

Role of probiotics in urogenital healthcare

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ABSTRACT

Urogenital infections are one of the most common causes for a woman to visit a gynecologist or a urologist. The well-known association between abnormal vaginal microbial flora and its formidable risk in the increased incidence of urinary tract infection underscores the importance of understanding the microbial flora and the efforts needed to maintain it, for ensuring urogenital health. Surprisingly in spite of the increased incidence urogenital infections receive very little attention from the medical fraternity. Growing awareness among people and newer advances in the medical field has brought them into the limelight. The importance of replenishing these depleting commensals with 'probiotics' has resurfaced in a big way. As the days go by science and medicines will touch new milestones, which will include probiotics. The value of a probiotics cannot be taken at face value. Probiotics must not be considered a panacea for treating urogenital infections. However, the available data promises that it will be a strong option in improving and maintaining urogenital health.

Key Words: Probiotics, urinary tract infections, urogenital infections

INTRODUCTION

Urogenital infections are one of the most common causes for a woman to visit a gynecologist or a urologist. P. B. Carter *et al.*, estimated that one billion women around the world suffer from infections such as nonsexually transmitted urogenital infections, which include bacterial vaginosis (BV), urinary tract infection (UTI), and yeast vaginitis.^[1] The well-known association between abnormal vaginal microbial flora and its formidable risk in the increased incidence of UTI underscores the importance of understanding the microbial flora and the efforts needed to maintain it, for ensuring urogenital health. Surprisingly in spite of the increased incidence, urogenital infections receive very little attention from the medical fraternity. Growing awareness among people and newer advances in the medical field has brought them into the limelight. The importance of replenishing these depleting commensals with 'probiotics' has resurfaced in a big way. Here we give a brief account of the health implications of probiotics in urogynecology.

VAGINAL MICROBIOTA

The microbial species that inhabit the vaginal

tract play an important role in the maintenance of health and prevention of infection. The number of microbial species inhabiting the vagina amount to 50 as compared to the 800 species inhabiting the gut. Despite the close proximity of the vagina to the anus, the different microbes present in the vagina is much lower than in the gut. The reason is still unclear. The species that are present in the vaginal mucosa vary between premenopausal woman and those who have gone through menopause. Microbial flora of a healthy premenopausal woman is generally dominated by the *Lactobacillus* species, the most common of which are *L. iners*, *L. crispatus*, *L. gasseri*, and *L. jenesenii*, followed by *L. acidophilus*, *L. fermentum*, *L. plantarum*, *L. brevis*, *L. casei*, *L. vaginalis*, *L. delbrueckii*, *L. salivarius*, *L. reuteri*, and *L. rhamnosus*. All the factors such as hormonal changes (particularly estrogen), vaginal pH, and glycogen content can affect the colonization of the *Lactobacilli* in the vagina. Menstrual cycle can also cause hormonal changes.^[2-11]

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ROLE OF COMMENSAL MICROBIAL FLORA IN PREVENTING URINARY TRACT INFECTIONS

L. iners is the most common habitant found primarily in the white population.^[9] After attaining menopause, some 25 to 30% of the women still have *Lactobacilli* present, and this number rises to between 60 and 100% with the use of vaginal or oral estrogen-replacement therapy.^[4,6,7,12,13] The interest in the potential role of the 'normal' vaginal flora began almost 30 years ago with the finding of low lactobacilli counts in the vagina and urethra, in women suffering from recurrent UTIs.^[14] J M Seddon *et al.*, in their study of normal volunteers showed a marked variation in introital organisms mediated by changes in urinary frequency.^[15] The defensive role of *Lactobacillus* also depends on multiple factors,^[16-19] namely:

1. Their symbiosis with potential pathogens.
2. Their capability of producing antibacterial materials, such as hydrogen peroxide, to limit pathogen growth.
3. Their production of biosurfactants that inhibit pathogen adherence.
4. Their ability to prime macrophages, leukocytes, cytokines, and other host defenses.

