

# NOVI PRISTUP U LIJEČENJU UPALA RODNICE

PREDAVANJE OMOGUĆILA TVRTKA REMEDIA d.o.o.

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→Upale rodnice predstavljaju heterogenu skupina poremećaja uzrokovanih infekcijom, upalom ili poremećajem vaginalne mikroflore

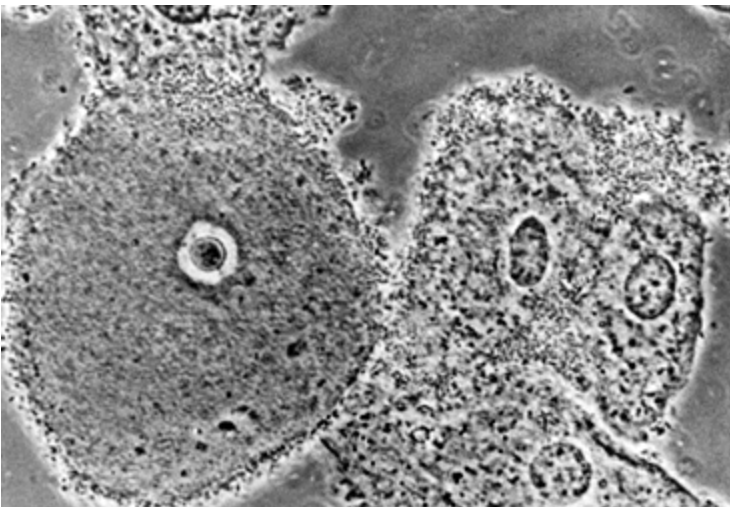
→Pojačani vaginalni iscjedak, često neugodna mirisa, svrbež praćen nelagodom

→Najčešći poremećaji u ginekologiji

→10% žena svake godine preboli barem jednu epizodu upale rodnice, samo polovica javlja se svom ginekologu

- sindrom koji nastaje zbog neravnoteže u vaginalnom ekosustavu
- smanjenjem broja laktobacila i porastom broja drugih anaerobnih bakterija (*Gardnerella vaginalis*)
- pojačani vaginalni iscjedak, neugodan miris po pokvarenoj ribi

- *Trichomonas vaginalis* (protozoa)
- spolno prenosiva bolest
- sama/kombinaciji
- obilan vaginalni iscjedak zeleno-žute boje, pjenušav, neugodna mirisa



## Treatment options for bacterial vaginosis (nonpregnant women)

### Drugs of choice

Metronidazole 500 mg oral twice daily for seven days **OR**

Metronidazole gel 0.75 percent 5 g\* (one full applicator)  
intravaginally once daily for five days **OR**

Clindamycin 2 percent cream 5 g<sup>†</sup> (one full applicator)  
intravaginally at bedtime for seven days

### Alternatives

Clindamycin 300 mg orally twice daily for seven days **OR**

Clindamycin ovule (vaginal suppository) 100 mg intravaginally  
once daily for three days **OR**

Tinidazole 2 g orally for two days **OR**

Tinidazole 1 g orally once daily for five days

## Treatment regimens used in studies demonstrating a reduction in preterm birth in treated high risk patients with bacterial vaginosis

Metronidazole 400 mg orally twice daily for two consecutive days. Repeat if a second test four weeks post-treatment is positive.<sup>[1]</sup>

Metronidazole 250 mg orally three times daily for seven days plus erythromycin base 333 mg orally three times daily for 14 days. Repeat test at 28 weeks of gestation and repeat treatment if test is positive.<sup>[2]</sup>

Metronidazole 250 mg orally three times daily for seven days. No second treatment.<sup>[3]</sup>

Clindamycin 300 mg orally twice daily for five days. No second treatment.<sup>[4]</sup>

Clindamycin 5 grams of 2 percent vaginal cream nightly for three nights. Repeat test three weeks after initial diagnosis, if still positive give a seven day course of the the same treatment.<sup>[5]</sup>

**ALTERNATIVNO...**  
**(2x500 mg p.o., 1x500**  
**mg vag./7 dana)**

→ kod primarne infekcije →  
jedan vagitorij (=1000mg  
metronidazola)

→ u težim slučajevima/  
rekurentne infekcija →  
“dvodnevno liječenje” (1  
vagitorij dnevno)

→ Nije preporučljiva tijekom I trimestra trudnoće

→ Tijekom II i III trimestra → opravdana nakon procjene odnosa koristi i rizika.

→ Lokalna primjena metronidazola je prihvatljivija od sustavne terapije



ali...

