Three-Day Combination Treatment for Vulvovaginal Candidosis with 200 mg Clotrimazol Vaginal Suppositories and Clotrimazol Cream for the Vulva is Significantly Better than Treatment with Vaginal Suppositories Alone – an Earlier, Multi-Centre, Placebo-Controlled Double Blind Study

Die 3-tägige Kombinationsbehandlung der Vulvovaginalkandidose mit Clotrimazol-200-mg-Vaginaltabletten und Clotrimazol-Creme für die Vulva ist signifikant besser als die mit Vaginaltabletten allein – eine ältere multizentrische, placebokontrollierte Doppelblindstudie

Authors W. Mendling[1], R. Schlegelmilch[2]

Affiliations
[1] Deutsches Zentrum für Infektionen in Gynäkologie und Geburtshilfe, Wuppertal
[2] Dr. Kade Pharmazeutische Fabrik GmbH, Berlin

Key words
- vaginal candidosis
- clotrimazol vaginal suppositories
- clotrimazol cream
- combination treatment

Schlüsselwörter
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- Clotrimazol-Vaginaltabletten
- Clotrimazol-Creme
- Kombinationstherapie

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Abstract

Problem: According to the guidelines, acute vulvovaginal candidosis (VVC) may be treated vaginally, through a combination of vaginal treatment and cream for the vulva or orally. However, there is a lack of investigations into whether combined treatment for the vagina and vulva achieves better results than vaginal treatment alone.
Method: In 1999, 160 patients with vulvovaginal candidosis from ten German gynaecological practices were included in a study and treated on a randomised basis with three 200 mg clotrimazol vaginal suppositories = clotrimazol 2% cream (verum n = 79) or + placebo (active-ingredient-free cream base n = 79). The examinations took place before treatment (T1), six to eight days following the end of treatment (T2) and approximately four weeks following the end of treatment (T3). In addition to demographic data, the clinical findings of each investigation were documented in a standardised way and a native preparation and a fungal culture were taken. The doctor and patient evaluated the healing process and tolerance. The main efficacy variables were the pre/post difference scores for extravaginal redness.
Results: On T1, there was no difference between the two groups. By T2, there was a significant difference in the extent of extravaginal redness between the verum and the placebo groups (p = 0.0002), as well as in the subgroup of the per-protocol analysis (verum 64, placebo 70 patients, p = 0.0015). Genital itching or burning had entirely disappeared in 51% and 56% of patients respectively in the verum group and in only 30% and 45% of patients in the placebo group on T2 (p = 0.0181). There was no difference in intravaginal redness on T1 and T2 in either group. The overall assessment by the doctor went accordingly (p = 0.0004). On T1, the extravaginal fungal culture was positive in 75 women in the verum group and in 76 women in the placebo group. On

Zusammenfassung

Problem: Die akute Vulvovaginalkandidose (VVK) kann nach den Leitlinien sowohl vaginal, kombiniert vaginal und mit Creme für die Vulva oder oral behandelt werden. Es fehlen aber Untersuchungen zur Frage, ob die kombinierte Therapie von Vagina und Vulva bessere Ergebnisse ergibt als die alleinige vaginale Behandlung.
Methode: Es wurden im Jahr 1999 in 10 deutschen gynäkologischen Praxen 160 Patientinnen mit Candida-Vulvovaginitis eingeschlossen und randomisiert mit 3 Clotrimazol-Vaginaltabletten 200 mg + Clotrimazol-2%-Creme (Verum n = 79) oder + Placebo (wirkstofffreie Cremegrundlage = 79) behandelt. Die Untersuchungen erfolgten vor Therapie (T1), 6–8 Tage nach Therapieende (T2) und etwa 4 Wochen nach Therapieende (T3). Neben den demografischen Daten wurden bei jeder Untersuchung standardisiert die klinischen Befunde dokumentiert sowie ein Nativpräparat und eine Pilzkultur abgenommen. Arzt und Patientin beurteilten den Heilungsverlauf und die Verträglichkeit. Primäre Wirksamkeitsvariable waren die Prä-/Post-Differenz der Scores für die extravaginale Rötung.
Ergebnisse: An T1 bestanden keine Unterschiede in beiden Gruppen. Zum Zeitpunkt T2 war zwischen der Verum- und der Placebogruppe die extravaginale Rötung signifikant verschieden (p = 0,0002), ebenso in der Untergruppe der Per-Protocol-Analyse (Verum 64, Placebo 70 Patientinnen, p = 0,0015). Der genitale Juckreiz bzw. das Brennen waren bei 51 bzw. 56% der Verumgruppe und bei nur 30 bzw. 45% der Placebogruppe an T2 ganz verschwunden (p = 0,0181). Bei der intravaginalen Rötung gab es an T1 und T2 in beiden Gruppen keinen Unterschied. Die ärztliche Gesamtbeurteilung fiel entsprechend aus (p = 0,0004). Bei T1 war die extravaginale Pilzkultur in der Verum- vs. der Placebogruppe bei 75 vs. 76 Frauen positiv, an T2 aber bei 51,9 vs. 73,1%

