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Review Article

Applications of Probiotics in Gynecological Health: A review

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ABSTRACT

The normal microflora of vagina is extremely important for maintenance of healthy vaginal state and consequently in prevention of urogenital infections. Since a healthy female vaginal microbiota is dominated by species of *Lactobacillus* , the perception of restoration and/or maintenance of a healthy vagina by exogenous administration of probiotic *Lactobacillus* seem feasible. Urogenital infections are treated using antibiotics. But use of antibiotics have several drawbacks, including a decrease in the numbers of beneficial bacteria and an increase of drug resistance; moreover, they are often ineffective and increase the risk of infection recurrence Unlike antibiotics, probiotics can be used over an extended period without adverse effects. Probiotics properly colonized in the vagina may help in reducing the recurrent infection. So, various strains of probiotics can be used in treatment and the load of probiotics may be used in the management of vaginal infections or its recurrence.

Keywords: Female fertility; Health; Infection; Infertility; *Lactobacillus* ; Probiotic

INTRODUCTION

Infertility is a worldwide problem, and has steadily increased over the last 30 years, with a foremost financial burden on the international health care industry. As the role of male in fertility is often overlooked, women are consistently blamed for infertility in a society where child bearing is of social significance. Infertility hence leads to emotional, social, and psychological problems in females. Thus, female infertility being a grave concern must be given utmost importance. The use of probiotics in genital tract infections was based on the reports of occurrence of *Lactobacilli* in the healthy vagina of women with no history of infection [1]. *Lactobacilli* may colonize the vagina of healthy women by traversing the perineum and block the entry of pathogens by forming a barrier. Probiotics use to treat genital tract infections could represent an alternative option to antibiotics since resistance to drugs; recurrent infections in addition to side effects are of major concern with antimicrobial treatment. In vitro studies and clinical trials in recent years have assembled evidence on the outcome of probiotics mainly *Lactobacilli* in the course of vaginal infection by counteraction of pathogens and competition [2,3]. Strains generally often exploited as probiotics belong to the *Lactobacillus* and Bifidobacteria. Various species employed as probiotics are presented in Table 1.

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Table 1: Commercially exploited Probiotics species

lactic acid bacteria	lactobacillus sp	l. fermentum
		l. acidophilus
		l. gasseri
		l. johnsonni
		l. rhamnosus
		l. salivarius
		l. caseii
		l. paracaseii
		l. lactis
		l. plantarum
		l. reuteri
	bifidobacterium sp	b. bifidum
		b. breve
		b. infantis
		b. lactis
	pediococcus sp	p. pentosaceus

Use of probiotics in genital tract infections

The use of probiotics in genital tract infections was based on the reports of occurrence of *Lactobacilli* in the healthy vagina of women with no history of infection [1,4]. *Lactobacilli* may colonize the vagina of healthy women by traversing the perineum and block the entry of pathogens by forming a barrier. *Lactobacilli* can defend against genital tract infection by: (i) preventing the adherence of potentially pathogenic microorganisms to the vaginal epithelial cells, biolfilm formation, co-aggregation with microbial pathogens (ii) producing antimicrobial products such as organic acid, H2O2 and bacteriocins, maintenance of low pH, competition for nutrients, production of surfactants with anti-adhesive properties and (iii) stimulating local immune response (innate as well as adaptive immune system) [5-11].

Coaggregation

Coaggregation of probiotic with pathogenic bacteria forms a physical-chemical hindrance that averts the pathogen entry, inhibits their growth, and prevents colonization of mucosal sites [12-16] observed a reduction in the adhesion by 57.7% upon coaggregation of *G. vaginalis* with *L. salivarius* FV2 and *L. gasseri* Coaggregation might be an essential factor in preserving the health of vagina as the antimicrobial products generated by *Lactobacilli* is highly concentrated in coaggregated area around the pathogen constituting a vital defense of host against the infection [17,18] and reducing the viability of pathogen [19-23].