→ ≈ one-third of pregnant women in the United States have BV

→ 2007 meta-analysis reported a statistically significant increased risk of preterm birth in these women

→ the increased risk of preterm birth → linked to preterm labor due to chorioamnionitis

→ postpartum endometritis, late miscarriage

- Leitich H, Kiss H. Asymptomatic bacterial vaginosis and intermediate flora as risk factors for adverse pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol* 2007; 21:375.
- Klebanoff MA, Hillier SL, Nugent RP, et al. Is bacterial vaginosis a stronger risk factor for preterm birth when it is diagnosed earlier in gestation? *Am J Obstet Gynecol* 2005; 192:470.

→ meta-analysis has not found any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects

→ CDC no longer discourage the use of metronidazole in the first trimester

→ an additional concern is that the drug is mutagenic in bacteria and carcinogenic in mice → no evidence of harm in humans

## Primjena METRONIDAZOL vag. 1000 g tijekom dojenja

→Metronidazol se izlučuje u majčino mlijeko→potrebno prekinuti ili dojenje ili liječenje

→1 doza tijekom dojenja=prekid dojenja u trajanju od 24 sata (izdojiti)



ali...

→ Clindamycin - potential to cause adverse effects on the breastfed infant's gastrointestinal flora

→ Metronidazole, when indicated → used for treatment of infection in neonates

→ No human data supporting an association between metronidazole use and cancer (rodents)


→ Outcomes data of maternal metronidazole use did not show a significant increase in adverse events compared to use of other antimicrobials

→ After vaginal administration, plasma levels less than 2 percent of those after a 500 mg oral dose → **vaginal use of metronidazole during breastfeeding is unlikely to be of concern**

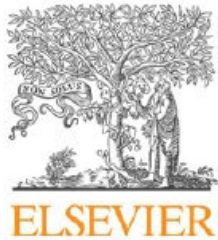
- LactMed available at <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~R2NQWq:1> (Accessed on January 19, 2010).
- Lactmed. Available at <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~R2NQWq:2>. (Accessed on January 19, 2010).



metronidazol vaginalete a 500 mg,  
7-10 dana



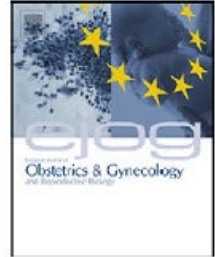
metronidazol vagitorij a 1000 mg,  
1-2 dana



Contents lists available at ScienceDirect

# European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: [www.elsevier.com/locate/ejogrb](http://www.elsevier.com/locate/ejogrb)



## Intravaginally applied metronidazole is as effective as orally applied in the treatment of bacterial vaginosis, but exhibits significantly less side effects

M. Brandt<sup>a</sup>, C. Abels<sup>d,\*</sup>, T. May<sup>b</sup>, K. Lohmann<sup>d</sup>, I. Schmidts-Winkler<sup>d</sup>, U.B. Hoyme<sup>c</sup>

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All study participants were closely monitored by clinical instructors. The study design was a randomized, placebo-controlled, double-blind, multicenter trial. All patients were treated with either a single dose of oral metronidazole 2000 mg (Arilin<sup>®</sup> 500, enteric-coated tablets containing 500 mg metronidazole, Dr. August Wolff GmbH & Co. KG Arzneimittel, D-33611 Bielefeld, Germany) and placebo pessaries or vaginal metronidazole 1000 mg once daily over a time course of 2 days (Arilin<sup>®</sup> Rapid, vaginal pessaries containing 1000 mg metronidazole, Dr. August Wolff GmbH & Co. KG Arzneimittel, D-33611 Bielefeld, Germany) and placebo tablets (double-dummy design). After clinical evaluation of the patient and obtaining written consent, the patient was included in the study and therapy was initiated on day 1. On day 8 the patient was again evaluated.



