

Special Article - Clinical Mycology: Diagnostic and Therapeutic Progresses

Probiotic Vaginal *Lactobacilli*: Are They Protecting Against Fungal Infections?

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***Corresponding author:** Ventolini G, Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center, USA**Received:** March 26, 2015; **Accepted:** May 29, 2015;**Published:** June 01, 2015**Abstract**

Vaginal *Lactobacilli* are an essential part of the vaginal microbiome. It is hypothesized that the vaginal microbiome protects against opportunistic infections. For instance, bacterial vaginosis can be effectively treated with probiotic *Lactobacillus*. Currently, questions surrounding the treatment of vulvovaginal candidiasis with probiotic *Lactobacilli* are being investigated. The purpose of this review is to determine the evidence for or against the treatment of vulvovaginal candidiasis with Probiotic *Lactobacilli* in addition to determining if vaginal *Lactobacilli* are protective against vaginal infection with *Candida*.

Keywords: Probiotics; Vulvovaginal candidiasis; Vaginal *Lactobacillus*

Introduction

The Healthy Microbial Flora of A Women's Vagina (MFHWV) plays a major role in preventing pathogenic bacterial genital infections [1]. Do *Lactobacilli* provide the same kind of protection toward Vaginal Candidiasis (VC)?

Vulvovaginal candidiasis is a highly prevalent infection throughout the world. It is mainly caused by *Candida* species including *C. albicans*, by far the most commonly involved fungus [2].

A healthy MFHWV is primarily colonized by *Lactobacilli*; therefore, the perception of using probiotics to reestablish or to preserve vaginal health is very appealing. Probiotics were defined in 2001 by the World Health Organization as live bacteria that confer a health benefit on the host, when they are prescribed in sufficient quantities [3].

Several studies have been published regarding the potential use of probiotics in the treatment of VC [4-6]. Also, recently Mendling concluded that prescribing appropriate *Lactobacillus* strains of probiotics as adjuvant in the treatment of VC deserve to be taken into consideration based on encouraging initial results [7].

Probiotics have many useful effects on the vaginal flora, including antagonistic and stimulatory immune effects. In using probiotics to stimulate the development of favored microorganisms, it stands to reason we may be able to reduce possible harmful bacteria and strengthen innate defense mechanisms [8,9]. The anti-pathogenic mechanism effect seems to occur by reducing/stabilizing the vaginal pH through production of lactic acid, acetic acid, and propionic acid. Moreover, it likely involves making crucial nutrients unobtainable by harmful bacteria, modifying the vaginal milieu, synthesizing hydrogen peroxide, bacteriocins and several other inhibitory microbiological products [10].

It has been proposed that vaginal *Lactobacilli* decrease the risk of VC, but supporting data are limited and controversy over the use of probiotics continues. Nevertheless, probiotic *Lactobacilli* are progressively being used in the prevention and treatment of vaginal infections. Therefore, a critical assessment of the rationale behind

their use, and consequently their effectiveness, is required.

Methods

The purpose of this review is to determine what kind of relationship exists between probiotic vaginal *Lactobacilli* and VC.

We conducted a search using the following scientific publication engines: Medline, Embase, Google scholar, Scopus, Science Direct and Index Medicus. We looked for publications containing the following terms: *Lactobacilli*, vaginal, vaginitis, *candida*, candidiasis, fungal, yeast, probiotics, protection or not, and beneficial or not. Period of search: January 1990 to February 2015.

Inclusion criteria for our search included: 1. Peer reviewed publications that were conducted in animal models and/or humans, 2. Randomized controlled trials, 3. Up to date basic science studies, 4. Studies that used current technologies including genetics, PCR, *Lactobacillus* genus-specific primers and cytokine quantification. Exclusion criteria: 1. Non peer reviewed publications, 2. Case reports, 3. Studies that did not use the following current technologies: genetics, PCR, *Lactobacillus* genus-specific primers and cytokine quantification.

Results

Our search returned 23 articles. We selected 10 articles based on our criteria.

The following articles concluded against *Lactobacilli* protection toward Candidiasis:

1. Hawes et al. performed a study in 2009 regarding vaginal *Lactobacilli* production of hydrogen peroxide (H₂O₂) and concluded that these micro-organisms protect against acquisition of Bacterial Vaginosis (BV) but do not protect against Vaginal Candidiasis (VC) or vaginal trichomoniasis [11].
2. Witt et al. published a study in 2009 on recurrent vaginal candidiasis treatment using monthly cycle-dependent itraconazole versus Classical Homeopathy (CH). The authors concluded that itraconazole was more effective than CH, and *Lactobacilli* did not confer any added benefit [12].

3. Abad and Safdar published a systematic review in 2009 to determine if *Lactobacilli* are useful in the prevention and/or treatment of bacterial vaginosis and VC. They obtained data from multiple computerized clinical trials that used *Lactobacilli* preparations. Largely, *Lactobacilli* were beneficial for the treatment of patients with BV; however, they did not find any clear benefit for the treatment of candidiasis. They advocated further larger research regarding types of *Lactobacilli* strains, optimal vehicle, route and dosage of administration [13].

