Probiotics for Mother and Child

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**Abstract:** For the survival of humankind, nothing can be as important as the health of a mother and a child. As the world’s population grows to more than 6 billion, it might seem ridiculous to suggest that any real threat exists to the human species. Diseases have long ravaged populations, as have wars, poverty, and malnutrition. Life today is no different with new and emerging diseases such as SARS and Mad Cow Disease leaving a trail of concern around the planet. All that is being said, the AIDS crisis is threatening humans like no other. In countries such as Botswana, close to half the population of pregnant women is infected. Of great concern, the disease is now prevalent among women and teenage girls, threatening not only their lives but those of their offspring. Efforts to control this spread are quite abysmal, albeit well intentioned. Likewise, the death of a child every 15 seconds from diarrheal disease is not being addressed with the same vigor as SARS, even though the risk of dying from the latter for most people is similar to being struck by lightning. In the end, it is the economy and politics that dictate health spending. Image and perception are everything. While deaths mount among women and children from AIDS and other infections, the potential to intervene with a low-risk natural concept of probiotics seemed all too distant. As evidence mounts of the attributes of certain probiotic strains to treat diarrhea and reduce the risk of urogenital and other diseases, the developing world has failed to embrace it, support its evaluation and implementation, and take it to where it is needed the most. In this review, the case for and against probiotics for urogenital and intestinal infections is presented based on current literature. The story is far from complete, but the potential for improving the health of the mother and child is significant. United Nations and World Health Organization guidelines have now been developed to vanquish the unproved marketing hype products that have given probiotics a bad name. It is now up to science to deliver the remedies, and to society to make sure that only proven products reach the marketplace and the people in most need.

**Key Words:** probiotics, mother, child, vaginal, *Lactobacillus*

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Each year an estimated 1 billion episodes of urogenital infection occur. This epidemic has largely gone unnoticed by governmental, pharmaceutical, and scientific sectors of society. Although figures for urinary tract infection (UTI), bacterial vaginosis (BV), and yeast vaginitis are difficult to acquire, rates of these and sexually transmitted diseases show a serious upward trend. Not only are cases of *Chlamydia* a concern, but HIV infections are especially increasing among women.

In terms of child health, 2 factors transfer from the mother to the infant that have an impact on health. During pregnancy, the presence of BV in the mother corresponds to a higher risk of preterm birth, which brings with it an increased risk of fatal necrotizing enterocolitis in the newborn. If pregnancy runs to term, an abnormal vaginal microflora that is colonized by group B streptococci, HIV, or other virulent organisms will have implications for the baby’s well-being, whereas depletion of lactobacilli may increase the risk of allergy development.

These problems are placing in jeopardy the very existence of some developing countries. For example, more than 30% of the population of Botswana and 25% of young adult women in South Africa are infected with HIV. The death rate of infants within the first year of life is still high (>100/1,000 births) in some parts of the world (www.geographiq.com/ranking/ranking_Infant_Mortality_Rate_all.htm). Such figures clearly indicate that drastic measures need to be taken. The growing antibiotic resistance, the expense and lack of availability of drugs in many communities, and the failure or side effects of drugs make it necessary to consider other management approaches.

**UROGENITAL INFECTIONS**

**Bacterial Vaginosis**

BV is currently regarded as a depletion or loss of lactobacilli in the vagina, with colonization by Gram-negative anaerobes or, in rare cases, aerobes. BV is common in women of all age groups, often without any symptoms. When symptomatic BV occurs, it is associated with odor, discharge, and an alkaline pH. Diagnosis can be achieved by detection of at least 20% of “clue” cells (vaginal cells heavily colonized by Gram-negative rods) in the squamous cell population on microscopic examination.
examination of a saline suspension of vaginal discharge, associated with 2 of the following:
1. Anterior fornix vaginal pH ≥ 4.7
2. Release of a fishy odor on addition of 10% KOH to the vaginal discharge (positive whiff test)
3. Presence of an increased thin, homogenous, white vaginal discharge

Another screening option uses a Gram stain of a vaginal swab specimen to generate a “Nugent” score, in which the presence of mainly Gram-positive rods (indicative of lactobacilli) is scored “normal,” and the presence of clue cells, Gram-negative rods, and absence of lactobacilli is scored as “BV”. Metronidazole is the agent of choice to treat BV, but recurrences are common. Often, BV is missed during diagnosis, and patients use antifungal therapies believing the problem is caused by yeast.

