobacillus predominance appears to protect from bacterial pathogens by maintenance of a low vaginal pH through lactic acid production. The majority of vaginal microbial community state types (CSTs) are dominated by *Lactobacillus* species (*L. crispatus*, *L. iners*, *L. Jensenii*, and *L. gasseri*), whereas some are composed of anaerobic bacteria associated with bacterial vaginosis (e.g. *Gardnerella vaginalis, Sneathia* spp., *Prevotella* spp., *Megasphaera* spp., and *Atopobium vaginae*) and an increased risk of sexually transmitted infections, preterm birth, chorioamnionitis, and spontaneous abortion. Non-pregnant women fluctuate between CSTs, whereas normal pregnant women who deliver at term maintain CSTs dominated by *Lactobacillus* species. The enhanced stability of *Lactobacillus* spp. during pregnancy is thought to provide a protective role against ascending infections [2].

### 2.2. The maternal gut microbiome

This also changes throughout pregnancy, independent of health status and diet, with a decrease in individual diversity by the third trimester, marked by an increase in Proteobacteria and Actinobacteria, and a decrease in *Faecalibacterium* spp., butyrate producers with anti-inflammatory effects [3]. These changes are similar to the changes seen with metabolic syndrome in non-pregnant individuals, and are likely beneficial to pregnancy by promoting the physiological insulin resistance that develops during a typical pregnancy course. This insulin resistance fosters adequate energy transfer to the developing fetus and ensures optimal fetal growth. When transferred to germ-free mice, third-trimester maternal fecal samples have been shown to induce greater adiposity and insulin insensitivity when compared to first-trimester fecal samples [3]. Other studies have demonstrated stability in the maternal microbiota, particularly in late pregnancy [4,5].

### 2.3. The placenta

The placenta maintains its own microbiome, which appears to occupy a niche separate from the maternal vaginal and gut microbiome. Surprisingly, this community most closely correlates with the maternal oral microbiome, as it is largely composed of non-pathogenic commensal organisms from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla [6]. Variations of the placental microbiome may be seen with preterm

birth, e.g. increased abundance of Actinomycetales and Alphaproteobacteria, and after remote antenatal infection, e.g. increased *Streptococcus* and *Acinetobacter* spp. [6].

## 3. Dysbiosis in pregnancy

Adverse health states during pregnancy may be associated with intestinal microbial changes. Obesity and excessive weight gain during pregnancy are associated with adverse gut microbiota alterations in mothers and their infants. Overweight pregnant women have significantly reduced numbers of intestinal bifidobacteria and significantly increased numbers of staphylococci, Bacteroides, Enterobacteriaceae (e.g. *Escherichia coli*) and clostridia with similar changes associated with excessive weight gain during pregnancy and with progression from the first to the third trimester of pregnancy [7]. Infants of overweight mothers have significantly higher concentrations of staphylococci, clostridia, and Bacteroides and lower concentrations of bifidobacteria in their fecal samples when compared to infants of normal weight mothers and infants of mothers with normal weight gain during pregnancy [8]. Furthermore, infants born to mothers with pre-gestational diabetes have a significant increase in bacterial diversity and a higher prevalence of Bacteroides, Parabacteroides, and Lachnospiraceae in their meconium when compared to infants born to mothers without diabetes [9]. Decreased *Lactobacillus* and *Bifidobacterium* spp. colonization during early infancy is associated with a greater risk for allergies at five years of life [10], and decreased bifidobacterial numbers and increased *S. aureus* numbers in infancy may predict childhood obesity [11]. These studies provide compelling evidence that the maternal microbiome affects the infant microbiome, which has lasting effects on childhood health.

Two lines of evidence support the hypothesis that maternal and/or placental dysbiosis is a trigger for preterm labor. First, bacterial vaginosis is associated with spontaneous abortion and preterm labor [12]. Bacterial vaginosis represents a marked state of vaginal dysbiosis, the complexity of which is still being characterized. Whether treatment of bacterial vaginosis in pregnancy decreases the risk of preterm birth remains uncertain [13]. Second, periodontal disease in pregnancy is associated with preterm labor and with low infant birth weight. The mechanisms connecting maternal oral dysbiosis and placental and fetal biology have been recently summarized [14]. Whereas treatment of periodontal disease in pregnancy has not resulted in improved pregnancy outcomes [15], animal models present compelling evidence of causality [16].

