Lactoferrin and Lactobacilli

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Vaginal infections are the most prevalent women's health problem. Incompetent diagnosis, inappropriate treatments, and antibiotic resistance are the main causes of the unsatisfactory results of conventional antimicrobic treatment for these infections. Consequently, several researches have been carried out to identify new treatments for these genital diseases. The significant enhancement in our knowledge of vaginal microbiota has permitted to develop new nonpharmacological strategies for the treatment of vaginal infections that seek to restore the balance of vaginal microflora, as opposed to modifying its components. Among these approaches, bioactive compounds, such as probiotics and nutraceutical proteins (like lactoferrin), deserve particular attention. The aim of this review is to examine the role of probiotics (mainly *Lactobacillus* spp.) and lactoferrin as new strategies for counteracting bacterial and fungal vaginal infections.

Lactobacillus lactoferrin bacterial vaginosis aerobic vaginitis vulvovaginal candidiasis safety

1. Introduction

The human vagina is inhabited by a variety of microorganisms, named vaginal microbiota, in varying quantities and proportions; among these, *Lactobacillus* spp., in particular *L. crispatus, L. jensenii,* and *L. iners*, are the most prevalent bacteria in the vaginal ecosystem of healthy caucasian women [1][2][3]. Lactobacilli that colonize the human vagina produce antimicrobial substances acting to counteract the growth of pathogenic microorganisms [4]. Nevertheless, for causes not completely elucidated, the vaginal microbiota composition can change and this alteration of the ecosystem can lead to vaginal dysbiosis and infections with various, adverse health outcomes, such as bacterial vaginosis (BV) and aerobic vaginitis (AV), both associated with a significantly increased risk of preterm birth [5][6], or vulvovaginal candidiasis (VVC). Clinical features of some vaginal infections, such as BV, VVC, and trichomonas vaginitis are well described, while other abnormal vaginal conditions are yet to be defined [7]. In particular, lack of inflammation is the basis of the definition vaginosis.

2. Warding Off Recurrent Yeast and Bacterial Infections of the Vaginal Tract: Lactoferrin and Lactobacilli

BV, the most prevalent vaginal infection worldwide, is characterized by an increase of vaginal pH, typically ≥ 4.5, increased vaginal discharge, fishy odor, and replacement of vaginal lactobacilli with mainly anaerobic bacteria [8]. As a matter of fact, women who have been diagnosed with BV have up to 1000 times more anaerobic bacteria than

healthy women. The vaginal microbiota of these patients typically contains a wider range of species than that found in healthy individuals, with *Gardnerella vaginalis, Atopobium vaginae*, *Bacteroides* spp., *Mycoplasma hominis, Peptostreptococcus,* and *Prevotella* being typically prevalent [9][10][11]. A characteristic feature of BV is the absence of inflammation, the finding of increased leukocytosis in a vaginal smear with bacterial vaginosis should prompt a more intensive search for another diagnosis [12]. In 2002, Donders et al. [13] suggested the term aerobic vaginitis (AV) based on bacteriological, immunological, and clinical characteristics.

AV, the aerobic counterpart of BV, is defined based on specific conditions including abundant yellow discharge (without fishy odor), enhanced vaginal pH (typically ≥ 5), inflammation with leukocyte infiltration (increased number of leukocytes), absence of the lactobacillary flora, and presence of predominant aerobic microorganisms such as *Escherichia coli*, *Staphylococcus aureus*, group B *Streptococcus* (GBS), and *enterococci* [6],[13]. *Escherichia coli* also represents one of most common causes of neonatal sepsis and chorioamnionitis [14]. Severe forms of AV, with prominent signs of epithelial atrophy, are also referred to as desquamative inflammatory vaginitis [15].

In pregnant women, GBS most often is found in the vagina and rectum and can cause infection of the urinary tract, placenta, womb, and amniotic fluid. Even if they have not had any symptoms of infection, pregnant women can pass the infection to their babies during labor and delivery. This is rare and happens to 1 or 2 babies out of 100 when the mother does not receive treatment with antibiotics during labor. In fact, the chance of a newborn getting sick is much lower when the mother receives intrapartum antibiotic treatment. For that reason, pregnant women are screened for GBS as part of routine prenatal care between 35 and 37 weeks of pregnancy.