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Bibliography
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Correspondence
Prof. Werner Mendling
Deutsches Zentrum für Infektionen in Gynäkologie und Geburtshilfe
Vogelsangstraße 106
42109 Wuppertal
w.mendling@t-online.de

T2, however, this was positive in 51.9% (verum) and 73.1% (placebo) of cases, and a positive culture was evinced in the vagina in 6 vs. 8 women (7.5 vs. 10.1%, p = 0.3802). The local tolerance in both groups was 70% very good, and 29 vs. 27% good. After four weeks (T3), 16 out of 23 patients in the verum group and only 8 out of 21 in the placebo group had negative extravaginal fungal cultures.

Discussion: There is a lack of studies into the issue of whether vaginal treatment or combined vulvovaginal treatment of acute VVC would be more advantageous. However, there are two studies that support the significant results of this paper that when it comes to acute VVC, the combination of three 200 mg clotrimazol vaginal suppositories with clotrimazol cream 2% is better than with vaginal suppositories alone.

(p = 0,0054), in der Vagina wurde nur bei 6 vs. 8 Frauen (7,5 vs. 10,1%, p = 0,3802) eine positive Kultur nachgewiesen. Die lokale Verträglichkeit war in beiden Gruppen mit 70% sehr gut bzw. 29 vs. 27% gut. Nach 4 Wochen (T3) waren aus der Verumgruppe 16 von 23 und aus der Placebogruppe nur 8 von 21 extravaginalen Pilzkulturen negativ.

Diskussion: Es fehlen Studien zur Frage, ob die vaginale oder kombiniert vulvovaginale Therapie der akuten VVK günstiger seien. Zwei Studien unterstützen aber die signifikanten Ergebnisse dieser Arbeit, dass bei akuter VVK die Kombination aus 3 Clotrimazol-200-mg-Vaginaltabletten mit Clotrimazol-Creme 2% besser ist als mit Vaginaltabletten allein.

Introduction

Based on the literature, it is sufficient and in line with the guidelines to treat uncomplicated, acute vulvovaginal candidosis in pre-menopausal women with vaginal therapy alone without additional cream for the vulva (introitus) [8, 10].

The decision as to whether cream is necessary for the vulva region (in addition or alone) is made by the doctor based on clinical signs and symptoms or by the patient in the case of self-treatment due to suffering discomfort.

Acute, uncomplicated vulvovaginal candidosis is currently recognised as an over-the-counter indication [11]. Approximately 80–90% of antimycotics sold for the vulvovaginal region are bought over-the-counter by the patient for the purposes of self-treatment without diagnosis by a doctor.

In recent years, however, there has been an increasing number of critical opinions that the non-indicated use of antimycotics applied to the genitals (primarily clotrimazol) leads to inadequate treatment [3] and to vestibulodynia syndrome [6] being induced or aggravated in approx. 5–8% of women.