**Yeast Vaginitis**

Yeast vaginitis is common, especially among black Americans. Diagnosis can be visual findings of white yeast mucus-like colonization and a dense presence of yeast cells in a wet microscope preparation. The discharge is characteristically white, and symptoms include vaginal and introital itching and irritation. *Candida albicans* is the major pathogen (around 85%) followed by *C. glabrata*, *C. krusei*, and *C. tropicalis*.

**Urinary Tract Infection**

Between 25 to 50% of females will suffer from UTI at some point in their life, and recurrences can be as frequent as 48%. Diagnosis usually requires ≥10^5 CFU/mL urine, but 10^3 organisms/mL can signal an infection if present with symptoms of dysuria, frequency of micturition, and occasionally hematuria (particularly terminal). Asymptomatic bacteriuria is very common. Gram-negative organisms, particularly *E. coli* (up to 85%), are the causative agents in most cases of UTI, followed by *Enterococcus faecalis* and *Staphylococcus saprophyticus*.

**GASTROINTESTINAL INFECTIONS**

The American Academy of Microbiology reports that around 1 child dies every 15 seconds in the world from diarrheal diseases, and there are an astounding 60 billion cases of these ailments each year. In children there are many causes of diarrhea, with rotavirus being the most common agent. Viruses such as Norwalk virus, astrovirus, calicivirus, and enteric adenovirus are also important etiologic agents, as well as toroviruses, coronaviruses, picobirnaviruses, and pestiviruses. Parasites such as *Strongyloides*, *Giardia*, and *Cryptosporidium* are quite common, especially in undernourished children, but *Campylobacter jejuni* and *C. coli* are the leading causes of bacterial food-borne diarrheal disease throughout the developed world, and *Clostridium difficile* is the most common cause of antibiotic-associated diarrhea. An estimated 20 to 50% of the 35 million people said to travel to developing countries each year suffer from traveler’s diarrhea caused by *Escherichia coli*, *Shigellos spp, Salmonella spp, Campylobacter spp, Vibrio parahaemolyticus* (in Asia), rotavirus (in Latin America), and *Entamoeba histolytica*. Such is the lethality of some intestinal pathogens that some of their virulence factors are being targeted for biologic warfare and terrorism.

Although diarrheal pathogens rarely cause urogenital infections, the impact of the disease can disrupt the mucosal immune system, thereby affecting the bladder and vaginal mucosa, and the rapid defecation of billions of indigenous organisms could increase the risk of the vaginal microflora being at least transiently imbalanced.

**PROBIOTICS**

For the past 21 years and more, our group has been studying the role of indigenous bacteria in urogenital health. This has led to the development, testing, and validation of lactobacilli strains to confer health benefits to women. Such therapy is regarded as probiotics, defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” In this mini review, the potential role of probiotics in urogenital and intestinal health is discussed.

**Evidence For and Against Probiotics to Reduce the Risk of UTIs**

A quality-of-life assessment has shown that women with UTIs suffer from a significantly reduced quality of life, including reduced general perception of well-being, physical functioning, role limitation, vitality, social functioning, and increased pain.

**Evidence For**

The evidence indicating a role for probiotics in reducing the risk of UTI originates from studies in 1915 by Newman, who showed that instillation of bacilli into the bladder could actually resolve some active infections. The concept, like much of the study of the urogenital microflora, was ignored during the antibiotic era, when the use of pharmaceutical drugs was viewed as the ultimate solution for treating and preventing UTI. However, as time passed, antibiotic resistance, and drug side effects including fixed drug eruption dermatitis, serious life-threatening ones such as Steven Johnson syndrome caused by sulfonamides, and failure of drug therapy led to a reexamination of the disease starting in the late 1970s. Although some people still recommend TMP/SMX and other agents at a daily dose for up to 5 years to reduce the risk of recurrences, others who have more closely examined the adverse effects strongly recommend its restricted use only for diseases such as *Pneumocystis carinii* pneumonia. This is particularly the case in HIV-infected children—a problem in itself that is poorly managed in most developing countries. The dropping of sul-
fonamides has not solved the problem, and trimethoprim resi-
tance is increasing. In short, problems with drug therapy
have led to a revised interest in alternatives such as probiotics.