Production of growth inhibitory substances

Various growth inhibitory substances produced by *Lactobacilli* are fatty acids, organic acids, biosurfactants, bacteriocins and hydrogen peroxide to facilitate the inhibition of both Gram +ve and Gram –ve microorganisms [24,25]. Antimicrobial acids and H2O2 produced by *Lactobacilli* are linked with restriction and the management of pathogens. Main products of carbohydrate fermentation by lactic acid bacteria are lactic acid and acetic acid. These acids in the UN dissociated hydrophobic form disperse through the cell membrane of the targeted microorganism. Once inside the cytoplasm of the bacteria, acids are exposed to neutral pH, gets dissociated subsequently to anions and H+ which in turn reduce the pH of the cytoplasm and the metabolic activities [17,26]. Low cytoplasmic pH interferes with signal transduction, inhibits glycolysis, and prevents active transport. Further, anionic protein accumulates inside the bacterial cell and cannot diffuse through the wall of the cell freely. This accumulation of anions in the bacterial cell leads to internal osmotic disorders. [27] Showed that *Lactobacilli* produce hydrogen peroxide at the concentration that is

inhibitory to *e.coli* and *G. vaginalis* Production of H2O2 in the vaginal milieu presents a nonspecific mechanism-based defense against microbial infections. The specific inhibition mechanism is splinted into two portions: (i) toxicity to microorganisms or (ii) acts as a peroxidase system catalyst [28]. In the vaginal fluid oxidation of halides into halogen or toxic hyphohalous acid is catalyzed by the peroxidase system through the use of H2O2.

Adherence and competition to pathogens

Major pre-requisite considered in the management of pathogenic species within the genital region to exert health promoting benefits is adherence of the *Lactobacilli* and to out-number the vaginal pathogens on Vaginal Epithelial Cells (VECs). Adherence is based on definitive interactions between the vaginal adhesions and complementary receptors. Several reports, show *In vitro* adherence of *Lactobacilli* to VECs [27,29]. Moreover, blockage of the adhesion of pathogens of urogenital origin to the VEC's has been identified by some reporters [30,31]. Some researchers consider that the stronger affinity of *Lactobacilli* to VEC receptors than pathogens result in the competitive exclusion manner of action, others propose that exclusion does take place as a result of mechanical obstruction by the fragments of *Lactobacilli* [30,32].

Competition is also included by some studies in the displacement assay form [31,33]. In such assays, VECs are mixed with pathogens for 30 minutes, subsequently *Lactobacillus* were added on to the mixture. Following the addition of *Lactobacillus* to the mixture a decrease was observed in the number of pathogens adhered per cell. The decrease is considered to take place because of a displacement of pathogens due to the higher affinity harbored by certain strains of *Lactobacillus* to the VEC receptors. [34,35] detected adherence of L. crispatus CTV-05 to VECs in large number of females. Although, little is known regarding the molecular mechanism involved in the adherence, different components, such as carbohydrates, lipoteichoic acids and glycoproteins, have been thought to be reasonably involved in the action [30,31]. Moreover, due to limited sources of nutrients, there is constant competition for the nutrients in this biological niche. Competition for nutrients and sites for binding are crucial in the management of pathogenic species in the genital tract of a woman.

Immunomodulation

Investigations regarding cytokine induction by probiotic bacteria present a great deal of interest. Regulating properties *In vitro* and *ex vivo* models have been identified by several studies among the *Lactobacillus* strains when *Lactobacilli* were cultured along with immune cells [36,37]. Probiotics increases the generation of anti-inflammatory cytokines for instance IL-10, IgA, host defense peptides such as β defensing 2, dendritic cell maturation and reduces the generation of proinflammatory cytokines (by means of action on NFκB pathway) [38]. Macrophages are found to secrete immune mediators on stimulation by the lipoteichoic acid (LTA) present on the cell surface of *Lactobacilli* . Improved anti-inflammatory activity has also been observed *in vivo* in murine colitis models on LTA removal or substitution [39,40]. Anti-inflammatory properties in the supernatant of *Lactobacilli* have also been observed in cultured decidual cells, placental trophoblastic cells, macrophages, and monocytes [41-44]. Induction in the generation of IL-12 and TNFα in primary splenocytes of mice was reported with internationally recognized *L. casei shirota* *L. rhamnosus* CNCM I-4036 supernatant was more effective than live bacteria in decreasing the production of pro-inflammatory cytokines in human decidual cells upon *E. coli* challenge [45].