Oddly enough, the literature lacks studies which explicitly deal with the issue of whether vaginal treatment alone is sufficient in the case of acute vulvovaginal candidosis or whether the additional application of cream for the vulva improves healing results. This question should be resolved by this study. The initial author (W. M.) inspired this publication after reading a study of Beikert et al. [1]..

Materials and Methods

160 women were included in the study, and were all over 18 years of age, had vulvovaginal candidosis that had spread to the labia minora and labia majora and had consented to participation in the study.

Excluded from the study were women with known allergies to the investigational products, those simultaneously receiving treatment with oral antimycotics, in the case of the type of candida having known resistance to clotrimazol, and pregnant and breastfeeding women.

Tests were broken off on a case by case basis in the event of a lack of compliance, unjustifiable and undesirable side effects or at the request of the patient.

Design of the study

The investigational products were:

- Treatment arm 1: 3 200 mg clotrimazol vaginal suppositories + clotrimazol cream (1 g contains 20 mg clotrimazol)
- Treatment arm 2: 3 200 mg clotrimazol vaginal suppositories + active-ingredient-free cream base (placebo).

The patients were assigned a treatment randomly based on computer randomisation. The vaginal suppositories were applied with a vaginal applicator at night before going to bed. The cream is also applied to the vulva.

No differences were ascertainable for the doctor or the patient due to coded package inscriptions.

The use of additional vaginal products (e.g. intimate spray, vaginal contraceptives etc.) was not permitted.

Medication not administered must be returned.

The examinations took place before treatment (T1), six to eight days following the end of treatment (T2) and approximately four weeks following T2 in the subsequent cycle (T3).

Investigations/action on T1:

- Collecting demographic data and information regarding concomitant illnesses, where applicable
- Diagnosis with native preparation (phase contrast)
- Evaluating extravaginal redness based on a 5-point scale (0 = none, 4 = very pronounced)
- Assessing the redness of the vagina, as well as itchiness and burning
- Patient consent
- Taking one smear sample from the vulva and one from the vagina for a fungal culture
- Administering study medication

Examinations/steps on T2:

- Assessing clinical symptoms as on T1
- Native preparation
- Fungal cultures as on T1
- Determining undesirable events
- Determining compliance
- Assessing the healing process
- Assessing local tolerance
- Returning any unused study medication

Examinations/steps on T3:

- Taking smears for the fungal culture as at T1

Statistical evaluation

Extravaginal redness was considered as the primary efficacy variable for pre/post difference. Statistical processing took place with the unilateral Wilcoxon-Mann-Whitney test at a 5% significance level. All other comparative parameters were evaluated on an exploratory basis without calculating statistical significance. The phase contrast microscopic assessment of the native preparations and the result of fungal cultures (evidence of candida without determining the type) on T2 was compared with the precise Fisher test.

In order to prove a statistically significant difference, a sample size of at least 76 patients per group was calculated ("Nnpar" programme from the Idv company, Gauting).

Results

Study population

The study was conducted in ten German gynaecological practices between July and September 1999. 16 patients were included per centre, meaning that 160 patients with (suspected) vulvovaginal candidosis could be accepted. Of these, 79 women in the verum group and 79 women in the placebo group fulfilled the inclusion criteria, meaning a total of 158 women.

One patient in the verum group additionally inserted garlic into the vagina every morning. She was not excluded from the analysis, as this primarily concerned redness of the vulva.

As no statistical difference was found in the demographic data by age (mean value at approx. 34 ± 14 years), height (approx. 166 ± 7 cm) and weight (approx. 62 ± 9 kg), no table was created to present the results.

There were four women with diabetes mellitus in each group. All other ancillary findings were insignificant for the results of the study.

All patients complied with the prescribed treatment regimen.

Extravaginal redness

On T1, there were no differences (p = 0.1516) between the verum and the placebo groups, with average redness scores of 3.13 (verum cream) and 3.32 (placebo cream).

On T2, extravaginal redness had fallen by 2.03 points in the verum group, while it had only reduced by 1.25 points in the placebo group (p = 0.0002). In the verum group, 45% of women had none and a further 27% were only experiencing slight redness (72% in total), whereas this was the case for 27% and 13% of women in the placebo group respectively (total of 52%).

