Vaginal Candida Infections [1]

Vaginal candida infections

Vaginal candida infections (VCI) such as vaginal (occurring inside the vagina) or vulvovaginal (occurring on the vulva) candidiasis, are common infections affecting an estimated 75% of sexually active women at least once in their lifetime. Physical symptoms include but are not limited to vaginal itching, dyspareunia, a burning sensation, and a thick lumpy white discharge[1 2]. VCI represent a heavy negative emotional and sexual burden for patients[2], especially as approximately 50% of women will develop a second episode, and 5% of those women will suffer from further recurrences[2].

Risk factors for VCIs include antibiotic use[3], use of hormonal (and other) contraceptives[4 5], sexual intercourse[6], use of vaginal lubricants[7], vaginal douching[8], menstruation[9 10 11 12], pregnancy[13], and stress[14 15 16]. The common feature of these risk factors is that they can cause an imbalance or dysbiosis in the vagina. If the natural vaginal microbiome is out of balance, it cannot prevent overgrowth of pathogens[2 17], thus women with a dysbiotic vaginal microbiome are likely at higher risk of developing various symptomatic infections[18].

Fungi are important microorganism of the vaginal ecosystem in healthy women[19 20 21] and Candida spp. colonize approximately from 20% to 65% of women without causing any symptoms[19]. However, the transition from normal vaginal resident to symptomatic infection is poorly understood and usually involves the combination of host inflammation, microbiome dysbiosis, and Candida spp. virulence factors.
The Vaginal Microbiome and Fungal Dysbiosis

The human vagina is inhabited by over 50 different inter-kingdom species\textsuperscript{22, 23}, including anaerobic bacteria (mostly \textit{Lactobacillus} spp.), viruses, and fungi\textsuperscript{19, 21}. One of the key functions of this microbiome is to maintain a low pH and thus prevent various pathogenic microorganisms from dominating the niche. It is thought that vaginal microorganisms originate in general from the GI tract\textsuperscript{24, 25} by migrating across the perineum\textsuperscript{26}, which acts as an extra-vaginal reservoir, further explaining the co-morbidities between GI complaints and urogenital infections noted in some patients\textsuperscript{27}. In general, vaginal microbiome research in humans focuses on identification of bacterial and viral microorganisms with very little emphasis on exploring the natural fungal population\textsuperscript{19, 20, 21}. Thus a majority of vaginal mycobiome studies are still limited to the pathology context and not to understanding how they contribute to health.

The \textit{Candida} spp. present in a healthy vaginal microbiome include \textit{Candida albicans}, \textit{Candida glabrata}, \textit{Candida krusei}, or \textit{Saccharomyces} spp.\textsuperscript{19, 21} and it is thought that in VCI, they outcompete the other vaginal microbiome residents to dominate the vaginal niche. The findings of Guo et al. (2012) demonstrated an increase in vaginal fungal diversity in patients with recurrent VCI compared to health volunteers. This subsequent dysbiosis characterized by an increased proportion of \textit{C. albicans} was also correlated with a reduced proportion of \textit{Saccharomyces} spp. and other uncultured fungi. This implies that \textit{Candida} spp. are in fact pathobionts, able to live peacefully in the vagina or able to become virulent pathogens and cause infections.
Interestingly enough, the pathology of VCI can be partly explained by the three main cellular forms or morphologies of *Candida*: yeast, pseudohyphae, and hyphae. The last form is the most virulent, while yeast and pseudohyphae are the reproductive and intermediate transitional forms, respectively. It should be noted that each morphology is genetically, metabolically, and physically different and that *Candida* spp. have evolved so that they can easily switch between forms\(^\text{29 30}\). The symptoms associated with VCIs are thought to be caused by an overgrowth of the hyphal morphology which causes inflammation\(^\text{31}\), forms biofilms\(^\text{32}\) and penetrates deep into vaginal epithelial tissue\(^\text{1 2}\). When viewed in a wet mount slide, vaginal discharge from a VC patient reveals budding yeast cells and psuedohyphae alongside mature hyphae and activated immune cells\(^\text{33}\).