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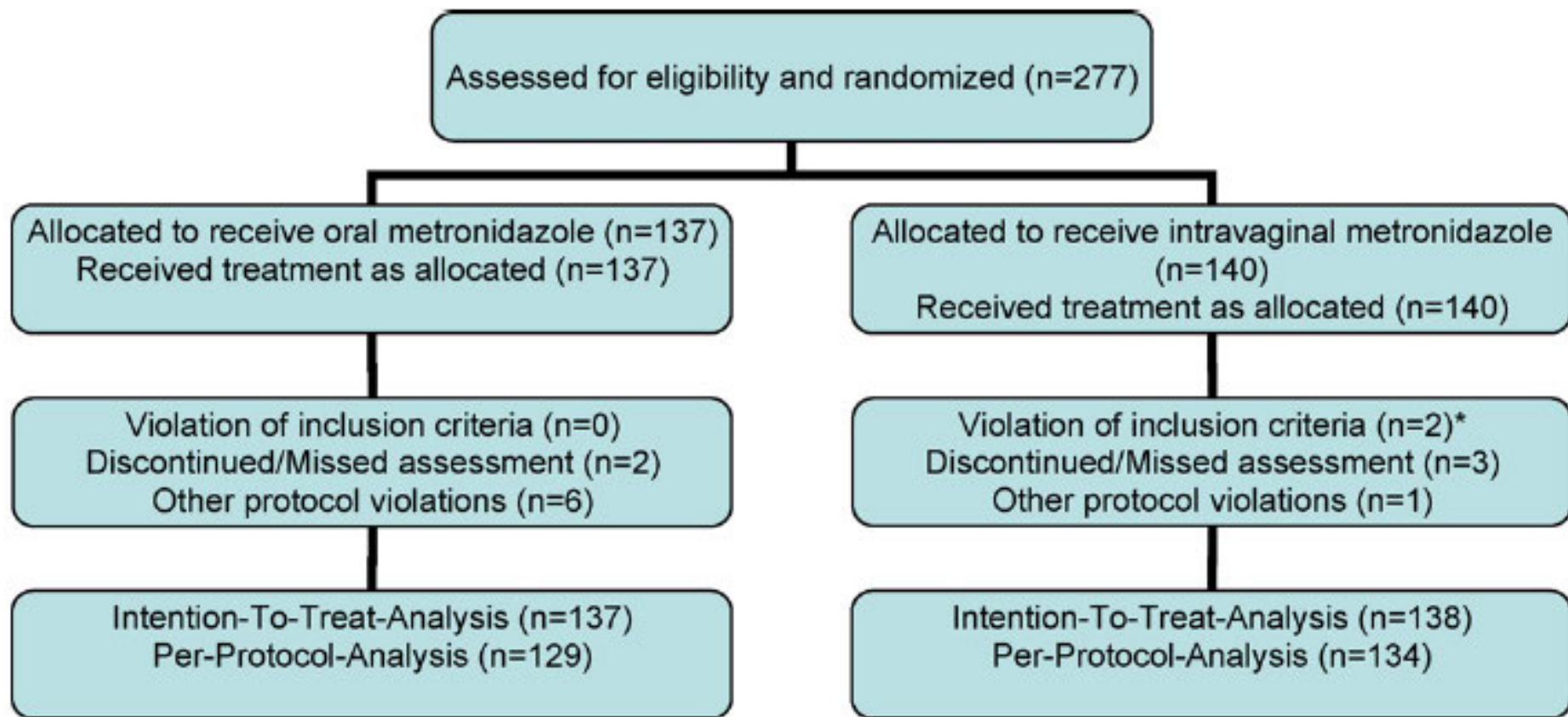
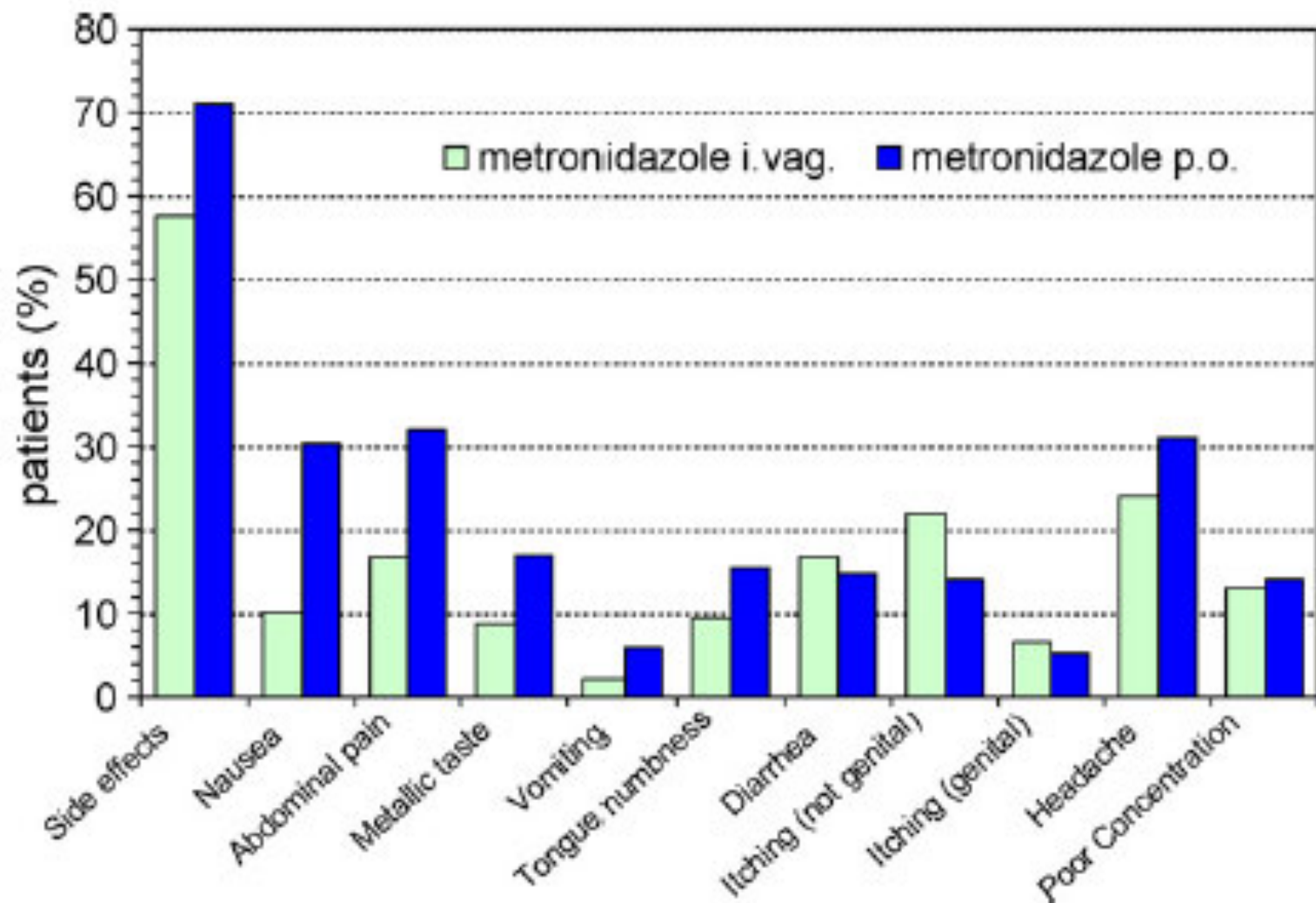