The group of patients that had fulfilled all of the test programme's criteria (per protocol, verum group 64, placebo group 70) also turned out to be highly significant with p = 0.0015.

This difference was also apparent in eight out of ten testing centres.

Itching

On T1, approx. 40% of women in both groups experienced very severe itchiness and a further 35–40% had severe itchiness with an average score of 3.09 in the verum group and 3.22 in the placebo group.

On T2, itchiness in the verum group had disappeared almost entirely in 51% of patients and in only 30% of women in the placebo group. In the verum group, 76% of women had no or mild itching, with this being the case in only 55% of patients in the placebo group (p = 0.0181).

Burning

At T1, the verum group gave an average score of 2.71 and the placebo group 2.86.

During the tests on T2, 56% of the verum group reported no burning (45% of the placebo group), with the average scores being 1.72 vs. 1.54 (p = 0.2161, not significantly different).

Intravaginal redness

As both groups were treated with a 200 mg clotrimazol vaginal suppository for three days, no pre/post-operative difference is to be expected here. The results were as follows:

Before treatment, redness was very severe in 25% of patients and severe in 35% of patients in the verum group, with an average score of 2.82. The figures in the placebo group were 42%, 28% and 3.03 respectively.

By T2, intravaginal redness was no longer observed in 86% of patients in the verum group and in 83% of women in the placebo group (score – difference 2.65 and 2.62 points) (p = 0.5538, not significantly different).

Overall assessment by the doctor

In the verum group, 54% of patients experienced complete healing and 22% had a significant improvement (average score 1.81). In the placebo group, this was the case in 30 and 2% of cases respectively (average score 2.42). The difference is highly significant (p = 0.0004).

Mycological findings

Phase contrast microscopy, vagina

On T1, all microscopic findings in the verum and placebo groups were positive (inclusion criteria).

On T2, 12 out of 78 women (15.4%) in the verum group and 15 out of 77 patients (19.5%) in the placebo group had positive findings (p = 0.3228).

Cultural findings

Unfortunately, only 25 patients from the verum group and 23 from the placebo group came to the T3 check-up after four weeks.

Extravaginal/vulva Before treatment, the extravaginal fungal culture was positive in 75 patients in the verum group and 76 patients in the placebo group, with 4 and 3 women respectively having negative results.

At T2, the fungal culture was negative in 73.1% of the verum group and in 51.9% of the placebo group (p = 0.0054).

At the examination after four weeks (T3), 7 out of 23 patients in the verum group and only 8 out of 21 in the placebo group had positive extravaginal fungal cultures.

Vagina Before treatment, all 78 patients in each group had positive fungal cultures.

At T2 following treatment, there were six positive cultures in the verum group and eight in the placebo group (p = 0.3802, not significantly different).

After four weeks (T3), two out of 25 cultures in the verum group and two out of 23 cultures in the placebo group were positive.

Undesirable events

One person in each of the groups experienced burning upon application of the cream from days 1 to 3.

A further patient in the placebo group complained of peeling skin lasting for over 2 days.

Table 1 Extravaginal (vulvar) redness, burning in the introitus and mycological findings before the start of treatment (T1), six days following the end of treatment (T2) and four weeks later (T3).

