SCIENTIFIC MEDICAL CLINICAL AFFAIRS

NEWS & VIEWS

schülke

March 2023

Vaginal health

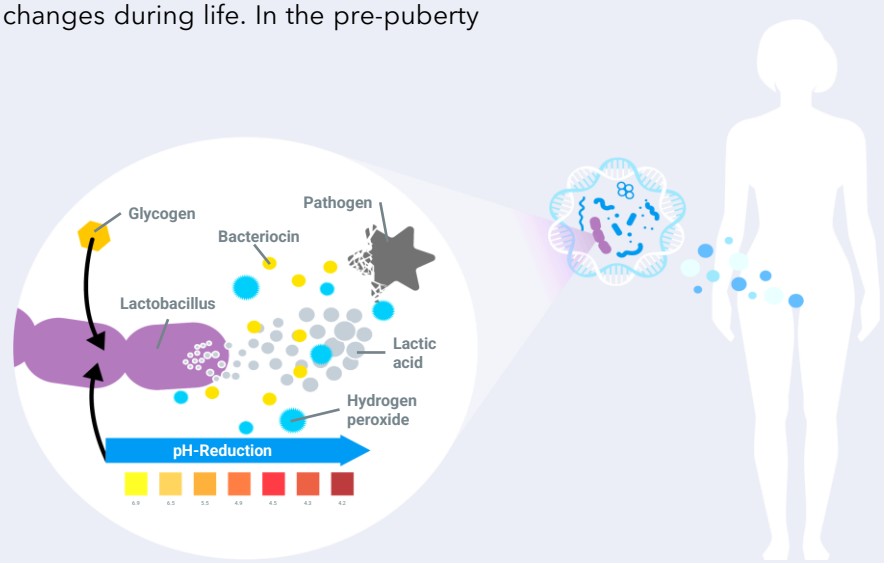
Vaginal health is an important part of women's overall health. Infections or changes in the normal balance of the vaginal microbiome can cause inflammation of the vagina (vaginitis). Symptoms include (unusual) vaginal discharge, unpleasant odor, swelling/redness, itching, dryness and pain. Most common types of vaginitis are bacterial vaginosis, yeast infections and trichomoniasis.

Aside of negative effects on sex life and self-confidence, ongoing vaginal health issues can lead to fertility problems and increase the probability for birth related complications like reduced birth weight or preterm birth. The risk for such complications is given even in asymptomatic infections, which constitute the majority of infections (asymptomatic infections: 48.37% bacterial vaginosis, 45.38% vaginal candidiasis, 30.35% trichomoniasis). According to treatment guidelines infections are treated with a range of systemic or topical antibiotics and antifungal agents with few recommendations for antiseptic treatment. Treatment with these conventional agents is however not always successful and recurring infections prevalent (recurrence rate: 30-60% bacterial vaginosis, 40-50% vaginal candidiasis). This is caused by individual resistance mechanism of the pathogens and evading mechanism like biofilm formation leading to a reduced efficacy of the treatment.[1,2]

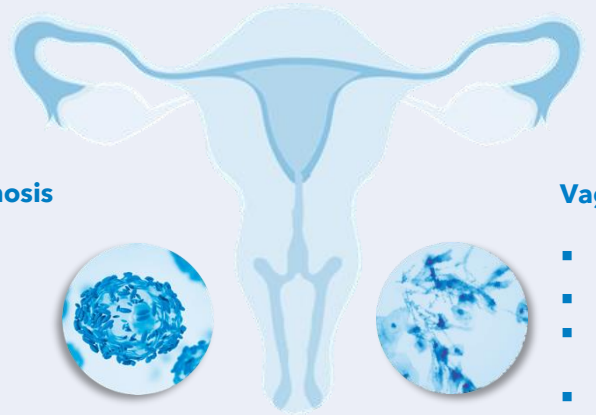
Therefore, research on alternative treatment options remains critical in the treatment of vaginal infections.