Fig. 1. Study design and patient allocation (\*exclusion from intent-to-treat and per-protocol analysis).

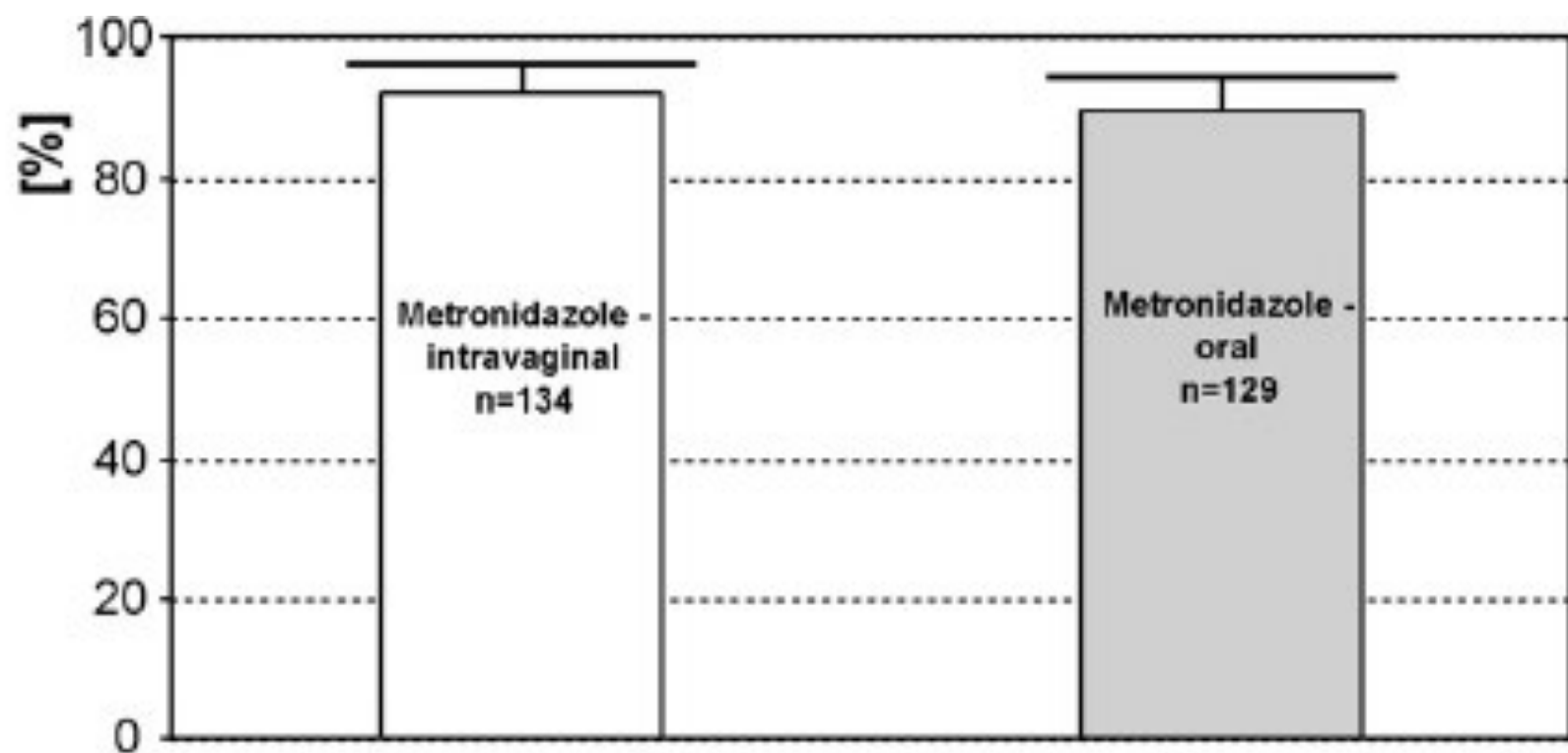
**Table 1**  
Significant differences of adverse events occurring in patients treated with either metronidazole p.o. ( $n = 135$ ) or metronidazole i.vag. ( $n = 137$ )

