Arch Gynecol Obstet (2015) 292:371–376
DOI 10.1007/s00404-015-3638-9

GENERAL GYNECOLOGY

Study results on the use of different therapies for the treatment of vaginitis in hospitalised pregnant women

Aleksandra Novakov Mikić · Sinisa Stojic

Received: 29 September 2014 / Accepted: 23 January 2015 / Published online: 5 February 2015

Abstract
Purpose During pregnancy, many women experience vaginal infections due to a weakened immune system and changes in hormonal status. Treating these infections is of crucial importance, because women are at high risk for serious complications such as preterm birth and late miscarriage. For this reason, the present study was conducted to investigate the effectiveness of octenidine dihydrochloride/phenoxyethanol (OHP) in comparison to antimicrobial therapies in pregnant women in hospital suffering from different types of vaginitis.
Methods A total of 1,000 patients were divided into 4 different groups according to their type of vaginal infection after smear analyses. Each group was again divided into two subgroups receiving treatment with OHP or antimicrobial therapies with neomycin/polymyxin B/nystatin, metronidazole or miconazole vaginal tablets.
Results The most frequent causes of vaginitis were unspecific bacterial infections (42.4 %) and vaginal candidiasis (44.8 %). The average time needed to obtain negative results from smear analyses was significantly shorter when treated with OHP, both in patients with bacterial vaginosis (BV) or vaginal candidiasis (VC) compared to antimicrobial therapy (1.7 ± 0.8 vs. 2.3 ± 1.1 days; 2.3 ± 1.4 vs. 3.4 ± 1.6 days; both $p < 0.001$). Equally, the maximum number of days until negative results were detected was significantly lower with OHP compared to antimicrobial therapy (BV: 3 vs. 5 days; VC: 5 vs. 7 days).
Conclusions OHP has a great effect in the treatment of vaginitis during pregnancy and thus should be an integral part of standard therapy regimens.

Keywords Vaginitis · Bacterial vaginosis · Candidiasis · Pregnancy · Octenidine dihydrochloride · Phenoxyethanol

A. Novakov Mikić (✉)
Policlinic "Novakov et al.", Kosovska 26,
21000, Novi Sad, Serbia
e-mail: aleksandranovakov@gmail.com

A. Novakov Mikić · S. Stojic
Medical Faculty, University of Novi Sad, Novi Sad, Serbia

S. Stojic
Department of Obstetrics and Gynecology, Clinical Centre of Vojvodina, Novi Sad, Serbia

Introduction

During the course of pregnancy, the entire female organism undergoes considerable changes which consequently also affect the vaginal microflora. Normal vaginal microflora is one of the most important defence mechanisms in maintaining vaginal health and preventing the proliferation of microorganisms [1]. In healthy women, vaginal flora consists of both aerobic and anaerobic bacteria, with *Lactobacillus acidophilus* (*L. acidophilus*) being the predominant microorganism [2, 3]. Hydrogen peroxide produced by *L. acidophilus* has toxic effects on pathogens and ensures a vaginal pH-level of 3.8–4.2 [4]. During pregnancy, changes in the normal vaginal flora and pH-level can occur due to a weakened immune system and changes in hormonal status. These changes may lead to an inflammation or irritation of the vagina called vaginitis.

The prevalence and causes of vaginitis are often partly unclear because the infection may be asymptomatic; on the other hand, it may have multifactorial causes. In 90 %, vaginitis is caused by bacterial, fungal or protozoal infections leading to excessive vaginal discharge [5, 6]. The

most common type of vaginitis is bacterial vaginosis representing 40–50 % of all cases. Another very common cause of vaginitis with a prevalence of more than 30 % is vaginal candidiasis, which can be very persistent and reoccur several times during pregnancy [7]. Depending on the type of infection, the vaginal discharge may be accompanied by unpleasant odour, the feeling of tension in the vagina, vulvovaginal irritation, and dysuria or dyspareunia [7].

In general, the treatment of vaginitis is determined by the cause of the infection. As standard therapy of bacterial vaginosis, metronidazole and clindamycin are used [8]. For the treatment of candidiasis, antifungicides such as fluconazole, ketoconazole, clotrimazole, miconazole and others are recommended. Infections with Lepthothrix or Trichomonas are treated with metronidazole as well [5, 9].