The vaginal microbiome – a complex ecosystem

More than 200 different bacterial species have been detected in the human vagina. The most prominent and often dominating type in a healthy vagina are *Lactobacillus* species. These *Lactobacillus* species protect the healthy microbiome.[3]
The vaginal microbiome is affected by environmental aspects as well as ethnic and genetic background. Several risk factors inducing a dysbiosis e.g., hormonal fluctuations, stress, immune deficiency and antibiotic treatment are known.[4,5]
The composition of the vaginal flora changes during life. In the pre-puberty and postmenopausal stage, a heterogeneous microbiome is found in which the Lactobacilli are not dominant. In the pre-menopausal stage, there is a thickened epithelium and mucus as well as high levels of estrogen and progesterone leading to glycogen storage and release, thereby creating an environment favorable for *Lactobacillus* spp.[6] A healthy vaginal microbiome is essential during pregnancy and giving birth. The birthing process and the contact of the neonates with the vaginal microbiome influences the gut, skin, nasopharyngeal and oral microbiota of neonates. A resulting atypical neonatal microbiota is associated with the development of several health problems e.g., allergies, asthma, obesity or autoimmune diseases [7-13].
Along the lines: a healthy vaginal microbiome plays also an important role in the prevention of vaginal infections, as dysbiosis is associated with common infections.
The most common infections are bacterial vaginosis (40–50%) and vaginal candidiasis (20-25%).[16,17,19,23,24]
A co-infection with *Candida* spp is observed in 20-30% of patients with bacterial vaginosis.[23] Bacterial vaginosis is caused by an imbalance of bacterial colonization, whereas vaginal candidiasis is an infection with a with a yeast fungus of the *Candida* spp. Associated with the symptoms such as vaginal fluor, burning and itching, the affected women often suffer from psychosocial discomfort. In addition, sexual life is impaired. According to guidelines the above-mentioned dysbioses are usually treated with antibiotics or antimycotics.[14-18,21,22]



The glycogen released by the vaginal tissue is metabolized by the resident Lactobacillus ssp. The resulting hydrogen peroxide and lactic acid stabilizes the pH ≤ 4.5 thereby creating a milieu unfavorable for the proliferation of pathogens.



Bacterial vaginosis

- Burning
- Itching
- rather thinner discharge
- amine odor (fishy)
- pH > 4.5
- Recurrence rate 30-60%

Vaginal candidiasis

- Burning
- Itching
- rather thicker & whiter discharge
- mostly low odor
- erythema
- pH < 4.5
- Recurrence rate 40-50%

The symptoms of bacterial vaginosis and vaginal candidiasis are similar and can easily be misjudged.[14-22]

Current German guidelines for the treatment of bacterial vaginosis & vaginal candidiasis

AWMF recommendation (S2k) for the treatment of bacterial vaginosis[21]

Initial therapy:

- Metronidazole (oral 2x 500 mg daily for 7 days; oral 1-2x 2g in 48 h; 0.75% gel 1x daily for 5-7 days; 100 mg Ovula 1x daily for 6 days; 1 g Ovula 1x daily for 2 days)
- Clindamycin (oral 2-3x 300mg daily for 7 days; 2% vaginal cream 5 g for 7 days; 100 mg Ovula 1x daily for 3 days)
- Antiseptics
  - Dequalinium chloride 10 mg 1x daily for 6 days
  - **Octenidine** 2x daily 1.day, 1x daily 2.-7.day
  - Povidone-Iodine 1x daily 6-7 days (limited efficacy)

Pregnancy therapy:

In pregnancy the recommendations are like the initial therapy (except Povidone-Iodine), but the respective product information need to be considered.

Biofilm therapy:

- Antiseptics
  - Dequalinium chloride 10 mg 1x daily for 6 days
  - **Octenidine** 2x daily 1.day, 1x daily 2.-7.day
  - Povidone-Iodine 1x daily 6-7 days (limited efficacy)

Biofilms consist of different microorganisms in a self created extracellular matrix adhered to the surface. Octenidine is effective against biofilms[27-30].

Vaginal pathogens associated with biofilm formation[25]:

- *C. albicans*
- *C. parapsilosis*
- *C. glabrata*
- *G. vaginalis*
- *A. vaginae*

AWMF recommendation (S2k) for the treatment of vaginal candidiasis[22]

Initial therapy:

The therapy of the acute vaginal candidiasis with topical or oral imidazole derivatives, polyenes and Ciclopirox olamine show equivalent therapeutic successes.