	Metronidazole p.o. (%)	Metronidazole i.vag. (%)	$p$ -Value <sup>a</sup>
One or more adverse event	71.1	57.7	0.023
Nausea	30.4	10.2	<0.001
Abdominal pain	31.9	16.8	0.005
Metallic (bitter) taste	17.0	8.8	0.047

<sup>a</sup> Two-sided, exact Fisher-test.



**Fig. 3.** Adverse events in patients treated with metronidazole either intravaginally or orally.



**Fig. 2.** Cure rates of patients treated with metronidazole intravaginally (92.5%) or orally (89.9%).



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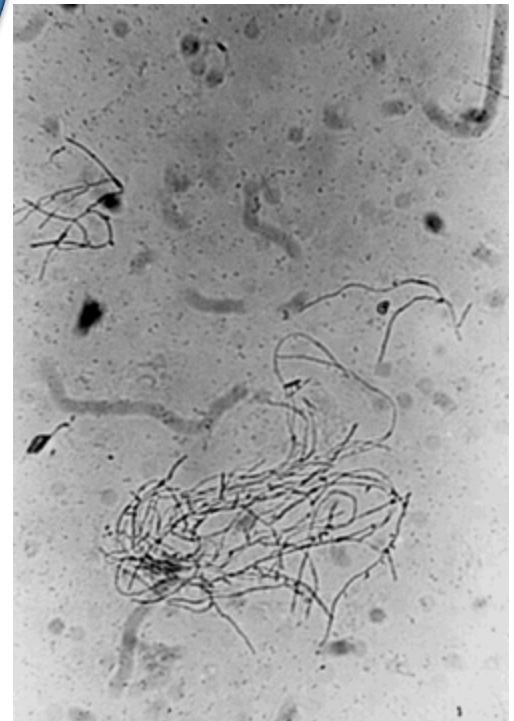
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Intravaginally applied metronidazole is as effective as orally applied in the treatment of bacterial vaginosis, but exhibits significantly less side effects

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In conclusion, the present clinical study showed clearly non-inferiority of the short-term intravaginal application of metronidazole as compared with the oral administration regarding the cure rate. Thus, both forms of application are equally effective. However, the tolerability of the medication due to significantly lower adverse events following the short-term intravaginal application was significantly better, leading to a higher overall patient satisfaction as compared to the oral administration of metronidazole. Thus, failure of patients to comply with the prescribed treatment is assumed to be less likely, when taking metronidazole pessaries. Moreover, costs resulting from adverse drug reactions after intravaginal application will be less as compared to the oral administration. Therefore, intravaginal pessaries of metronidazole applied for only 1 or 2 days should be considered as a very effective, well-tolerated alternative treatment for BV.

- oko 35% svih vaginitisa
- *Candida albicans* (80-90%)
- svrbež, crvenilo, otok i karakterističan vaginalni iscjedak
- 10-20% bez simptoma
- antimikotici