The first evidence of indigenous bacteria such as lacto-
 bacilli protecting the host from ascension of urinary pathogens
into the bladder came from studies in the 1970s that showed the
predominant organism in the vagina of healthy women was
lactobacilli, whereas that of women with recurrent UTI was the
pathogen itself. More recent studies support this observation
and hypothesis. An inverse correlation between the presence
of hydrogen peroxide-producing lactobacilli in a study of 140
women provides indirect evidence that the lactobacilli could
protect against E. coli UTI. Studies on the lactobacilli strains
that might be particularly effective were done in the early
1980s, and certain strains were shown to inhibit the growth
and adhesion of uropathogens in vitro. At the time, this was
believed to be a critical step in identifying probiotic strains.
However, more recently it has been recognized that no proven
correlation exists, as yet, between in vitro properties and clini-
cal benefits. Nevertheless, strains such as Lactobacillus rham-
nosus GR-1 were selected and tested quite successfully in ani-
mal models of chronic and acute UTI. The protocols
essentially had lactobacilli instilled into the bladder followed
by direct intravesical challenge by E. coli. This is not the sys-
tem that would be used in humans, whereby the lactobacilli
would be inserted vaginally to prevent ascension of the path-
ogens into the bladder, but no such animal model exists for test-
ing. These findings have quite recently been verified by a Japa-
nese study using L. casei shirotia, in which a single intraure-
 thral instillation of the lactobacilli “dramatically” inhibited
E. coli growth, inflammation, and infectivity. The mecha-
nism of action was reported to be the result of a growth-
 inhibiting product of lactobacilli, which (administered intra-
urethrally at 100 μg/mouse) gave a protective effect. Human
studies followed in the late 1980s, in which L. rhamnosus
GR-1 in a douche suspension was instilled into the vagina.
This was followed by studies using a gelatin capsule contain-
ing freeze-dried lactobacilli instilled into the vagina. In both
cases, the process did not result in any adverse events but did
show an effect of reducing the risk of recurrence of UTI.

Oral use of probiotic lactobacilli has also resulted in re-
ducing the risk of UTI, as well as BV and yeast infections. The mechanism of action is likely multifactorial and could includethe ingested lactobacilli ascending from the rectal skin to
the vagina, or causing a reduced pathogen ascension, or in-
fluencing the immune or host system in a way that reduces
infectivity.

In postmenopausal women, UTI is common and, coinci-
dently, lactobacilli are only present in about one third of sub-
jects. The incidence of UTI is significantly reduced when
vaginal estriol cream is applied, but only after oral prema-
arin, not oral estriol. In the latter study, the authors noted
that unless the lactobacilli population increased, no reduction
in UTI prevalence occurred. The reduction in UTI cases with
premarin use is further supported by a Chinese study of 45
women in which UTI incidence was significantly lower
(2 of 27) than oral antibiotic (12 of 15), particularly when lac-
tobacilli reappeared (0–59% reappearance). Animal experi-
ments have also shown that β-estradiol therapy combined with
Lactobacillus fermentum administration induced protection
against uropathogenic E. coli challenge, supporting the con-
clusion of Raz et al that lactobacilli are needed for protection
from UTI in postmenopausal women.

Evidence Against

One randomized, placebo-controlled, double-blind Nor-
wegian study of 47 women with recurrent UTI using twice-
weekly vaginal instillation of lactobacilli showed a 6-month
infection rate of 1.41 in each group. However, given that the
lactobacilli strain did not colonize the vagina, it is no surprise
that no clinical impact occurred. A better study design would
have been to follow women with low or absent lactobacilli
presence and to determine their incidence of UTI. If this was
significantly higher than 1.41 over 6 months, it would imply
that the indigenous lactobacilli presence in the group studied
here had indeed reduced the recurrences of UTI.