	Verum T1 (%)	Placebo T1 (%)	Verum T2 (%)	Placebo T2 (%)	Verum T3 (%)	Placebo T3 (%)
Extravaginal redness (introitus, vulva)						
No and slight	2.5	1.3	26.9	13.0		
Moderate, severe, very severe	97.5	98.7	28.2	60.4		
Average score	3.13	3.32	2.03	1.25		
	n. s.		**p = 0.0002**			
Intravaginal redness						
No and slight	86	83				
Severe + very severe	60	70				
Average score	2.82	3.03	2.65	2.62		
	n. s.		**n. s.**			
Itching						
No and slight	2.6	3.8	75.7	54.6		
Moderate, severe, very severe	97.4	96.2	24.3	45.5		
Average score	3.09	3.22	2.09	1.65		
	n. s.		**p = 0.0181**			
Burning (average score)	2.71	2.86	1.72	1.54		
	n. s.		**n. s.**			
Positive mycological culture						
Vagina	98.7	98.7	7.7	10.4	2/25: 8.0	2/23: 8.7
	n. s.		**n. s.**		**n. s.**	
Vulva	94.9	96.2	26.9	48.1	7/23: 8.7	8/21: 8.0
	n. s.		**p = 0.0054**		**n. s.**	
Overall assessment by the doctor (double blind, average score)					1.81	2.42
Healing + significant improvement (%)					76	32
					p = 0.0004	

Tolerance (doctor assessment)

The local tolerance of clotrimazol vaginal suppositories + clotrimazol cream or placebo cream was rated as very good in 70% of cases and good in a further 29 and 27% respectively.

All the results are summarised in **Table 1**.

Discussion

Comments on nomenclature

The vulva is defined as the "external female genitals" [13].

Clinically speaking, we can also see "symptom boundaries" between the vagina and its introitus including the internal part of the labia minora on the one hand and, on the other, the squamous epithelium of the outer vulva and the external part of the labia minora, the labia majora and the transition to the perianal and intercrural region.

In order to have consistent definitions for the various manifestations of vulvovaginal candidosis, e.g. including for the conducting of clinical studies, recommendations for nomenclature were drafted and published in 1991 by five experts, all of whom were members of the Management Board of the German-speaking Mycological Society and/or the "Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie in der Gynäkologie und Geburtshilfe" (working group for infections and infection immunology in gynaecology and obstetrics [DGGG]) [4].

This is divided into

1. Vulvar candidosis, in which a distinction is made between its vesicular, diffuse eczematoid, follicular and (rare) candida granuloma forms,
2. Vaginal candidosis, subdivided into colonisation, latent, mild, moderately severe and severe vaginal candidosis, and
3. Vulvovaginal candidosis, in which the vulva and the vagina are affected in the subdivisions described.

The Sexually Transmitted Diseases Treatment Guidelines 2010 from the USA's Centers for Disease Control and Prevention define under "Diagnostic Considerations": "A diagnosis of Candida vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, or thick, curdy vaginal discharge…" [10].

The German and English-language guidelines published on vulvovaginal candidosis to date [8] and the revised version from 2014 [2] describe pruritus, discharge, vaginal redness, dysuria and potentially the swelling of the labia minora. It is also noted that differentiation may be made between the vulvar manifestations, specifically vesicular, eczematoid and follicular forms.

There is no reliable information on the frequency of vaginal candidosis (alone) or (combined) vulvovaginal candidosis (both occur under the influence of oestrogen) or vulvar candidosis (alone) (which is primarily a post-menopausal phenomenon in the case of obesity or diabetes mellitus). There also appears to be no clear distinction between vaginal and vulvovaginal candidosis in specialist literature, as even influential international authors have used both terms within the same article.

It is therefore unsurprising that there are currently no clear rules when it comes to treatment.

Treatment of vaginal candidosis based on guidelines, literature and practice

Vulvovaginal candidosis, both in its acute and especially in its chronic recurrent form, significantly impacts the quality of life of the women affected by it, which has been proven through validated surveys designed to assess physical and mental states [7].

The treatment for uncomplicated vaginal candidosis recommended by the USA's Centers for Disease Control and Prevention is "short course topical formulations (i.e. single dose and regimens of 1–3 days) … The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80–90% of patients who complete therapy." [10]. The simultaneous treatment of the asymptomatic partner is not recommended. A table lists nine over the counter medications as vaginal creams **or** vaginal suppositories as well as a further five preparations that are prescription-only in the USA as vaginal creams **or** vaginal tablets as well as oral treatment with one 150 mg dose of fluconazole.

Similar recommendations for the treatment of acute vulvovaginal candidosis follow point 10.3 of the new German guidelines [2].