Vaginal yeast infections (also called yeast vaginitis or vulvovaginal candidiasis) are characterized by white vaginal discharge, local itching, burning, soreness, and pain during intercourse and urination. More than 90% of cases are due to *Candida albicans* but, recently, the number of infections due to non-*C. albicans Candida* (NCAC) species, such as *C. glabrata, C. krusei*, etc., has increased significantly and becomes problematic [16].

BV, AV, and yeast vaginitis require treatment based on microscopy findings and a combined oral or local (vaginal cream or tablet) treatment with antibiotics or antifungals (for bacterial or yeast infections, respectively), steroids (inflammatory component in bacterial infections), and/or estrogens (atrophy component in bacterial infections).

Antibiotic and antifungal treatment of genital infections is not always effective, and complications persist due to microbial resistance, side effects, and recurrent infections (many bacterial and yeast vaginitis patients will have a recurrence). Persistent or recurrent BV is common and detection of some organisms associated with BV has been associated with antimicrobial resistance and could be predictive of the risk of failure of subsequent treatment [17]. On the other hand, it is known that healthy vaginal microbiota is disturbed by antibiotics and that the risk that pathogenic microorganisms will develop resistance to antimicrobial drugs increases dramatically with an overall increase in the use of antimicrobial preparations [18]. For example, the treatment of BV with clindamycin or metronidazole has been associated with marked evidence of antimicrobial resistance among vaginal anaerobic bacteria [19][20][21].

It has been also suggested that recurrent BV could be due not only to antibiotic treatments that do not eradicate persistent infection but also to reinfection by sexual partners [22]. Recurrent infections are also probably due to the elimination of the commensal microorganisms in the vagina by the antimicrobial therapy, thereby increasing susceptibility to recolonization by resistant pathogens [23]. Moreover, concerning BV, although the results of numerous researches are controversial, most studies have been in favour of probiotics in the prevention or treatment of the disease [24]. This is an important issue for considering the use of *Lactobacillus* spp., to replenish the commensal microbes and reduce the risk of reinfection. It is not surprising therefore that alternative remedies are of great interest and, in fact, complementary and alternative medicine is already widely used in women with bacterial and yeast genital infections, particularly in those with chronic vaginitis [25]. As already reported, in healthy women, the predominant microorganism in the vaginal microbiota is *Lactobacillus* spp. and its depletion during vaginal infections has resulted in the development of oral or vaginal use of probiotic *lactobacillus* strains for the treatment and prevention of these infections [4].

According to the World Health Organization definition, probiotics are “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [26].

With regard to nutraceutical-based treatments, not only probiotics but also prebiotics and immunomodulatory compounds, are of great interest. Whereas probiotics use live microorganisms, “prebiotics are non-viable substrates that serve as nutrients for beneficial microorganisms harboured by the host, including administered probiotic strains and indigenous (resident) microorganisms” [27]. In this regard lactoferrin (Lf), a natural component of most exocrine biological fluids (i.e., vaginal secretions, semen, tears, saliva, nasal and bronchial secretions, gastrointestinal fluids, colostrum and particularly breast milk), deserves particular attention for its therapeutic effect on vaginal health [28].

Lf, one of the major antimicrobial components of the innate immune system, is a ~80 kDa nonhemic iron-binding multifunctional glycoprotein normally found in milk and secreted in most external mammalian fluids [29]. Lf is involved in numerous physiological functions such as iron adsorption and immune response regulation; it also possesses anti-inflammatory and antioxidant properties, as well as antimicrobial effects against a wide range of pathogenic bacteria, fungi, protozoa and viruses [29], and prebiotic activity [30][31]. In particular, this prebiotic activity deserves special attention.

In this review, we describe the capability of Lf and lactobacilli, alone or in combination, to counteract vaginal bacterial and fungal infections, as well as discussing their application in clinical trials.

Due to indiscriminate antibiotic treatments, the onset of infections caused by resistant pathogenic strains is dramatically increasing [32]. As a result, research and the development of new therapeutic strategies has become essential. With this in mind, there is an increasing interest in the use of lactobacilli and prebiotics to combat these important pathogens and the combination of lactic acid bacteria with bovine lactoferrin may represent a very promising tool to provide protection from BV and AV, as well as yeast vaginal infections and offer a new, interesting, alternative approach for reducing the symptomatic recurrences of vaginal infections.