## 4. Prebiotic administration in pregnancy

Altering the prenatal microbiome during pregnancy can affect both the health of the mother and fetal outcomes. Animal studies have shown that prebiotic supplementation during pregnancy and lactation confers benefits to offspring, including improved weight gain independent of intake, increased colon length, increased muscle mass, increased bone mass, and decreased incidence of allergies and asthma symptoms [17,18]. Human studies are limited, but supplementation with indigestible oligosaccharide prebiotics, specifically fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) has been shown to significantly increase the number of maternal fecal *Bifidobacterium* spp., and most importantly

*Bifidobacterium longum*; however, this bifidogenic effect may not be transferred to the neonatal gut [19]. Supplementation with synbiotics has been shown to significantly decrease serum insulin concentrations in women [20] and reduce the risk of pre-eclampsia and dyslipidemia [21].

## 5. Probiotic administration in pregnancy

Probiotic supplementation during pregnancy is safe and may have a protective role in preeclampsia, gestational diabetes, vaginal infections, maternal and infant weight gain, and later childhood diseases [22]. Studies linking probiotics to improved glycemic control have been mixed. One randomized placebo-controlled study of 256 healthy women showed that dietary interventions plus probiotics (*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*) decreased postpartum waist circumference [23] and significantly reduced the incidence of gestational diabetes from 34–36% to 13% [24]. However, another study of 175 obese women showed that a shorter, four-week administration of probiotics during early third trimester of pregnancy did not improve glycemic control [25]. The mixed results may be due to differences in demographics, genetics, or phenotypes, durations of probiotic intervention, or differences in probiotic strains or doses.

As pre-eclampsia can be thought of as an excessive, severe maternal generalized inflammatory reaction, it is an appealing disease target for probiotics. There have been no controlled trials, but a large prospective cohort study in Norway found an association between intake of milk products containing probiotic lactobacilli and reduced risk of pre-eclampsia, which was most pronounced in severe pre-eclampsia (Table 2) [26]. Additionally, probiotics have been shown to decrease high-sensitivity C-reactive protein [27], a marker of inflammation associated with adverse maternal conditions such as pre-eclampsia and gestational diabetes.

Bacterial vaginosis is another target for probiotics with combined benefits of restoring the vaginal microbiota after (or in place of) antibiotic treatment and decreasing the vaginal pH to an optimum value. Supplementation with a probiotic mixture in late pregnancy counteracts the decrease in *Bifidobacterium* spp., modulates the decrease in anti-inflammatory cytokines interleukin (IL)-4 and IL-10 and induces a decrease in pro-inflammatory cytokines [28]. One meta-analysis showed an 81% reduction in genital infections with oral probiotics, but data were inconclusive on whether this would decrease preterm labor [29]. A cohort study in Norway demonstrated an association between high intake of probiotic dairy products and reduced risk of spontaneous preterm delivery (Table 2) [30]. A more recent study showed no significant difference in the vaginal microbiota after eight weeks of probiotics, starting at the end of the first trimester [31]; however, the incidence of bacterial vaginosis was low (2.8%) in the treatment group.

Perhaps even more compelling are several meta-analyses which have shown that administration of probiotics during pregnancy prevents atopic dermatitis in children (Table 2) [32], and a large cohort study showed that probiotic lactobacilli and bifidobacteria during pregnancy decrease eczema and rhinoconjunctivitis in children [33]. Administration of probiotics to mothers during pregnancy and/or breastfeeding alters the cytokine profile of

mother's milk, increases infant fecal sIgA [34], and may moderate excessive weight gain of children during early childhood [35].

### 5.1. The intestinal microbiota and dysbiosis in term and preterm infants

Carefully performed studies suggest that term breast-fed infants in developing countries are more likely to be dominated by bifidobacteria compared to breast-fed infants in more industrialized nations and that this early dysbiosis is causally linked to increases in type 1 diabetes and food allergies in the latter [36]. In a cohort in Bangladesh, higher numbers of fecal bifidobacteria were associated with improved growth and vaccine response [37]. In developed countries, dysbiosis is widespread among term infants, even those who are born vaginally, breast-fed, and not treated with antibiotics. In premature infants, dysbiosis is almost universal with pro-inflammatory Proteobacteria in high abundance, particularly from 28–33 weeks corrected gestational age [38]. Dysbiosis and systemic inflammation have been demonstrated in such markedly diverse processes as infantile colic in term infants and necrotizing enterocolitis (NEC) in premature infants [39,40]. The loss of the intestinal microbes that have inhabited the intestinal tract of neonates and infants over millennia through formula feeding, antibiotics, and environmental and hygiene changes may have profound implications.

## 6. Prebiotics for term infants

Studies of non-human milk prebiotics in term infants are limited. Two recent randomized controlled trials are noteworthy. In the first, infants receiving formula supplemented with GOS had less colic than did infants receiving standard formula, and, among the infants with colic, those receiving the prebiotic formula had lower fecal clostridia and higher fecal lactobacilli and bifidobacteria [41]. In the second, infants receiving a fermented milk formula with added oligosaccharides (synbiotic) had a lower incidence of colic than infants receiving either a fermented milk formula (probiotic) or a formula containing a combination of oligosaccharides (prebiotic) [42].