Octenidine is also used as antiseptic and has been tested as an alternative for acute VVC.

Therapy during pregnancy, including first trimenon:
Therapy in pregnancy, also in the first trimester, should be topical with clotrimazole according to the S2k guideline.

Complicated infection with *C. krusei* & *C. glabrata*:
reserve antifungal drugs can be used especially when infected with *C. glabrata*

Chronic recurrent vaginal candidiasis: oral triazoles

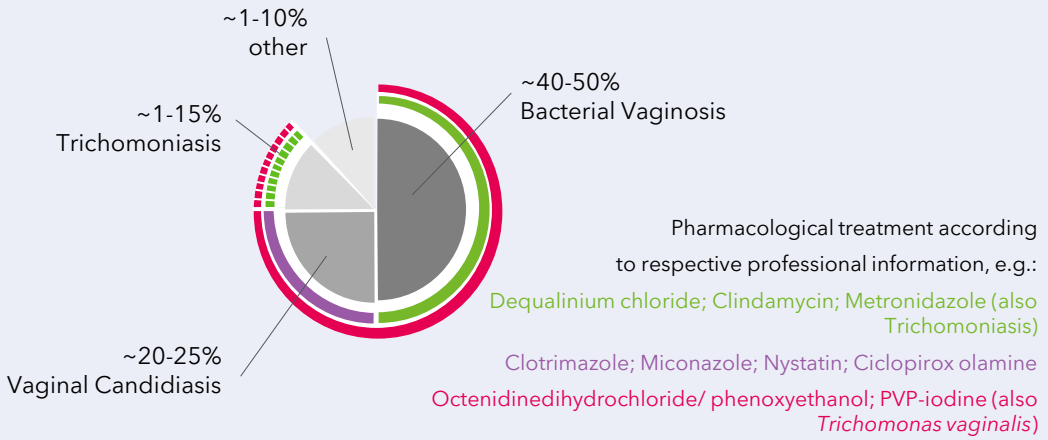


Fig: Epidemiology of vaginal Infections[16,17,19,23,24]

Good efficacy & tolerance during pregnancy under octenisept® vaginal solution treatment*,[30]

open-label, uncontrolled and non-randomized multi-center study, University of Rostock

1156 pregnant women
105 pregnant women with symptoms of bacterial vaginosis including pH > 4.5
octenisept® vaginal solution for 7 days (10 pump strokes, once daily)

A high number of pregnant women were examined for the presence of bacterial vaginosis and treated with octenisept vaginal solution. Negatively tested women were evaluated for comparison of preterm birth rate and effect on birth weight. Effectiveness of the treatment was analyzed by evaluation of pH and accompanying symptoms (redness, pruritus, presence of clue cells and amine test) via data collection at screening and at end of treatment. Tolerability was evaluated based on occurrence of adverse events (AEs). In addition, potential fetal risk was evaluated based on time of child delivery and birth weight.
68.6% of treated women achieved pH < 4.5 at day 7 (n = 72, confidence interval 58.8% / 77.3%, p < 0.001). Accompanying symptoms were also significantly reduced. There have been no AEs with a causal relation to the treatment. Preterm birth rate and birth weight was equal to the untreated group with no bacterial vaginosis diagnose. As a conclusion of this trial the antiseptic treatment is considered effective, well tolerated and safe during pregnancy.

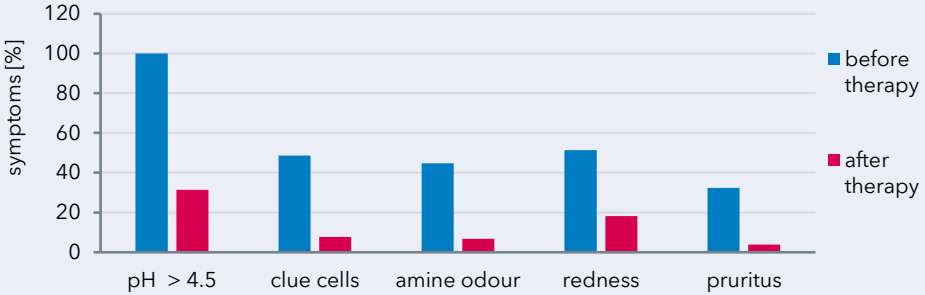


Figure adapted to: Briese et al., Arch Gynecol Obstet. 2011.