The only other negative study was by the same group
from Finland who subsequently achieved success in prevent-
ing UTI. In their earlier study, they found that 100 mL of a
drink containing L. rhamnosus GG 5 days a week did not re-
duce the rate of UTI versus control subjects. In this study a
specific probiotic drink was tested, whereas in the recent paper
the findings were based on 139 women without a history of
UTI who ingested a fermented milk drink more than 3 times
weekly versus 185 women with acute UTI who ingested less
than 1 such drink per week on average.

In summary, there is significantly more evidence for
than against an effect of probiotics in reducing the risk of UTI.

Evidence For and Against Probiotics to Reduce the Risk of Vaginal Infections

A study from in Sweden in 1996 described “the silent,
suffering women,” referring to their finding that one quarter of
611 healthy young women (age, 19–25 years) studied reported
symptoms of lower genital tract illness particularly itching,
discharge, and soreness associated with a disturbed vaginal
flora depleted in lactobacilli, and in some cases to past Chla-
mydia infection.

Evidence For

In vitro studies have indicated that certain lactobacilli
strains can inhibit the growth and adhesion of Candida, yet
lactobacilli were present in the vagina of most (72–88%) patients with candidiasis. Other in vitro studies have shown
that certain lactobacilli strains produce H2O2, lactic acid, and...
bacteriocians active against a primary cause of BV (namely \textit{G. vaginalis})\textsuperscript{58}, implying an antiinfectious role in BV. However, as stated earlier, this does not confirm clinical efficacy.

A strong link exists between absence of lactobacilli in the vagina and risk of sexually transmitted diseases. This has led to one call for promotion of “women-controlled prevention methods” in addition to proactive detection kits for pathogens such as HIV.\textsuperscript{59} Convincing data comes from a recent study of 255 US women who had sex with an infected partner, in whom the absence of lactobacilli in the vagina correlated with a positive test for \textit{Neisseria gonorrhoeae} (odds ratio [OR], 4.1) and \textit{C. trachomatis} (OR, 3.4).\textsuperscript{60}

As stated earlier, evidence indicates that daily oral use of \textit{L. rhamnosus} GR-1 and \textit{L. fermentum} RC-14 can benefit some patients with BV.\textsuperscript{43–45} Use of these strains also appears to reduce the risk of yeast vaginitis. Data on \textit{L. crispatus} CTVO5 is sparse, but Web-based reports suggest that if given after metronidazole to prevent a 1-month recurrence of BV, it can do so successfully when it colonizes the host.

The absence of lactobacilli is a predictor of preterm delivery at less than 33 weeks,\textsuperscript{61} but no studies have tested whether probiotic use can delay or prevent preterm birth.

\section*{Evidence Against}

In patients with \textit{Candida} infections in the vagina, there is little evidence to suggest that lactobacilli can be effective in eradicating the yeast. In one study of 1110 cervicovaginal smears from premenopausal women, the prevalence of lactobacilli was 85\%, but this did not correspond to any evidence of inhibition of \textit{Candida} or reduced presence of \textit{Candida}.\textsuperscript{62} One mouse study showed that commensal lactobacilli supported the growth of \textit{N. gonorrhoeae} by promoting solubilization of iron on mucosal surfaces.\textsuperscript{63} This is contrary to findings showing a potential role of lactobacilli in protecting the host against this pathogen, but it emphasizes that further studies are necessary.

\section*{Evidence For and Against Probiotics to Treat and Prevent Diarrhea}

\section*{Evidence For}

The Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) have concluded that there is sufficient data to indicate that certain probiotic organisms are able to provide significant clinical benefits to patients at risk for, or suffering from, diarrhea.\textsuperscript{23} Without repeating the extensive data on this subject, reviewed in depth elsewhere, some examples of studies are worthy of citation.