REVISITING 'PROBIOTICS'

In our daily practice as private practitioners, specialists, and super specialists we come across many instances where the patients complain of loose motions after or during a course of antibiotics. We prescribe '*Sporolac*,' which alleviates the symptoms. Once again the *Lactobacillus* does the trick. Even the food industry has begun exploiting this 'bug' through a variety of their products, for example, Probiotic-curd/yogurt, which is nothing but usual *dahi* fortified with the 'probiotic bug'. When a new concept is introduced in the field of medicine, efforts are made to apply the same to various subspecialties like urogynecology. Defined as, "live microorganisms, which when administered in adequate amounts confer a health benefit on the host,"^[20] probiotic strains have already been shown to effectively prevent diarrhea and hold a potential in preventing and treating tonsillitis, caries, renal calculi, and respiratory infections. The concept of probiotics came from the belief that a 'dismantled' microflora in the host could be restored by the exogenous application of bacteria commonly found in that area. Probiotic therapy was probably practiced many hundreds of years ago via fermented milk products such as those used by Nobel Laureate Elie Metchnikoff in the early part of the twentieth century. On account of the association with milk fermentation, most probiotic organisms

have been ingested as dairy products, to confer benefits to the gut. Food products containing probiotics are almost exclusively dairy products — fluid milk and yogurt — due to the historical association of lactic acid bacteria with fermented milk. The most frequently used bacteria in these products include the *Lactobacillus* and *Bifidobacterium* species.

Commercially used probiotic species

Lactobacillus species

L. acidophilus, *L. casei*, *L. fermentum*, *L. gasseri*, *L. johnsonii*, *L. lactis*, *L. paracasei*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, *L. salivarius*

Bifidobacterium species

B. bifidum, *B. breve*, *B. lactis*, *B. longum*.

Streptococcus species

S. thermophilus

SCOPE OF THE PROBLEM

Urinary tract infection

All around the world, it is estimated that several hundred million women suffer from UTIs annually. This figure may even be an underestimate, given that the incidence of uncomplicated UTI in women is 0.5 episodes per person per year, with a recurrence rate of between 27 and 48%.^[21] The annual cost of healthcare services is staggering, reaching \$2 billion in the United States alone and over \$6 billion worldwide.^[22]

Multiple risk factors predisposed to UTI include, sexual intercourse with multiple partners and exposure to spermicidal agents.^[23,24] Spermicides lead to loss of *Lactobacilli* and an increase in pH, which stimulates the growth of gram-negative organisms and subsequent UTI. McGroarty^[25,26] has clearly demonstrated the impact of nonoxynal-9 on the growth and adherence of urogenital bacteria and *Candida*. Additional risk factors found in postmenopausal women include a history of previous genitourinary surgery, altered bladder function and loss of estrogen.^[27,28]

Stamm and Hooton^[29] reported *Escherichia coli* as the agent responsible in most cases (up to 85%), followed by *Staphylococcus saprophyticus*^[29] and *Enterococci*.^[30] The incidence of asymptomatic bacteriuria increases with age. Krieger *et al.*, found that among school-aged girls, 1 to 2% are afflicted, compared to 2 to 5% of premenopausal women and 10 to 15% of postmenopausal women.^[31] An estimated 13 to 27% of pregnant women with asymptomatic bacteriuria will develop acute pyelonephritis,^[32] and if this occurs late in the third trimester, it may result in premature labor.

Yeast vaginitis

Abbott reported a high incidence, increased propensity for recurrence, and the increasing prevalence of non-albicans vaginitis which have underscored the need to better understand the epidemiology and pathogenesis, and to develop more accurate, rapid diagnostics and effective treatments.^[33]

Even though treatment of yeast vaginitis, mainly with topical antimycotic drugs, is reasonably effective^[34] recurrences are extremely frequent. Resistance to these drugs is increasing because many women self-diagnose, self-treat, and resort to over-the-counter antifungal medications.^[35]

Synergy between an abnormal vaginal microbiota and the spread of human immunodeficiency virus in women

The data from 2001 reveals that the proportion of women between 15 and 24 years of age, living with HIV / AIDS is 62% worldwide (and 67% in the sub-Saharan Africa).^[36] The main reasons are multifactorial, namely, lack of awareness and access to health information, rape, and dependence on men for housing and income, diminished educational opportunities, low male use of condoms, and young age at first intercourse. Multiple studies have also shown that the absence or depletion of *Lactobacilli* in the vagina, associated with overgrowth of anaerobic pathogens causing BV, results in significantly increased risk for HIV, gonorrhoea, chlamydia, and herpes simplex virus infections.^[37-41]

PROBIOTICS FOR VAGINAL AND BLADDER HEALTH

L acidophilus NCFM for the gut^[42] and *L rhamnosus* GR-1 and *L fermentum* RC-14 for the urogenital tract^[43] have been extensively studied since the commercial introduction of *L. casei*, in the 1930s.

One must understand that simply showing an absence of *Lactobacilli* associated with disease does not mean that application of *Lactobacilli* to the vagina will prevent or treat that ailment. Colonization of that particular strain over a sufficient period of time (maybe days or weeks) may be necessary to confer health benefits to the host.^[42-45] However, longer-term colonization for months or years may not be necessary if the person's own *Lactobacilli* recolonize or the exogenous therapy is re-administered.