Normalisation of the vaginal pH value plays an important role in the treatment of vaginal infections. In this context, a temporary improvement of the vaginal flora can be achieved by the repeated application of Lactobacillaceae preparations in cases of mild dysbiosis or bacterial vaginosis [10, 11]. However, according to Briese et al. [10] no long-term success is achieved. In the past few years, the application of the antiseptic agent octenidine dihydrochloride/phenoxyethanol (OHP) has been established as an effective treatment option for the therapy of vaginitis, since it is indicated for all types of vaginal infections [7, 12–14]. OHP is also known to reduce the vaginal pH value, and thus promotes the restoration of lactobacilli [13]. Combined with the antiseptic efficacy, a successful long-term treatment can be achieved.

The aim of the present study was to evaluate the therapeutic effect of OHP in comparison to antimicrobial therapies in pregnant women in hospital suffering from different types of vaginitis. The focus of the study was on the time needed to obtain negative results of vaginal smear analyses depending on the different therapies as the main target parameter.

Patients and methods

The prospective study started in February 2007 at the Clinic for High Risk Pregnancies at the Department of Obstetrics and Gynecology, Clinical Centre Vojvodina, Novi Sad, Serbia and was terminated in 2009. The study was performed in accordance with local laws and approved by the Ethical Committee of the Clinical Centre of Vojvodina, Serbia. Written informed consent had to be signed by all participants themselves or by a parent/guardian in case of underage patients.

The studied population consisted of a total number of 1,000 pregnant women hospitalised between the 14th and 41st week of gestation. The most common reasons for hospitalisation of patients were hyperemesis gravidarum, imminent spontaneous abortion, imminent preterm delivery, preeclampsia, insulin dependent diabetes mellitus type I, gestational diabetes mellitus, lupus erythematosus, preterm rupture of membranes, postterm pregnancy, polyhydramnios, oligohydramnios and foetal malformations.

Study design

Patients were selected during routine clinical practice according to a vaginal swab analysis conducted as part of the routine screening for vaginal infections, regardless of whether patients complained about symptoms or not. Vaginal smears were collected by opening the vaginal canal with a speculum, then collecting samples from the outer opening of the cervix of the uterus and the endocervix. At the clinical laboratory, fresh, unstained vaginal samples were smeared directly onto a microscope slide after collection and were examined under a microscope without the use of any reagents. The Nugent score was used to grade bacterial vaginosis and the existence as well as the type of infection was noted.

Taking into account the type of infection, the patients ($N = 1{,}000$) were classified into four groups (Table 1). The women of each group were then alternately assigned into two subgroups, and were provided with different types of treatment: one subgroup was treated with the antiseptic agent octenidine dihydrochloride/phenoxyethanol (OHP), which is established under the trade name octenisept® (company Schuelke & Mayr GmbH, Norderstedt, Germany). The second group received antimicrobial therapies with either neomycin/polymyxin B/nystatin, metronidazole or miconazole vaginal suppositories, regarding the type of infection (Table 1). The patients were assigned randomly to the subgroups, regardless of age and gestation. Patients with normal vaginal flora, i.e. dominated by *L. acidophilus*, were not included into the study.

Study procedure

Patients treated with OHP initially received a 15-ml intravaginal injection by usage of a speculum. Following this, three gauze pads soaked in OHP were applied and the vagina was cleaned for about 15 s, after which the swabs were removed. In contrast, patients treated with antimicrobial therapies obtained commercial vaginal suppositories of the corresponding medications, which were inserted into the posterior fornix of the vagina by themselves. Antimicrobial therapies were dosed as follows: neomycin 100,000 IU + polymyxin B 35,000 IU + nystatin 100 mg (Polygynax® vaginal suppositories, INNOTECH International, France); metronidazole 500 mg

Table 1 Classification of pregnant women according to their type of vaginal infection

Smear analysis	OHP, *n* (%)	Antimicrob. Th.		Total, *N* (%)
		n (%)	Medication	
Bacterial vaginosis	212 (42.4)	211 (42.2)	Neomycin/polymyxin B/nystatin	423 (42.3)
Lepthothrix	61 (12.2)	61 (12.2)	Metronidazole	122 (12.2)
Trichomonas vaginalis	3 (0.6)	4 (0.8)	Metronidazole	7 (0.7)
Vaginal candidiasis	224 (44.8)	224 (44.8)	Miconazole	448 (44.8)
Total	500 (100)	500 (100)		1,000 (100)

OHP octenidine dihydrochloride/phenoxyethanol, *Antimicrob. Th.* antimicrobial therapy

(Orvagil® vaginal suppositories, Galenika AD, Serbia); miconazol vaginal suppositories 200 mg (Gyno-Dactanol®, Galenika AD, Serbia).