Human milk oligosaccharides (HMOs) are produced in large diversity and abundance in human milk. These glycans are not digestible by the infant and appear to serve a variety of functions, including prebiotic stimulation of growth of specific bacterial species. More than 100 HMO structures have been characterized, and there is wide variability among the various gut microbes in their capacity to consume intact HMOs. Many bifidobacteria and bacteroides species are able to transport and consume HMOs, whereas Enterobacteriaceae are able to consume non-HMOs, such as GOS and maltodextrin, but not intact HMOs [43]. A careful characterization of changes in the fecal microbiota of the term infant and the ingested HMOs that pass through the intestinal tract to later appear in the infant feces confirms that, as the numbers of bifidobacteria and bacteroides increase in the feces, the amounts of fecal HMOs decrease, suggesting that HMOs play a significant role in shaping the microbiota of the breast-fed infant [44]. A single subspecies, *Bifidobacterium longum* subsp. *infantis* has evolved the capacity to transport and consume all the various HMO structures, providing it with a significant advantage in colonization over other gut microbes [45]. It is likely that the prebiotic HMOs, which are produced at significant cost to the

mother, play a significant role in many of the observed beneficial effects of human milk. The discovery of novel methods for commercial production of large quantities of simple HMO structures has prompted the recent addition of HMOs to term infant formulas, though evidence of benefit from a single HMO structure is limited.

## 7. Prebiotics for preterm infants

In premature infants, various mixtures of non-human milk galacto-, fructo- and acidic oligosaccharides have been extensively studied. These prebiotic mixtures alter the fecal microbiome, decrease fecal pH, improve gastric motility, decrease feeding intolerance, and increase fecal sIgA [46]. However, a meta-analysis of seven placebo-controlled randomized clinical trials of prebiotics showed no decrease in NEC, sepsis or death [47]. Infants treated with prebiotic mixtures did not differ in intestinal permeability, vaccine response, neurodevelopmental outcome, or allergic/infectious diseases from placebo infants [48].

The variability of HMOs is greater in milk from mothers delivering preterm compared to milk from mothers delivering at term. Specific HMO structures appear to impact the fecal microbiome in premature infants [49] and may explain a portion of the protective benefit of human milk against NEC. Studies of single HMO structures are thus far limited to animal studies, which demonstrate benefit in prevention of NEC [50,51].

## 8. Probiotics for term infants

The impact of probiotic administration for the treatment of infant colic has been the subject of several randomized clinical trials. A recent meta-analysis of six studies of *L. reuteri* demonstrated significant improvement with a mean decrease in crying time of 56 min per day in the infants receiving the probiotic [52]. A single small trial of a synbiotic combination of FOS and seven probiotic bacteria also demonstrated significant improvement in colic symptoms compared to placebo [53]. Several of the clinical trials of probiotic administration during pregnancy included administration of the same probiotic organism to the infants after birth. A recent analysis of four such clinical trials included long-term outcomes and found that perinatal *L. rhamnosus* was associated with decreased allergic diseases in children without safety concerns [54].

## 9. Probiotics for preterm infants

To date, 35 randomized controlled trials of probiotics have been published, with mixed results. A recent meta-analysis of these studies concluded that probiotics decrease the risk of NEC and death, but not sepsis (Table 2) [55]. Cohort studies of probiotics in premature infants have yielded strikingly similar results (Table 2) [56]. Although these trials utilized differing doses and probiotic strains, it appears that doses of $\geq 10^9$ microbes per day are more beneficial than lower doses, that combinations of probiotics may have advantages over single organisms, and that probiotics are more effective in premature infants receiving human milk than formula [57].

## 10. Safety of prebiotics and probiotics

The safety of probiotics and prebiotics has been extensively reviewed. The most frequent adverse effect of prebiotic oligosaccharides is intestinal discomfort including bloating, flatulence, and diarrhea. Risks associated with probiotic microbes include probiotic sepsis, contamination of the probiotic product, and lack of efficacy related to reduced viability. Probiotic sepsis has been reported for a variety of commercial products, but appears to be rare. In countries where registries of all positive blood cultures are available, marked increases in probiotic sepsis have not been seen in spite of marked increases in consumption of probiotics [58]. Contamination of commercial probiotics with organisms not advertised on the package is frequent [59]. Contamination with pathogens appears to be much less widespread, but this has been associated with nosocomial infection and death in a premature infant [60].

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**Practice points**

During pregnancy:

- Prebiotics:
  - May decrease the risk of pre-eclampsia and dyslipidemia.
- Probiotics:
  - They have beneficial role in modulating gestational diabetes, pre-eclampsia, excessive weight gain, and bacterial vaginosis.
  - Evidence is mixed regarding their role in preventing preterm labor and low birth weight.
  - They decrease the incidence of atopic dermatitis in later childhood. Evidence is compelling and suggests a need for practice change.