Although it is difficult to verify that all subjects are equally exposed to pathogens, one such study of 204 undernourished children 6 to 24 months old in Peru, showed that once-daily intake of \textit{L. rhamnosus} GG 6 days a week for 15 months led to significantly fewer episodes of diarrhea (5.21 episodes diarrhea/child/year vs 6.02 episodes diarrhea/child/year in placebo group; \(P = 0.028\)).\textsuperscript{64}

The strongest evidence that probiotics can alleviate acute diarrhea comes from studies primarily using 3 strains: \textit{L. rhamnosus} GG, \textit{B. bifidum}, and \textit{L. reuteri} SD2222.\textsuperscript{65–67} The strength of the evidence comes from the randomized, double-blind, placebo-controlled design of the studies. The statistically significant reduction in duration of diarrhea is consistent, especially for the \textit{L. rhamnosus} GG strain.\textsuperscript{68,69} Even in low-birth weight premature infants, the use of \textit{L. acidophilus} and \textit{B. infantis} has been found to reduce not only cases of necrotizing enterocolitis, but also death.\textsuperscript{70} Additional studies in patients with inflammatory bowel diseases such as pouchitis have shown that a combination of 8 strains of lactobacilli, streptococci, and bifidobacteria can reduce recurrences.\textsuperscript{71} In some cases a yeast strain of \textit{Saccharomyces boulardii} has been used with some effects in patients with \textit{C. difficile} infections.\textsuperscript{72}

\section*{Evidence Against}

The main source of criticism of probiotics has come from gradually decreasing number of physicians, some of whom prefer pharmaceutical interventions and are reluctant to consider a food or dietary supplement alternative. As more and more evidence about probiotic clinical benefits is generated, this innate bias may dissipate. Having said this, the medical community is right to question the methodologies of clinical studies, and to that end more trials are needed using probiotics to show specific mechanisms of action for specific strains against infecting agents.

A prospective, randomized, double-blind, placebo-controlled trial of 20 patients who had a previous history of pouchitis and endoscopic inflammation, showed that \textit{L. rhamnosus} GG b.d. for 3 months increased the ratio of total fecal lactobacilli to total fecal anaerobes (\(P = 0.03\)), but did not alter the mean pouchitis disease activity index.\textsuperscript{73}

The GG strain was shown to colonize a portion of preterm infants of less than 2000 g birth weight. Infants received the lactobacilli twice daily for up to 21 days, and colonization occurred in 5 of 24 babies (21\%) less than 1500 g and in 11 of 23 larger infants (47\%),\textsuperscript{74} implying the potential to prevent necrotizing enterocolitis. However, although 1 week of GG therapy decreased the incidence of necrotizing enterocolitis (1.4\% vs 2.7\%) in another study, the level did not reach statistical significance.\textsuperscript{75}

A study of 45 patients with Crohn disease treated with strain GG or placebo for 12 months showed no differences in endoscopic and clinical remission.\textsuperscript{76}

A controlled pilot study showed that 3-week supplementation of elderly people with milk fermented with yoghurt cultures and \textit{L. casei} DN-114 001 did not significantly reduce the incidence of winter infections (gastrointestinal and respiratory), but duration of disease was significantly lower in the treat-
ment group (7.0 ± 3.2 days, n = 180) than in the control group (8.7 ± 3.7 days, n = 180; \( P = 0.024 \)).

A double-blind, placebo-controlled, crossover, 4-week trial of *L. plantarum* 299V in 12 previously untreated patients with irritable bowel syndrome showed no effect on symptom score or median hydrogen production.

In short, there have been clinical failures of probiotic therapy. This is not necessarily unexpected or restricted to the strains referenced here. Rather, it illustrates the need to select strains and product formulations carefully for specific health targets, and to understand how they work or fail. In this way, scientific progress will continue, and untested or unproved products will hopefully either get out of the market or under-take the research necessary to fulfill the FAO/WHO guidelines discussed later.

**IS THERE A ROLE FOR ORAL AND VAGINAL PROBIOTICS IN PREGNANCY?**

Figure 1 is a rather complicated diagram designed to illustrate the potential for probiotics to reduce the risk of preterm labor. Studies have shown that oral administration of *L. rhamnosus* GG is safe during pregnancy. The question is, can oral and/or vaginal probiotics alter the process that appears to involve inflammatory mediators perhaps induced by pathogens such as *Gardnerella*, *Prevotella*, *E. coli*, and others at the mucosal surfaces of the vagina and cervix? This inflammatory process can then stimulate cyclooxygenase (COX) expression, leading to prostaglandin release and preterm labor.