4. McClelland et al. conducted a prospective cohort analysis involving 151 sex workers and concluded that vaginal *Lactobacilli* colonization was associated with a nearly 4-fold increase in the likelihood of symptomatic VC [14].

The following article concluded partially in favor of *Lactobacilli* protection toward Candidiasis:

5. Wagner and Johnson studied vaginal epithelial gene expression in response to *C. albicans*, probiotic *Lactobacillus*, and 17 β -estradiol. Their results suggest that *C. albicans* infection induces the production of pro-inflammatory reactions in vaginal epithelial cells. Additionally, they found that *Lactobacilli* and estrogen suppress the expression of nuclear factors related to inflammatory genes. Moreover, they reported that *Lactobacilli* may induce several interleukin expressions by an alternated signal mechanism pathway. Therefore they postulated that *Lactobacilli* may be modifying vaginal epithelial cell cytokine production to modulate the morbidity of *C. albicans* infections [15].

The following articles concluded favorably of *Lactobacilli* protection toward Candidiasis:

6. Villena et al. performed an animal study on the effect of *L. casei* supplemented to a repletion diet to malnourished mice and controls, to assess resistance to intraperitoneal infection by *C. albicans*. Mice that received *Lactobacilli* had improved survival and resistance to this infection. They observed that malnutrition impaired the production of several interleukins normally responsive to infection and that repletion treatments normalized the immune response to *C. albicans*. This included a well-organized recruitment and activation of phagocytes, along with an effective released of pro-inflammatory cytokines, which would have prevented inflammatory damage [16].

7. Martinez et al. in Brazil, used culture-dependent (PCR-amplified rRNA gene restriction analysis) and culture-independent (PCR-denaturing gradient gel electrophoresis) to examine vaginal *Lactobacilli* from healthy women and those who had been diagnosed with Vaginal Candidiasis (VC). Their analysis found only *L. crispatus* and that these *Lactobacilli* were not associated with the protection of VC [17].

8. Vitali et al. made an effort in 2007 to study the structure and dynamics of vaginal micro-flora in healthy women and those who developed VC. Their integrated approach included PCR-Denaturing Gradient Gel Electrophoresis (PCR-DGGE), real-time PCR universal *Eubacterial* primers, and *Lactobacillus* genus-specific primers. They found that the healthy vaginal flora was dominated by *Lactobacillus* species. *Lactobacilli* were also the main bacterial population in patients with VC but not in patients with BV [18].

9. Martinez et al in 2009 concluded that a strain of *L. reuteri* alone and with *L. rhamnosus* in an in vitro model had the potential to inhibit yeast growth and their CFS may up-regulate some interleukins secretion which, according to them could play an important role in helping to clear VC *in vivo* [19].

10. Martinez et al. performed a randomized, double blind, placebo controlled trial of the treatment of culture confirmed vulvovaginitis with fluconazole with or without a 4 week treatment probiotic *Lactobacillus*. After 4 weeks of treatment, the probiotic group exhibited less vaginal discharge associated with symptoms of itching, burning, dysuria, or dyspareunia. This suggests that probiotic augmentation of current treatments can improve symptom resolution in women treated for vulvovaginitis [20].

Discussion

Fungal infections may result from deficient recognition by the immune system or by an excess stimulation of the inflammatory response. Recent findings associated to fungal immune response in mammals have suggested that diverse functional mechanisms have evolved in order to accomplish optimal interaction between fungi and hosts [21]. Furthermore; it appears these mechanisms are at least in part regulated via interaction between vaginal epithelial cells and vaginal microbial flora, specifically *Lactobacillus* species. Alteration of these responses, via alterations in the composition of the MFHWV could lead to an increased susceptibility to infection with fungal organisms. It further stands to reason that maintenance and repair of the MFHWV with probiotics could augment, or possibly even prevent, vaginal *Candida* infections.

The number of publications regarding the use of probiotics as an adjuvant in the prevention or treatment of vaginal candidiasis keeps increasing [22,23]. However, the usefulness of probiotic prophylaxis for recurrent vulvovaginal candidiasis is still lacking a conclusive scientific verdict. In our opinion, until all of the intricacies and relationships of the vaginal microbiome are completely understood, we recommend the use of professional judgment when prescribing probiotics with the use of current information available on the subject.

Based on the above findings we may venture to determine:

- Vaginal *Lactobacillus* species support the innate immune function of the vaginal epithelium
- Specific species of vaginal *Lactobacilli* are associated with protective effects (*Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14).
- Probiotic *Lactobacillus* species are an effective treatment of BV, but not vulvovaginal candidiasis, when used alone.
- Supplementation of current standard-of-care treatment for vulvovaginal candidiasis with probiotic *Lactobacillus* species may help resolve symptoms.
- More clinical trials need to be done to determine the effectiveness of probiotic prophylaxis for recurrent vulvovaginal candidiasis.

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