For infants:

- Prebiotics:
  - They decrease symptoms of infantile colic.
  - They do not decrease the risk of NEC, sepsis or death in premature infants.
- Probiotics:
  - They decrease symptoms of infant colic.
  - They decrease the risk of NEC and death with consistent trends towards prevention of sepsis in premature infants. Evidence is compelling and suggests a need for practice change.

### Research directions

- Development of optimal probiotic strains for prevention of diseases associated with intestinal dysbiosis (it is likely that different strains will protect against different disease processes).
- Interactions between ingested probiotic microbes and dietary prebiotic glycans (it is likely that the foods consumed by the probiotics are important in colonization and efficacy).
- Interactions between host genotype and probiotic or prebiotic response (e.g. individuals with a common mutation in the fucosyl transferase 2 gene, widely referred to as “non-secretors,” likely respond differently than those without the mutation).
- Novel methods of probiotic delivery (current probiotic products are limited to organisms resistant to gastric acid, bile acids, and digestive enzymes).

**Table 1**

Key bacterial taxa in pregnancy and during perinatal period.

| Phylum | Class | Order | Family | Genus |
|---|---|---|---|---|
| Firmicutes | Bacilli | Bacillales | Staphylococcaceae | Staphylococcus |
| | | Lactobacillales | Streptococcaceae | Streptococcus |
| | | | Enterococcaceae | Enterococcus |
| | | | Lactobacillaceae | Lactobacillus |
| | Clostridia | Clostridiales | Clostridiaceae | Clostridium |
| | Negativicutes | Selenomonadales | Veillonellaceae | Veillonella |
| Tenericutes | Mollicutes | Mycoplasmatales | Mycoplasmataceae | Ureaplasma |
| | | | | Mycoplasma |
| Proteobacteria | γ-Proteobacteria | Enterobacteriales | Enterobacteriaceae | Klebsiella |
| | | | | Escherichia |
| | | | | Proteus |
| | | | | Serratia |
| | | | | Enterobacter |
| | | | | Cronobacter |
| | | Pseudomonadales | Pseudomonadaceae | Pseudomonas |
| | | | Moraxellaceae | Acinetobacter |
| | α-Proteobacteria | | | |
| Bacteroidetes | Bacteroidetes | Bacteroidales | Bacteroidaceae | Bacteroides |
| | | | Prevotellaceae | Prevotella |
| Actinobacteria | Actinobacteria | Bifidobacteriales | Bifidobacteriaceae | Bifidobacterium |
| | | | | Gardnerella |
| | | Propionibacteriales | Propionibacteriaceae | Propionibacterium |
| | | Coriobacteriales | Coriobacteriaceae | Atopobium |
| | | Actinomycetales | | |
| Fusobacteria | Fusobacteria | Fusobacteriales | Leptotrichiaceae | Leptotrichia |
| | | | | Sneathia |

**Table 2**

Summary of large cohort studies and meta-analyses of prenatal and postnatal probiotics

| Intervention | Patient type | No. of patients | Outcome | RR or OR | 95% CI |
|---|---|---|---|---|---|
| Cohort studies | | | | | |
| Milk containing lactobacilli [26] | Primiparous women | 33,399 | Severe preeclampsia | 0.79 | 0.66–0.96 |
| Milk containing lactobacilli [30] | Pregnant women | 18,888 | Pre-term delivery | 0.86 | 0.74–0.99 |
| Probiotic milk products [33] | Pregnant women ± their infants | 40,614 | Eczema | 0.94 | 0.89–0.99 |
| Probiotic milk products [33] | Pregnant women ± their infants | 40,614 | Rhinoconjunctivitis | 0.87 | 0.78–0.98 |
| Various probiotics [56] | Premature infants | 10,800 | Necrotizing enterocolitis | 0.55 | 0.39–0.78 |
| Various probiotics [56] | Premature infants | 8139 | Death | 0.72 | 0.61–0.85 |
| Various probiotics [56] | Premature infants | 6893 | Sepsis | 0.86 | 0.74–1.0 |
| Randomized controlled trials | | | | | |
| Various probiotics [32] | Pregnant women ± their term infants | 4755 | Eczema | 0.78 | 0.69–0.89 |
| Various probiotics [55] | Premature infants | 10,520 | Necrotizing enterocolitis | 0.53 | 0.42–0.66 |
| Various probiotics [55] | Premature infants | 9507 | Death | 0.79 | 0.68–0.93 |
| Various probiotics [55] | Premature infants | 8707 | Sepsis | 0.88 | 0.77–1.0 |

RR, relative risk; OR, odds ratio; CI, confidence interval.