The beginning of treatment was defined as day one. Vaginal swab samples of the women were taken once daily and smears were subsequently analysed. In case of negative laboratory findings, i.e. no signs of infection were detected, the treatment was finalised. In case of a positive laboratory result, the treatment was continued with the corresponding treatment until no further evidence for an infection was found. Patients, who were released from the hospital before a negative smear result was detected, were not taken into account for the analysis of the study results.

At the end of the treatment, data of patients were stratified according to their age, week of gestation, type of infection, and average time needed for obtaining a negative smear result and analysed in a descriptive statistics. Furthermore, the distribution of the number of days until negative results were detected was examined considering the most common infections.

Statistics

The statistical analyses performed in this study were calculated by using the software SPSS Statistics 13.0 (© SPSS Inc.).

Results

Patient's characteristics

The age of patients at study entry was relatively homogeneous and did not differ between treatment groups (Table 2). The largest group of patients was between the ages of 25 and 29 years (33.9 %).

Pregnant women were mainly admitted to hospital between 25 and 29 gestational weeks (27.0 %), followed by women hospitalised between 20 and 24 weeks of gestation (22.8 %). Only 7.2 % of women entered the study at a later phase in pregnancy, between 35 and 39 gestational weeks (Table 3). There was no significant difference in gestational age distributions between patients treated with OHP or antimicrobial therapy with neomycin/polymyxin B/nystatin, metronidazole or miconazole vaginal suppositories ($p = 0.955$, Pearson's Chi-square).

Referring to the type of vaginal infection detected by vaginal smear, the majority of women suffered from bacterial vaginosis (42.3 %) and vaginal candidiasis (44.8 %), showing almost equal distribution among treatment groups (Table 1).

Time until negative infection results

Due to the fact that the groups with bacterial vaginosis and candidiasis encompassed the majority of patients, they were chosen to be examined regarding the duration and efficacy of the therapy. Both in women suffering from bacterial vaginosis and vaginal candidiasis, the time needed for eradication of the infection was significantly shorter after OHP treatment compared to antimicrobial therapy (1.7 ± 0.8 vs. 2.3 ± 1.1 days; 2.3 ± 1.4 vs. 3.4 ± 1.6 days; both $p < 0.001$, Mann–Whitney-test; Fig. 1).

In addition, similar results were found considering the maximum time to eradicate the infection: in both patient groups significantly fewer days were detected in patients with OHP treatment compared to women with antimicrobial therapy (3 vs. 5 days for bacterial vaginosis; 5 vs. 7 days for candidiasis). No signs of vaginal infection were observed in 52 % women with bacterial vaginosis and 38 % patients with vaginal candidiasis after the first day of OHP treatment compared to 22 and 12 % in patients treated with antimicrobial therapy (Fig. 1).

Throughout the entire study, no adverse events occurred in any treatment group.

Discussion

Treatment of vaginitis in pregnancy is of crucial importance, because due to the kind of infection women are at high risk for complications during pregnancy. In particular, bacterial vaginosis may cause serious complications leading to a significant number of obstetric and gynaecologic complications, such as preterm labour and delivery,

Table 2 Age of pregnant women with vaginitis at study entry treated on either OHP or antimicrobial therapy

Age groups (years)	OHP *n* (%)	Antimicrob. Th. *n* (%)	Total *N* (%)
15–19	84 (16.8)	64 (12.8)	148 (14.8)
20–24	119 (23.8)	114 (22.8)	233 (23.3)
25–29	164 (32.8)	175 (35.0)	339 (33.9)
30–34	74 (14.8)	61 (12.2)	135 (13.5)
35–39	59 (11.8)	86 (17.2)	145 (14.5)
Total	500 (100)	500 (100)	1,000 (100)
Average (SD)	26.0 (6.1)	26.9 (6.2)	26.5 (6.2)

OHP octenidine dihydrochloride/phenoxyethanol, *Antimicrob. Th.* antimicrobial therapy, *SD* standard deviation

Table 3 Study entry from pregnant women with vaginitis at different weeks of gestation by therapy

Week of gestation	OHP *n* (%)	Antimicrob. Th. *n* (%)	Total *N* (%)
14–19	75 (15.0)	80 (16.0)	155 (15.5)
20–24	110 (22.0)	118 (23.6)	228 (22.8)
25–29	140 (28.0)	130 (26.0)	270 (27.0)
30–34	90 (18.0)	84 (16.8)	174 (17.4)
35–39	35 (7.0)	37 (7.4)	72 (7.2)
≥40	50 (10.0)	51 (10.2)	101 (10.1)
Total	500 (100)	500 (100)	1,000 (100)