One (non-representative, but practical) impression of the general approach taken by gynaecologists was obtained through a targeted, anonymous, written poll conducted by the author in 2002 of 50 gynaecologists each from the Kreuzberg (former West) and Friedrichshain (former East) districts of Berlin (both districts have since merged). It indicated that 29 out of the 50 gynaecologists in Kreuzberg and 19 out of 50 in Friedrichshain prescribe a combination of medications for the vagina and vulva in the case of vaginal candidosis depending on the individual situation. It indicated that 21 out of the 50 gynaecologists in Kreuzberg and 15 out of 50 in Friedrichshain simultaneously treat the asymptomatic partner (which evidence has shown not to be necessary) [5].

From many publications, it emerges that the results of treatment in the case of vaginal candidosis when only vaginal treatment is provided are similar to those achieved with oral treatment, as well as in a Cochrane analysis [12].

In a comparative study, Sobel indicates that the individual wishes of the patient are taken into account in the case of the same healing results with oral fluconazole 1 × 150 mg opposed to seven days of treatment with intravaginal clotrimazol [15].

A multi-centre study with 679 women with acute vulvovaginal candidosis compared the results of patients treated either with 150 mg fluconazole or 500 mg clotrimazol vaginally as single day treatment or with 10% clotrimazol vaginal cream. The women were also allowed to apply 1–2% clotrimazol to the vulva in addition to the type of vaginal application depending on their own requirements. Vulvar itchiness was not eliminated until the third day at the earliest in all treatment arms (a known effect). The healing results of the three study arms were not statistically significantly different [9].

This study – potential bias in diagnosis

In addition to clinically, microscopically and culturally confirmed vaginal candidosis, inclusion criteria included "pronounced vulvitis with infestation of the labia majora", which was assessed before and following treatment based on redness. In the sense of definition of vaginal candidosis (see "Comments on nomenclature"), the involvement of the squamous epithelium of the labia majora – redness in this case – is the beginning of eczematoid vulvar candidosis. (It was possible that the peeling of the skin reported by one patient in the placebo group was not an "undesired side effect" of the placebo, but rather the progression of skin candidosis without an antimycotic effect).

In fact, vulvar candidosis of the labia majora always requires separate local treatment when not treated orally. On the other hand, the extent of vulvar involvement is subjectively influenced despite the criteria of "pronounced vulvitis with infestation of the labia majora".

The change to the skin/redness is the only symptom appropriate for the medical assessment, as itchiness and burning are unspecific, subjective parameters on the part of the patient. In any case, it may be assumed that the extent of the vulvar candidosis cannot have corresponded to the definition of a pronounced eczematoid vulvar candidosis despite the redness of the labia majora, as no knowledgeable doctor would be able to permit the use of a placebo as part of a study in this case.

In these common borderline cases, however, study results are used as a basis for practice.

As with the fungal culture, the evidence of fungus in the native preparation could only mean colonisation or a misinterpretation on the part of the doctor, as can also be clearly seen from the fact that fungus in the native preparation on the check-up examination on T2 was reported by doctors in 15.4% (verum) and 19.5% (placebo) of cases, although the vaginal fungal culture taken at the same time was only positive in 7.7% and 10.4% of cases respectively!

The fact that the clinical diagnosis before treatment was the same is not in doubt, as all patients included had a positive candida culture as well as clinical symptoms.

Discussion of results

In this study, it is clear that the combination of vaginal clotrimazol treatment with additional cream containing clotrimazol for the vulva is statistically significantly superior to vaginal treatment alone.

To date, there is only one publication known to the author in which acute vaginal candidosis is compared with vaginal treatment alone or combined vaginal and vulvar local treatment. It found that: "When candidosis is both vulvar and vaginal, the combination of sertaconazole cream with a monodose sertaconazole vaginal suppository trends to improve clinical cure at D (day) 7 and D 14 and to relief more patients as early as D2 than the vaginal suppository used as a single treatment" [14].