octenidinedihydrochloride / phenoxyethanol provides a better outcome in vaginal infections than classical therapeutics during pregnancy.*,[19]

prospective randomized observational study, Policlinic Novi Sad, Serbia

1000 hospitalized pregnant women
500 treated with octenidine dihydrochloride / phenoxyethanol

In this study, the efficacy of octenidinedihydrochloride / phenoxyethanol was investigated in comparison to conventional antimicrobial therapies in the treatment of vaginal infections. The study involved 1000 hospitalized pregnant women, which were divided into 4 different groups depending on the type of the vaginal infection detected with smear analysis. Every group was again subdivided in two subgroups: one of the subgroup was treated with octenidinedihydrochloride / phenoxyethanol, the other one with alternative therapies (neomycin / polymycin B / nystatin, metronidazole or miconazole vaginal tablets). The treatment with octenidine dihydrochloride / phenoxyethanol resulted on average in an earlier negative test compared to a treatment with conventional antimicrobials. This applied for the bacterial vaginosis (1.7 ± 0.8 vs 2.3 ± 1.1 days; p < 0,001) as well as for the vaginal candidiasis (2.3 ± 1.4 vs. 3.4 ± 1.6; p < 0,001). In addition, the maximum number of days for complete cure was significantly lower in the octenidinedihydrochloride / phenoxyethanol groups compared to the conventional antimicrobial therapy (bacterial vaginosis: 3 vs. 5 days; vaginal candidiasis: 5 vs. 7 days).

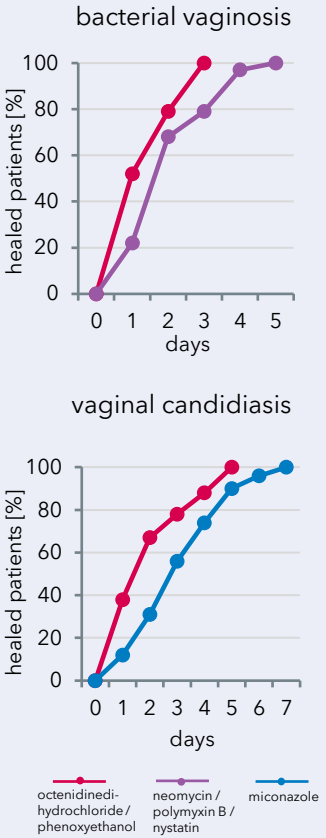


Figure adapted to: Novakov et al., Arch Gynecol Obstet. 2015.

*octenisept® vaginal solution can be applied after the first trimester of pregnancy.

octenidinedihydrochloride / phenoxyethanol comparison to PVP- iodine in the treatment of vaginal infections caused by bacteria[31]

multicenter, prospective, randomized phase III case control study

308 women diagnosed with bacterial vaginosis
161 octenidinedihydrochloride / phenoxyethanol for 7 days (10 pump strokes, twice day 1; once daily day 2-7)
147 PVP iodine vaginal suppositories 7 days (once daily)

In this trial, the treatment efficacy was compared between octenidinedihydrochloride / phenoxyethanol and PVP iodine vaginal suppositories for treatment of bacterial vaginosis. Efficacy was assessed based on pH, clue cells and accompanying symptoms (redness/pruritus, amine test, pathological flour, presence of *Lactobacillus spp.* and cytomorphical analysis of vaginal epithelial cells). Overall, the treatment efficacy of the octenidine based treatment was superior (74.5% vs. 64.6%). Notably, in addition to reduction of bacterial vaginosis symptoms, the reconstitution of *Lactobacillus spp.* was significantly faster compared to PVP treatment (46% vs. 29%). Both treatments were accompanied with only few mild adverse reactions where the number of octenidine related adverse reaction was slightly lower (1.2% vs. 3.4%). These results indicate an improved overall tolerability for the octenidine based treatment. In addition, the compliance has been improved in that group mainly due to easier handling and the absence of unwanted cloth staining.