Route of administration

Probiotics have to reach intact and populate the vagina to bestow the benefits. The recognized methods of administration are orally and vaginally. Vaginal probiotic capsules or inclusion of *Lactobacilli* into vagina by means of a pessary have been widely used to directly introduce the probiotic bacteria into the vagina to overcome the pathogen or reduce their ability to proliferate. Probiotics are also administered orally to offer health benefits. A pioneering research held at the University of Western Ontario in 2001, reported the ability of specific strains of *Lactobacilli* to repopulate and maintain the normal urogenital flora on oral consumption for just 28 days [46,47]. Reid found that bacterial and yeast pathogens in the vagina were reduced after combination of *Lactobacilli* strains were taken orally. It may be assumed that probiotic microbes should be competent of ascending to vagina via perineum following excretion from the rectum comparable to the pathogenic microorganisms of colonic origin that causes genital disorder. This is justified by the observation of clinical trials where vagina was colonized with the micro flora of intestinal origin revealing microbial ascension is a normal process [46]. Strus reported the recovery of orally administered *Lactobacilli* from the vagina. Thus, daily oral probiotic intake is effective at shifting pathogen friendly environments to a pathogen resistant vaginal microflora. However, the preferred route of delivery for probiotic *Lactobacilli* in genital infections is intravaginal, as the time of vaginal colonization after oral consumption is longer compared to intravaginal administration. Further, the viability and survival in the gastric acid and bile salts and the *Lactobacilli* load that could be delivered orally to colonize the vagina is lower than direct vaginal administration. Moreover, the treatment duration with oral capsules is longer than the vaginal capsules [48]. However, oral route has an advantage of reducing pathogen ascendance from the rectum to vagina through perineum, concerns with intravaginal approach is more invasive instillation of microbes.

ADMINISTRATION VEHICLES

Probiotics can be administered in various forms comprising oral capsules, vaginal capsules and vaginal tablets. Positive effects of oral administration of capsules for treatment of vaginosis have been reported within clinical trials [46,47,49,50]. Alleviation of symptoms and decreased occurrence of Bacterial Vaginosis has been reported with vaginal probiotic tablets [51-55]. Some studies have also stated the efficacy of vaginal capsules in easing the symptoms of Bacterial Vaginosis [49,56,57]. Limited studies support food as probiotic vehicles. Shalve reported reduced BV episodes on use of fermented milk consisting of *Lactobacilli*.

RELATION BETWEEN PROBIOTICS AND FERTILITY

Reproduction process is simple and starts with conception upon contact of sperm with egg and failure is frequent. Infertility studies have provided useful insights into the details of reproduction success. One third of the infertility cases are of unexplained origin, while remaining is attributed to anatomical and physiological conditions. Complete and multiple system complications including reproductive potency is caused due to atrophy of cell layers or tissues of a morphological organization. Although detailed research is lacking on the relationship between reproductive morbidity (infertility) and reproductive tract microflora (vagina), studies have reported correlation between microbes (infections) and infertility. Kaur and Prabha reported infertility in female BALB/c mice colonized with *staphylococcus aureus* and *escherichia coli* in vagina (frequent colonizers of genital tract) [58,59]. Many of the microorganisms present in vagina and cervix are not cultural and thus, not providing a types and number of bacteria present and which are beneficial and which are harmful that needs to be eradicated. It is hypothesized that microorganisms associated with vaginal infections might play a role in reduced ability of conception [60,61] as the vaginal disorder therapy improved the pregnancy rate. Presence of microorganisms in the reproductive tract might affect the transport of spermatozoa; result in immobilization/ agglutination or loss of acrosome pertinent in successful conception. Impediments associated with microorganisms are measured as preventable and treatable. However, adverse effects associated with antimicrobial therapy are increasing, reduction in use of these agents should be reasonable.