The presence of multiple simultaneous morphologies make it extremely difficult to eradicate this organism especially because therapies often only target one morphology\(^\text{34}\). Another challenge is when *Candida* spp. reside in a biofilm; *Candida* biofilms show uniform resistance to a wide spectrum of the currently available antimycotics\(^\text{35}\). This could be explained in part because the physical biofilm matrix slows down the penetration and diffusion of drugs and thus only the top few biofilm layers are targeted, leaving the remaining biofilm to persist, regrow, and dominate. These particular hallmark virulence factors of *Candida* endow it with a number of mechanisms by which it can evade the immune system and antimycotic treatment. With high recurrence rates, high treatment failure rates, and the adverse effect on quality of life, there is a need to develop adjuncts and alternative treatments for VCI.
Probiotics and VCI

Studies have shown that probiotics can increase the effectiveness of anti-fungal therapy\textsuperscript{2, 40} that they are safe and have minimal-to-no side effects\textsuperscript{2, 37, 38, 39}. The evidence suggesting that VCI is a result of, or causes, a disruption of the vaginal microbiome, cites research that targets VCI infections or prophylaxis using microbiome management options such as probiotics\textsuperscript{2}. Pre-clinical data show that probiotics can increase the effectiveness of anti-fungal therapy\textsuperscript{2, 39} and inhibit the growth and virulence of urogenital pathogens\textsuperscript{23}. The efficacy of probiotics to populate the vagina and prevent or treat infection has been shown for multiple endpoints, including adjuncts together with antimicrobial treatment to improve cure rates and prevent recurrences\textsuperscript{23}. An huge advantage for patients is that vaginal probiotics have no reported adverse side effects\textsuperscript{23, 38, 39}, present minimal discomfort\textsuperscript{37} [Antonio 2009], and can be self-administered\textsuperscript{23}.

Ecologic® FEMI+ Medical Device, for improving the disbalance in the vaginal microbiome

Winclowe has developed a probiotic Medical Device for vaginal use: Ecologic® FEMI+. This vaginal capsule aims to improve the natural vaginal microbiome by preventing or improving the disbalance in the microbiome, inhibiting the growing of pathogens and/or preventing the recurrence of vaginal infections.

Selection of strains of Ecologic® FEMI+

The research formulation of the medical device Ecologic® FEMI+\textsuperscript{[2]} contains a combination of six different bacteria and lactoferrin, an iron-binding protein well known for its anti-candida activity. Pre-clinical data demonstrate that the bacterial strains in Ecologic® FEMI+ are able to produce hydrogen peroxide, D- and L-lactic acid, inhibit the growth of urogenital pathogens, including \textit{C. albicans} and \textit{Candida glabrata}, and can survive high concentrations of common antimicrobial and antymycotic drugs.

The selected strain combination from the Ecologic® Femi+ formulation:

- \textit{Bifidobacterium bifidum} \textsuperscript{W28}
- \textit{Lactobacillus acidophilus} \textsuperscript{W70}
- \textit{Lactobacillus helveticus} \textsuperscript{W74}
- \textit{Lactobacillus plantarum} \textsuperscript{W21}
- \textit{Lactobacillus brevis} \textsuperscript{W63}
- \textit{Lactobacillus salivarius} \textsuperscript{W24}

Preclinical and clinical evidence

The bacterial strains in Ecologic® FEMI+ are able to produce hydrogen peroxide, D- and L-lactic acid, inhibit the growth of urogenital pathogens, including \textit{C. albicans} and \textit{Candida glabrata}, and can survive high concentrations of common antimicrobial and antymycotic drugs. Furthermore, the bacterial strains in Ecologic® FEMI+ were also shown to adhere strongly to and prevent \textit{C. albicans} from forming the virulent hyphae morphology in addition to reducing the number of pre-formed hyphae. Equally important, a reduction in the number of adhering hyphae was noted in the presence
of compounds produced by the probiotics and this also prevented *C. albicans* biofilm formation. From the preclinical data, it can be concluded that Ecologic® FEMI+ shows promising evidence regarding mechanisms that can be effective against certain important *C. albicans* virulence factors.

Winclove Probiotics is further exploring options for a clinical trial in VCI patients. Additionally, Ecologic® FEMI+ is currently being tested in pilot clinical trial in 60 bacterial vaginosis patients.

The research formulation of the medical device Ecologic® FEMI+ is not sold as a consumer product. However, our worldwide business partners offer the formulation of the medical device Ecologic® FEMI+ as their own branded product. Thus the specific bacterial composition can be found in different products around the world.

**References**

2. a, b, c, d, e, f, g, h, i, Martinez RCR, Improved treatment of vulvovaginal candidiasis with fluconazole plus probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14, The Society for Applied Microbiology, Letters in Applied Microbiology 48 (2009) 269–274.

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