Beikert et al. [1] referred to the potential "fungal reservoir" of the skin of the vulva in the case of chronic recurrent vulvovaginal candidosis due to frequent, positive symptomatic fungal cultures from the interlabial sulcus and therefore call for an additional cream (in this case, ciclopiroxolamin) for the vulva despite oral treatment with fluconazole (despite the fact that fluconazole contains a sufficiently high level of active ingredient). The study lacked a comparison group, however.

Summary

The combination of vaginal clotrimazol treatment with additional cream containing clotrimazol for the vulva is statistically significantly superior to simple vaginal treatment. On the basis of this result alone, this study has merited being published and discussed despite it being conducted 14 years ago, as its results are of practical use.

Conflict of Interest

The first author receives royalties for the publication of the paper from Dr. Kade Pharmazeutische Fabrik GmbH Berlin.

References

1 *Beikert FC, Le MT, Koeninger A et al.* Recurrent vulvovaginal candidosis: focus on the vulva. Mycoses 2011; 54: e807–e810
2 *Brasch J, Cornely O, Effendy I et al.* Leitlinie Die Vulvovaginalkandidose. AWMF 015/072. 2014. Online: www.awmf.org/uploads/tx_szleitlinien/015-072l_S2k_vulvovaginalkandidose_2013-12.pdf
3 *Ferris DG, Nyirjesy P, Sobel JD et al.* Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. Obstet Gynecol 2002; 99: 419–425
4 *Mendling W.* Die Vulvovaginalkandidose. Der Frauenarzt 1992; 33: 195–196
5 *Mendling W.* Vaginose, Vaginitis, Zervizitis und Salpingitis. Heidelberg: Springer; 2006
6 *Mendling W.* Burning vulva, Vulvodynie, vulväres Vestibulitis-Syndrom. Frauenarzt 2008; 49: 314–317
7 *Mendling W, Birkner V.* Die Vakzination mit inaktivierten Laktobazillen oder Heliotherapie kann die Lebensqualität von Frauen mit chronisch rezidivierender vulvovaginaler Kandidose verbessern – Eine prospektive, 3-armige randomisierte Studie. Geburtsh Frauenheilk 2011; 71: 767–772
8 *Mendling W, Brasch J; German Society for Gynecology and Obstetrics; Working Group for Infections and Infectimmunology in Gynecology and Obstetrics; German Society of Dermatology, the Board of German Dermatologists; German Speaking Mycological Society.* Guideline vulvovaginal candidosis (2010) of the German Society for Gynecology and Obstetrics, the Working Group for Infections and Infectimmunology in Gynecology and Obstetrics, the German Society of Dermatology, the Board of German Dermatologists and the German Speaking Mycological Society. Mycoses 2012; 55 (Suppl. 3): 1–13
9 *Mendling W, Krauss C, Fladung B.* A clinical multicenter study comparing efficacy and tolerability of topical combination therapy with clotrimazole (Canesten, two formats) with oral single dose fluconazole (Diflucan) in vulvovaginal mycoses. Mycoses 2004; 47: 136–142
10 *Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC).* Sexually transmitted disease treatment guidelines, 2010. MMWR Recomm Rep 2010; 59 (RR-12): 1–110
11 *Mohr P.* Clotrimazol in der Selbstmedikation bei Vaginalmykosen. Der Deutsche Apotheker 1994; 46: 2–6
12 *Nurbhai M, Grimshaw J, Watson M et al.* Oral versus vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (Thrush). Cochrane Database Syst Rev 2007; 4: CD002845
13 *Pschyrembel W.* Klinisches Wörterbuch. 264. Auflage. Berlin: Walter de Gruyter GmbH; 2012
14 *Quereux C, Gelas B, Chevallier T et al.* [Evaluation of the efficacy and speed of action of sertaconazole nitrate suppository and cream combined treatment for vulvovaginal candidiasis]. Gynecol Obstet Fertil 2000; 28: 238–244 (Artikel in französischer Sprache)
15 *Sobel J, Brooker D, Stein GE et al.* Single oral dose fluconazole topical therapy of Candida vaginitis. Am J Obstet Gynecol 1995; 172: 1263–1268