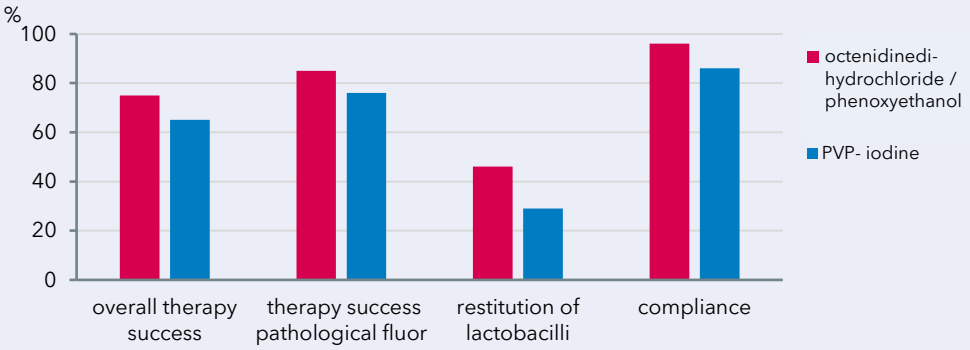


Figure adapted to: Friese K. et al. Geburtsh Frauenheilk. 2000.

octenisept® vaginal solution vaginal applicator: easy & painless application with good efficacy[32]

20 patients (11 bacterial infections, 9 vaginal candidiasis) octenisept® vaginal solution once daily for 7 days (on the first day twice daily), 10 pump strokes

A clinical and microscopical examination was performed before and 6-14 days after treatment with octenisept® vaginal solution regarding pH, odor, leucocytes, clue cells and number of Lactobacilli.

- ✓ pH < 4.5 in all patients
- ✓ protection of the Lactobacilli flora
- ✓ no adverse events
- ✓ great improvement of clinical symptoms and parameters
- ✓ good compliance
- ✓ no backflow after intravaginal application
- ✓ 19/20 patients stated: easy & problem free application

octenisept® vaginal solution efficiency in treating vaginal candidiasis[20]

prospective, multicenter, randomized, case - control study
244 patients treated with octenisept® vaginal solution;
247 patients treated with clotrimazole vaginal tablets

Overall, the efficacy of octenisept® vaginal solution for vaginal candidiasis caused by *C. albicans* lays within range described for topical antifungal agents (70-90%). Effectiveness was slightly lower when directly compared to clotrimazole 84% vs. 94% (agar cultures). *C. albicans* constitutes 72% of the infections. However, 15% of candidiasis were caused by *C. glabrata* implicated in recurring infections, which displayed an improved efficacy for the antiseptic treatment (72% vs. 59%, agar cultures).

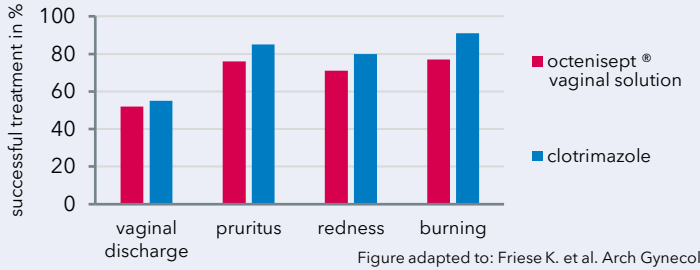


Figure adapted to: Friese K. et al. Arch Gynecol Obstet. 2003.

Octenidine – effective against (multi) drug resistant *Candida* isolates - *in vitro*[33]

quantitative suspension test
12 (multi) drug resistant *C. glabrata & C. albicans* isolates
required reduction factor: ≥ 4 $\log_{10}$

The antifungal activity of different concentrations of octenidine (OCT 0.001% - 0.05%) and octenisept® was determined against 12 (multidrug) resistant isolates of *Candida ssp* under low organic load (0.3 g/L bovine serum albumin) and high organic load (3 g/L bovine serum albumin + 3 mL/L defibrinated sheep blood).* Pure 0.05% octendine with a contact time of 30 sec was fully effective for all *Candida* isolates even in the presence of a high organic load. **octenisept® achieved a reduction of ≥4 log10 for all *Candida* strains under high organic load within a maximum of only two minutes.**

* Further investigations with octeniderm® not shown.

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