## Treatment of uncomplicated vaginal candidiasis

Drug and trade name (§)	Requires a prescription in US	Preparation	Intravaginal* dose for adult
<b>Clotrimazole</b>			
Gyne-Lotrimin <sup>®</sup>	No	1 percent cream	1 applicatorful (~5 g) daily for 7 days
Gyne-Lotrimin 3 <sup>‡</sup>	No	2 percent cream	1 applicatorful (~5 g) daily for 3 days
Gyne-Lotrimin <sup>§</sup>	Not applicable (not available in US)	100 mg vaginal tablet <sup>§</sup>	Insert 1 vaginal tablet daily for 7 days or 2 tablets daily for 3 days
<b>Miconazole</b>			
Monistat 7 <sup>¶</sup>	No	2 percent cream (combination kit may include 2 percent miconazole cream for external use)	1 applicatorful (~5 g) daily for 7 days
Monistat 3 <sup>¶</sup>	No	4 percent cream	1 applicatorful (~5 g) daily for 3 days
Monistat 7 <sup>¶</sup>	No	100 mg vaginal suppository	1 suppository daily for 7 days
Monistat 3 <sup>¶</sup> , Vagistat-3	No (combination kit) Yes (generic suppository)	200 mg vaginal suppository (combination kit may include 2 percent miconazole cream for external use)	1 suppository daily for 3 days
Monistat 1	No	1200 mg vaginal suppository (combination kit may include 2 percent miconazole cream for external use)	1 suppository for 1 day
<b>Nystatin<sup>¶</sup></b>			
Nystatin vaginal <sup>§</sup> (former US trade name Mycostatin)	Not applicable (not available in US)	100,000 unit vaginal tablet	Insert 1 vaginal tablet daily for 14 days
<b>Terconazole<sup>¶</sup></b>			
Terazole 7, Zazole <sup>¶</sup>	Yes	0.4 percent cream	1 applicatorful (~5 g) daily at bedtime for 7 days
Terazole 3, Zazole <sup>¶</sup>	Yes	0.8 percent cream	1 applicatorful (~5 g) daily at bedtime for 3 days
Terazole 3, Zazole <sup>¶</sup>	Yes	80 mg vaginal suppository	1 suppository daily at bedtime for 3 days
<b>Tioconazole</b>			
Vagistat-1, 1-Day (from Monistat) <sup>¶</sup>	No	6.5 percent ointment	1 applicatorful (~5 g) at bedtime as a single dose
<b>Butoconazole</b>			
Gynazole-1	Yes	2 percent cream	1 applicatorful (~5 g) as a single dose
<b>Fluconazole ORAL ADMINISTRATION<sup>¶</sup></b>			
Diflucan <sup>¶</sup>	Yes	150 mg oral tablet	Single dose by mouth

There are no significant differences in efficacy among topical and systemic azoles (cure rates >80 percent for uncomplicated vulvovaginal candidiasis).

g: grams.

\* Except fluconazole (oral administration).

‡ Generic equivalent preparation(s) are available in US.

§ Not available in US.

◊ Cure rate with nystatin is 70 to 80 percent.

¶ Itraconazole is another oral antifungal that appears to be effective. Pitsouni E, et al. Am J Obstet Gynecol 2008; 198:153.

‡ Rare cases of anaphylaxis and toxic epidermal necrolysis have been reported during terconazole therapy.

## Treatment of complicated vaginal candidiasis

### Severe vaginitis symptoms

Oral fluconazole 150 mg every 72 hours for 2 or 3 doses (depending on severity)

**OR**

Topical azole antifungal therapy daily for 7 to 14 days. A low potency topical corticosteroid can be applied to the vulva for 48 hours to relieve symptoms until the antifungal drug exerts its effect.

### Recurrent vulvovaginal candidiasis

Induction with fluconazole 150 mg every 72 hours for 3 doses, followed by maintenance fluconazole 150 mg once per week for 6 months.

If fluconazole is not feasible, options include 10 to 14 days of a topical azole or alternate oral azole (eg, itraconazole) followed by topical maintenance therapy for 6 months (eg, clotrimazole 200 mg [eg, 10 grams of 2 percent] vaginal cream twice weekly or 500 mg vaginal suppository once weekly).

### Non-albicans *Candida* vaginitis

Therapy depends upon species identified:

*C. glabrata*: Intravaginal boric acid\* 600 mg daily for 14 days

If failure occurs: 17 percent topical flucytosine cream, 5 grams nightly for 14 days

*C. krusei*: Intravaginal clotrimazole, miconazole, or terconazole for 7 to 14 days

All other species: Conventional dose fluconazole

### Compromised host (eg, poorly controlled diabetes, immunosuppression, debilitation) and *Candida* isolate susceptible to azoles

Oral or topical therapy for 7 to 14 days

### Pregnancy

Topical clotrimazole or miconazole for 7 days

- Treatment of pregnant women is primarily indicated for relief of symptoms
- Vaginal candidiasis → not associated with adverse pregnancy outcomes (!!)
- Administration of oral azoles during the first trimester is not recommended
- Topical imidazole (clotrimazole or miconazole)-vaginally