It is probable that after the induction phase with probiotic plus azole or antibiotic, the maintenance intervention in a specific phase of the cycle (during menstrual phase for RBV and in the luteal phase for RVVC) could be useful and strategic in these specific forms of complicated vaginitis/vaginosis. Theoretically, the potential synergistic effect between this specific bLf RCX™ and the two specific strains of lactobacilli might not only promote the growth of beneficial bacteria but also balance the local immunity. Further data will be needed to confirm these extremely important results.

Another speculative aspect is linked not only to the efficacy of Lf and lactobacilli, alone or in combination, to counteract the infection of the urogenital tract in women, but also to their safety [33][34][35][36][37]. Women suffering from BV treated with vaginal capsule containing 10^8 CFU *L. crispatus* for three days per month for three consecutive months, after a single oral dose (2 g) of metronidazole at recruitment, tolerated the treatment. A percentage ranging from 3.6% and 7.8% reported mild side effects, mainly stickiness [33]. A randomized, placebo-controlled clinical trial with a small group of women with BV, showed that the vaginal administration of *L. crispatus* or placebo for five initial consecutive days, followed by a weekly application over two weeks, was generally well tolerated. Only mild and moderate side effects occurred including vaginal discharge (46%), abdominal pain (46%), dysuria (21%), pollakiuria (21%), vaginal odor (21%), and genital pruritus (17%); endoscopic examination revealed no epithelial injury in the vagina [34]. Similar evidence was found by other studies [35][36] involving women with history of recurrent UTI equally randomized for receiving vaginal capsule containing either *L. crispatus* or placebo. No serious adverse events were reported. The most frequent signs were vaginal discharge, irritation, and abdominal discomfort; anyway, no statistically significant difference was found between the two study arms. Urinary tract infections and cystitis could happen at follow-up [34] but the incidence of vaginal infections such as BV and VVC was very low (0%–5%) [36]. This body of evidence, as well as a review [36] assessing the efficacy and safety of lactobacilli for counteract recurrent UTIs confirm that such approach represents an effective and well tolerated strategy useful for rebalancing the urogenital microflora and hampering the overgrowth of fastidious microorganisms causing diseases. In such a way, lactobacilli may be used as strategy complementary to antibiotics, whose use could be limited to acute phases, thus avoiding the insidious risk of developing resistance due to long term therapy with antibiotics.

Another important area of interest is the research of supportive measures able to reduce the rate of pregnant women colonized by bacteria in their anal-vaginal tract (GBS carriers) during the third trimester of gestation. They need in fact to be treated with an antibiotic during labor to reduce the early onset of disease in the newborn. We know also that women with higher *Lactobacillus* spp. colonization in their vaginas are more likely to have no detectable bacteria or GBS colonization in their recto-vaginal tract. In 2016 Ho et al. [38] showed that oral probiotics containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 could reduce the recto-vaginal GBS colonization rate in pregnant women and should subsequently reduce the rate of pregnant women to treat with antibiotics during labor. Different data from Australia reported that pregnant women treated with probiotics did not show a reduction in the incidence of GBS in their vaginas in comparison to the control group [39]. The effectiveness of probiotics as a surrogate or adjunctive therapy for intrapartum antibiotic prophylaxis in GBS colonized pregnant women needs to be evaluated within this growing body of knowledge. Probiotics in general and specifically probiotics use in

pregnancy need RCT trials. All studies should consider multiple avenues of exploration for future research in terms of length of intervention times, probiotic strains, doses, outcomes, etc.

Briefly, the conflicting data could justify the investment of future research into testing the effects of probiotics on vaginal GBS colonization rates.

This entry has highlighted the additional role of bLf that could facilitate the development of new approaches by simultaneously combining typical Lf preparations and specific lactobacilli (such as the combination of bovine lactoferrin RCX™ with *L. acidophilus* LMG S-29159 and *L. rhamnosus* SD5675, Respecta® complex) ensuring a huge improvement in women's health through probiotic/prebiotic input. Other, new RCT trials will be useful for confirming current findings and opening up new opportunities in other areas of interest, such as during pregnancy.

In conclusion, the market is flooded with hundreds of formulations based on probiotics, the safety and efficacy of which is based on bibliographic evidence referring to the individual components of the product. Clinicians should be warned about this situation and use in their day to day practice only original branded products that unlike the generics have been tested for safety and efficacy in randomized, controlled human trials.

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