There is growing evidence of the presence of certain species in the healthy genital tract defending the host against diseases by pathogenic microbes. Microbes in the body's natural orifices e.g., vaginal cavity form a symbiotic host microorganism relationship through immune system regulation. Fluctuation in the microbial community leaves the host susceptible to bacterial over colonization and pathogen entry. It is proposed that the understanding and recognition of host microbe interactions will change much of medical views. Further, various pharmaceutical formulations enclosing probiotic *Lactobacilli* strains upon administration, being well-tolerated have been found to reduce, treat, or prevent genital infections and improve the microflora profile in vaginal milieu [62-64].

In contrast, despite the therapeutic efficacy of probiotics, there is no relevant evidence of their expression *in vivo* on the fertility aspect. Further, reproductive tract pathogenesis and potential causes of impaired fertility can be understood by illumination of host microbe interactions inside the vaginal cavity. Based on the positive impact on vaginal infection Borges reported the prevention of colonization of Listeria monocytogenes in pregnant women by the use of a vaginal probiotic (Pediococcus pentosaceus SB83) [65]. Sirota reported increase in implantation rates and reduction in immigration of pathogenic microbes upon inoculation with *L crispatus* in uterine microbiome at the moment of embryo transfer [66,67]. Although there is a lack of detailed research, further evidence is required in the field of association between the microbiota of the reproductive tract and the fertility rates. A meeting held in Aberdeen, Scotland in 2014 by the International Scientific Association for Probiotics and Prebiotics summarized the research on the role of microbes in conception (reproduction). [68] Have documented the presence of *Lactobacilli* in human follicular fluid and associated the *Lactobacilli* with embryo maturation and transfer while reporting correlation between microbes and infertility causes [69]. It has reported the presence of *Lactobacilli* in the ovaries that could have ascended from vagina and cervix and traversed all the way to the fallopian tubes. Functions of *Lactobacilli* in the healthy ovary or follicular fluid of fertile females can only be speculated at this point.

Noted displacement of sperm agglutinating *E.coli* by *Lactobacillus plantarum*, reinforcement of normal vaginal flora and finally restitution of fertility while evaluating the profertility effect of *L. plantarum* [70]. In a study it was observed that the sperm agglutinating strain of *E. coli* produced a factor with negative effects on the spermatozoa and rendered the female mice infertile on colonization in the vagina [58,59]. Displacement of this sperm impairing *E.coli* led to the restoration of fertility in female mice. Blockage of the sperm impairing *E. coli* adherence to vaginal epithelial cells can be the possible explanation of the displacement of pathogens and restoration of normal vaginal microflora. Moreover, the possible harmful effects of the sperm impairing E. *coli* on the conception might be affected by the displacement of pathogens by *L. plantarum* that led to the restitution of fertility. Also reported a correlation between *Lactobacilli* and increased rate of fertilization potential [71]. They found *Lactobacilli* can improve the fertilization potential of females by exerting a protective role on spermatozoa from free oxygen radical species present in the milieu in vaginal infections. The study of *Lactobacilli* and its effect on the reproductive potential is in its infancy due to the enduring influence of the focused paradigm on pathogen associated infertility rather than why *Lactobacilli* is associated with fertility and the difficulties of collecting samples from healthy pregnant women. Albeit, studies have not addressed the role of probiotics in fertility outcome, there is evidence that probiotics are effective in vaginal infections associated with infertility. Thus, supplementation of probiotics aimed at improving reproductive health status and fertility makes sense. Further, more studies are required to confirm the concept of the role of probiotics and elucidation of the beneficial effects of probiotic therapy, strain composition, duration, route of administration, dosage and understanding of the mechanism involved, that could impact or improve conception, successful pregnancy and fertility outcome and result in efficacious intervention.