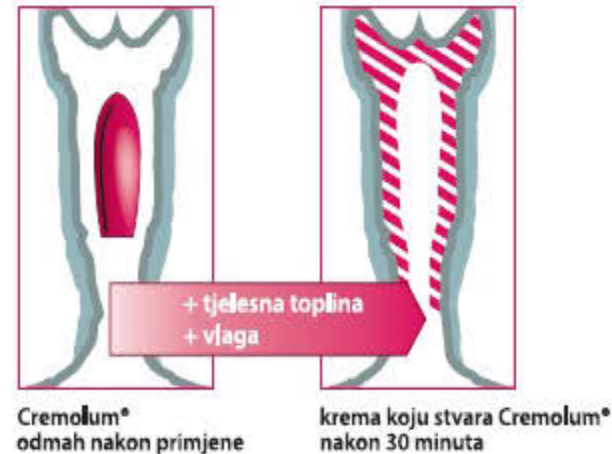
500 mg vagitorij i 10 mg/g krema

Djelatna tvar: klotrimazol

## ▶ Jednodnevno liječenje kandidijaze rodnice sa 500 mg klotrimazola

### JEDAN vagitorij sa 500 mg klotrimazola u jedinstvenoj Cremolum® tehnologiji za primjenu u rodnicu:

- topi se pri tjelesnoj temperaturi
- apsorbira vlagu iz rodnice
- stvara kremastu masu, emulziju tipa ulje-u-vodi koja oblaže sluznicu rodnice
- nema neotopljenih ostataka vagitorija u rodnici
- vagitorij se jednostavno primjenjuje u rodnicu, nije potreban aplikator



### i krema s 1% klotrimazola za primjenu na vanjsko genitalno područje:

- dva puta dnevno tijekom jednog tjedna
- smiruje i ublažava iritaciju vanjskog genitalnog područja uzrokovanu kandidijazom
- krema se lako razmazuje na vanjsko genitalno područje (stidnicu i okolno područje)

# Učinkovitost jednokratne doze

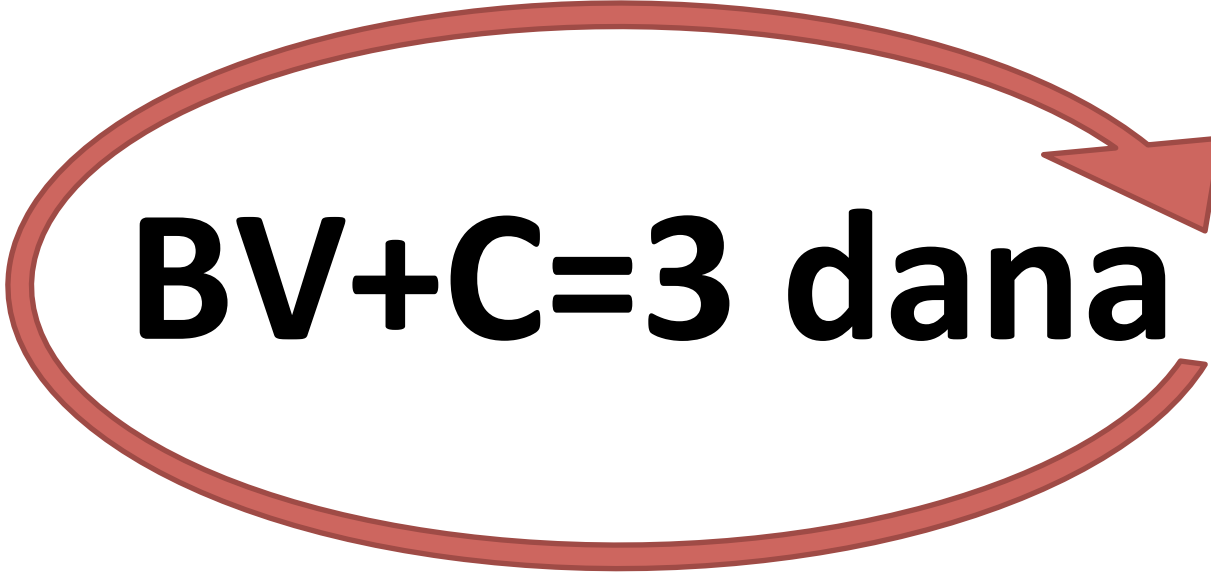
## **Treatment of vaginal candidiasis with a single 500-mg clotrimazole pessary**

There was no significant difference in the eradication rate between the single-dose and three-day regimens (89%)

Four weeks after completion of treatment the recurrence rates by culture were 18% with the single dose and 24% with the three day regimen.

The former treatment was well tolerated and as effective as the three-day clotrimazole regimen.