Reid *et al.*, and Gardiner *et al.*, suggest that insertion of *Lactobacilli* into the vagina via a pessary or capsule is an effective means of boosting the content of the flora and

overcoming some pathogens or reducing their ability to dominate. This seems to be true for UTI pathogens.^[46,47]

There is only anecdotal evidence to suggest that *Lactobacilli* can treat yeast vaginitis.^[48,49] Use of skim milk-based preparations can also be effective,^[50] but compliance may be a problem for some women which would negate the potential benefits. Reid *et al.* suggested an oral dosage which seems to require around 10⁹ viable bacteria once or twice weekly, although a once-per-day vaginal protocol for three days might initially be required to deal with the urogenital tract.^[51]

Most urogenital microflora originate from the gut. Studies have shown that the daily oral intake of *L rhamnosus* and *L fermentum* can modify the vaginal flora.^[51,52] Administration of the probiotic organisms even normalized the flora, opening opportunities of a possible long-term therapy for pregnant women and those susceptible to UTI.^[53]

The interactions among microbes at the vaginal mucosal surface has not been elucidated to date. A recent study conducted by Rachmilewitz D *et al.*, on a dextran sulfate-induced mouse colitis model suggested that DNA extracted from probiotic organisms and *E. coli* could mediate anti-inflammatory activity and ameliorate disease through toll-like receptor 9 signaling.^[54,55]

Although the actual mechanisms of action of probiotics in the vagina have not been proven they are probably multifactorial. *Lactobacilli* have been shown to produce biosurfactants and collagen-binding proteins that inhibit pathogen adhesion.^[56,57] This may explain why vaginal mucosa is dominated by *Lactobacilli*, they can still be less receptive to pathogens. Mack *et al.*, Pathmakanthan *et al* and Pessi *et al* mentioned cell-to-cell communication as another probable mechanism of action which may involve the signaling of mucus production, which in turn acts as a barrier to pathogens or as the signaling of anti-inflammatory cytokine production.^[58-60] However, the question still remains as to how the normal flora becomes susceptible to infection. Rapid epithelial turnover could be the answer to it. Due to this, new surfaces are exposed to these pathogens. Also perianal or anal pathogens can gain easy access to the urinary tract via the bladder courtesy a small length of the urethra. This contributes to the change in milieu and makes one susceptible to infection.

Uehling *et al.*, introduced the concept of the vaginal mucosal vaccine, which contained nonviable bacteria.^[61] Although the results were encouraging it was still hard to believe that nonviable bacteria could 'tickle' the

immune system, when live pathogens present in the vagina, in large numbers, in patients with recurrent UTI, did not.

PRACTICAL APPLICATION

At present, the practical application of probiotics to improve urogenital health is difficult. Although, what one can do is be vigilant regarding the same. A simple vaginal swab sent for bacterial culture or Gram staining will definitely help to ascertain whether the number of *Lactobacilli* are depleting with rising age or not. It will also help to catch the notorious gram-negative bacilli and treat them accordingly. Avoiding the injudicious use of antibiotics and discouraging over-the-counter prescription of drugs should be the 'mantra' adopted by all. Gregor Reid *et al.*, mentions about an independent, third-party survey of more than 100 urologists attending the American Urological Association Annual Conference about 10 years ago, where almost 80% of the urologists stated that they would offer probiotics to patients with recurrent UTIs if available (unpublished data).^[62]

ROUTE OF ADMINISTRATION

The known modes of administration are orally, vaginally, and so on. Insertion of *Lactobacilli* into the vagina via a pessary or capsule is an effective means of boosting the content of the flora and overcoming some pathogens or reducing their ability to dominate. This seems to be true for treatment of BV and possibly UTI pathogens. Reid and colleagues found that combination of *lactobacilli* strains reduce both yeast and bacterial pathogens in the vagina even when taken orally. It also provides a better cure rate when used with metronidazole instead of an antibiotic alone. A daily oral dose of 108 viable probiotic lactobacilli can restore and maintain the urogenital health of women.^[63,64]

CONCLUSION

As the days go by science and medicines will touch new milestones, which will include probiotics. It is also necessary to make available valid and conclusive data on the various probiotic strains available commercially and their role in treating urogenital infections. The value of a probiotic cannot be taken on face value. Probiotics must not be considered a panacea in treating urogenital infections. However, the available data promises that it will be a strong option for improving and maintaining urogenital health.

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