Arachidonic acid production by anaerobes such as *Fusobacterium* also can stimulate prostaglandin release through liberation of phospholipase.

The potential for remediation of this process by probiotics is illustrated in several ways. Studies have shown that lactobacilli can stimulate IL-10 and IL-12 production in the gut—a process that can inhibit matrix metalloproteinase (MMP)-1 synthesis, whereas MMP-2 stimulated by IL-8 can be inhibited by modulation of IL-10. Studies with *L. paracasei* NRC2461 have shown that it can induce the development of a population of CD4(+) T cells with low proliferative capacity that produced TGF-β and IL-10 while *L. rhamnosus* GG has been shown to induce NO production through the iNOS pathway, potentially influencing the COX-2 pathway. An experimental colitis study has shown that *L. reuteri* R2LC reduced the protein content of inducible nitric oxide synthase by 50% and the median of the protein content of inducible COX by 30%, whereas *L. rhamnosus* GG reduced the median of inducible nitric oxide protein content by 40% and actually increased the median of inducible COX protein content by 30%. This illustrates the potential to block the COX-2 pathway, but also suggests that a cocktail or strains may be required.

Three other steps might interfere with the preterm labor cascade. The production of collagen-binding proteins by *L. fermentum* RC-14 and the stimulation of mucus production could theoretically reduce MMP degradation. The displacement of pathogens on the vaginal surface by oral or vaginal lactobacilli use and IL-10, while others sell products containing dead organisms or contaminated contents. In an effort to “clean up” the mess, and ensure that companies follow guidelines for the creation and manufacture of probiotics, the FAO/WHO established a set of guidelines for probiotics in food. If implemented properly by member nations, these guidelines will ensure that probiotic organisms are speciated properly, named and numbered so that evidence for their use in humans and animals, and their mechanisms of action can be followed in the scientific literature, and that consumers can be reassured of their quality at time of use in any given part of the

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**FIGURE 1.** An illustration of the types of reactions that could lead to preterm labor via infection of the vaginal and cervical mucosa (outline boxes), and the means by which probiotics could potentially interfere with this process (boxed gray panels).
world. One end result of such efforts will be to provide the medical community with reliable probiotics for evaluation in appropriate clinical settings. This will advance the field of science, nutrition, and medicine, and will lead to a broader based use of these remedies, thereby resulting in larger profit opportunities for companies meeting the guidelines.

SUMMARY

There is growing evidence that indigenous vaginal microbiota provides a protective barrier against various vaginal and bladder infections. Furthermore, the application of some strains of probiotic lactobacilli indicates that this protective effect can be delivered to women whose flora has been depleted of these organisms. After menopause, estrogen therapy will likely be needed to support dense lactobacilli colonization, although the reason why some women still harbor these strains needs to be investigated.

Future studies are not only needed to identify mechanisms of protection of lactobacilli, but also to determine whether any indigenous organisms other than lactobacilli have a protective function in the urogenital tract of prepubertal children and elderly women. Nevertheless, such is the enormity of the crisis facing many mothers, potential mothers, and children especially but not exclusively in developing countries, that serious consideration must now be given to probiotics. The evidence of efficacy may not be as solid as would be preferred, but because HIV vaccines have failed, because relief to communities is inadequate, and because people die unnecessarily, any contribution to human well-being surely is worthy of pursuit.

Probiotics have significantly more benefits than risks. Indeed, the risk of adverse effects is extremely small. The technology exists to deliver reliable dried and other food preparations—including a dairy, nutritional product line—to outlying communities, making it feasible to improve the health of women and children in developing countries and the poorer districts of developed countries. Access to oral and vaginal probiotics could provide a means of self-empowerment whereby individuals use them without requiring hospitalization, high costs, or approval from sexual partners. If colonization of the intestine of a newborn by lactobacilli and bifidobacteria were to save 1 life, and colonization of the vagina of a woman by lactobacilli were to prevent 1 case of HIV, our contribution to humanity would indeed be great.

REFERENCES


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