PROBIOTICS COMMERCIALLY AVAILABLE FOR UROGENITAL TRACT

Although at present, a small number of probiotic products are commercially available for the urogenital tract, research is expanding in the area of urogenital probiotics, further it will possibly not be long prior the products for various genital conditions with different probiotic components may be offered in the market.

- VSL#3: A combination consisting of 8 distinct strains four *Lactobacilli strains* (*L. plantarum*, *L. delbrueckii subsp bulgaricus*, *L. acidophilus* and *L. casei streptococcus salivarius subsp thermophilus*) and three *bifidobacteria strains bifidobacterium longum*, *infantis* and breve was found to improve pregnancy outcome with some success in terms of modulation in immune parameters and vaginal microbiota on oral administration [72].
- Probalac Vaginal: Vaginal capsule containing *L. acdophilus*, *L. rhamnosus* and *S. thermophilus* resulted in lower recurrence rate of infection [57].
- Eco Vag R: Vaginal capsule containing *L. rhamnosus* Lbp PB01-DSM14870 and *L. gasseri* Lba EB01-DSM14864 supplementation after clindamycin treatment significantly reduced the bacterial vaginosis recurrence rate [73].
- Florisia vaginal tablets: A probiotic product for vaginal use comprises *L. salivarius* FV2, *L. brevis* CD2 and *L. plantarum* FV9. These strains are chosen on the basis of characteristics such as mucosal colonization that is capability to attach the epithelial cells and to temporarily colonize human vagina, for production of antimicrobial compounds effective towards pathogenic microorganisms and its capacity to inhibit pathogen binding to cell membrane [45,74].
- Fem-Dophilus™: Available as vaginal capsules contain *Lactobacillus* RC-14 and *Lactobacillus* GR-1. With respect to their potential probiotic properties, these strains have been selected for use in the urogenital tract [46,47,75].

ASPECTS OF SAFETY

Lactobacilli mainly referred to as "good" commensal microbes participate in the defense in opposition to pathogenic microorganisms in the gut and the reproductive tract. Diseases caused by *Lactobacillus* are uncommon and infections associated with the ingestion of probiotic *Lactobacillus* have occurred not more than in a few cases relating to *L. rhamnosus* GG [76]. These cases are related with patients suffering from chronic infection or devastating situations that present direct access from leaky gut to bloodstream. On the other hand, products consisting of probiotic *Lactobacillus* are considered safe corresponding to the approximate worldwide sale of 20 billion doses per annum [77]. Over 1 billion doses administered annually for urogenital health have been well tolerated and bacteremia caused by *Lactobacillus* is extremely rare. Moreover, no reports of toxicity or infections as a consequence of genital probiotics (species of *Lactobacillus* and Bifidobacteria) have been described [78]. Probiotics are viable microorganisms, its use in healthy people is safe, but it should be used cautiously in immunocompromised persons. As a result of an amplified concern on the subject of conjugative transfer of antibiotic resistance genes, safety or risks must be considered besides benefits [79]. Several clinical trials that place efficiency corresponding to side effects or safety, infectivity in immunocompromised are therefore needed [49,80-82].

CONCLUSION

As the vaginal microflora is frequently affected by various physiological factors of females, it can cause changes in the microbial ecosystems, thereby increasing the risk of infections. *Lactobacilli* are among the dominant microflora of vagina and it can contribute to control of growth of pathogens. So the use of probiotics can prevent or they can be used as alternative to use of antibiotics and many researchers have supported this idea. Probiotics can help in maintaining the health of vagina, as probiotics produces various natural antimicrobial substances that inhibit the growth of various pathogens and also promotes the growth of normal microflora. Authors conclude that once clinically tested, probiotics provide a very promising role in fertility of females, but its safety aspects need to be studied at a larger level. Also efficacy and cost effectiveness of these vaginally administered probiotics makes them a good choice treatment or prophylaxis of female urogenital infections.

DECLARATIONS

The authors have no conflict of interest and all the authors have contributed equally for the article.

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