*Br J Vener Dis 1982; 58:124-6*



**BV+C=3 dana**

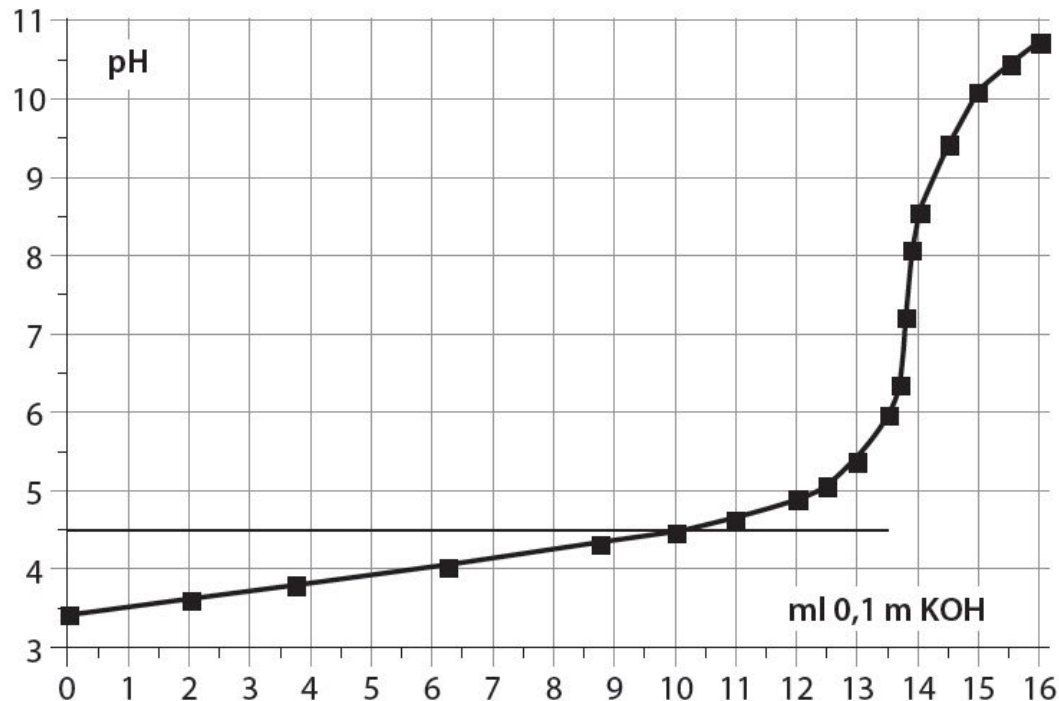


### In vitro study<sup>3</sup>:

#### Determination of buffer capacity of Vagisan Lactic Acid

Up to 10 ml of a potassium hydroxide solution with pH 14 can be buffered by Vagisan Lactic Acid, thereby maintaining a pH of up to 4.5 (physiological pH of vaginal fluid: 3.8 – 4.4). Hence, fluids with a lower pH than 14 in the vagina (e.g. semen, pH 7.0 – 7.8, or blood, pH 7.4) are also effectively buffered by Vagisan Lactic Acid.

### Progression of pH in a titration of one pessary Vagisan Lactic Acid in 100 ml water



<sup>1</sup> Petersen EE. Final report of a clinical microbiological study on the treatment of female patients suffering from a disturbed vaginal milieu (in particular amine colpitis) with lactic acid ovules. Unpublished study, 1993. Dr. August Wolff; data on file

<sup>2</sup> Schalla W. Subacute vaginal tolerability of lactic acid ovules in humans. Unpublished study 1993. Dr. August Wolff; data on file

<sup>3</sup> Titration of one Vagisan pessary in 100 ml water with 0.1m potassium hydroxide solution. Dr. August Wolff; data on file.

## Indikacije:

→ kao pomoćna terapija za regulaciju sadržaja mliječne kiseline u rodnici tijekom blažih ili srednje teških kroničnih i/ili recidivirajućih vaginitisa (bakterijski vaginitis, nespecifični kolpitis)

## **Indikacije:**

**→uspostavljanje stabilnoga i normalnoga kiselog okoliša (pH-vrijednosti) u kratkom vremenu u rodnici kod:**

- I. trudnica i dojilja (>pH)
- II. trudnica s DM/GDM (>>pH)
- III. netrudnih žena s DM
- IV. istovremene primjene antibiotika i kontracepcijskih sredstava
- V. miješanih bakterijsko gljivičnih infekcija

## **Doziranje i način primjene:**

→vagitorij uvesti navečer duboko u rodnicu

→Trajanje liječenja je 5-7 dana (preporuča se primjena svaka 2 – 3 dana)

## Prednosti primjene:

- 1) → jedini registrirani lijek odobren od Agencije za lijekove RH, dok su ostali pripravci na tržištu RH registrirani kao dodaci prehrani ili kao medicinski proizvodi
- 2) Primjena klinički dokazana u liječenju bakterijskih vaginoza
- 3) Primjena odobrena je od strane Agencije tijekom trudnoće i dojenja, uključujući i prvi trimestar trudnoće;
- 4) Za razliku od probiotika, posjeduje brzi učinak te unutar nekoliko sati značajno snižava pH rodnice te ga održava kiselim zahvaljujući puferu u lijeku (Na-laktat/laktatna kiselina).