OHP octenidine dihydrochloride/phenoxyethanol, *Antimicrob. Th.* antimicrobial therapy

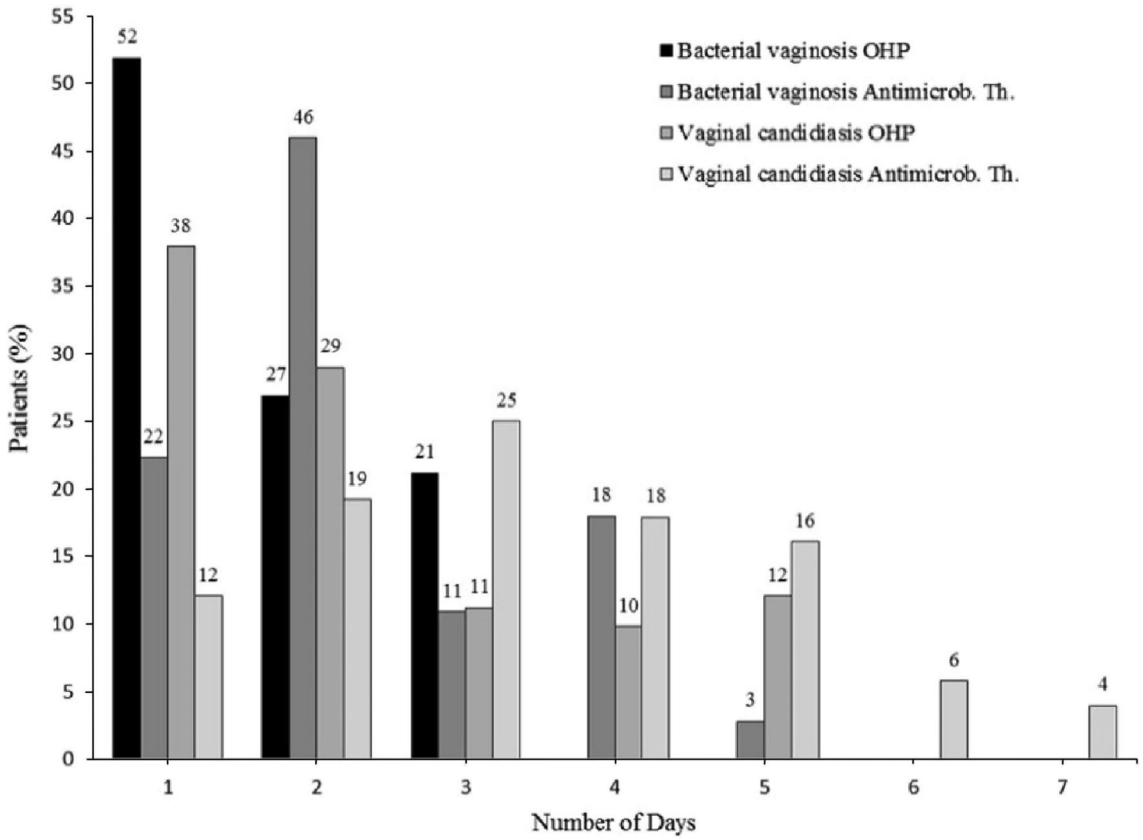

Fig. 1 Time until achieving negative vaginal smear results in patients with different forms of vaginitis by therapy

preterm premature rupture of membranes, spontaneous abortion, chorioamnionitis, postpartum endometritis, postcaesarean delivery wound infections, postsurgical infections, and subclinical pelvic inflammatory diseases [3].

In general, the prevalence of bacterial vaginosis varies from 5 to 50 % [6, 15]. Bacterial vaginosis is characterised by an imbalance of the normal vaginal flora with an overgrowth of anaerobic bacteria, including *Gardnerella vaginalis*, *Mycoplasma hominis* and *Mobiluncus species*, as well as a lack of the normal hydrogen peroxide-producing lactobacillary flora, which in turn leads to an increase in the vaginal pH-level over 4.5 [16, 17]. Symptoms of this type of vaginitis comprise excessive secretion with unpleasant smell followed by itching and dyspareunia in some cases. In about 25–30 % of all cases this infection remains asymptomatic.

The other very common cause of vaginitis vaginal candidiasis can be very persistent and reoccur several times during pregnancy [7]. Vaginal candidiasis results of an infection with *Candida albicans* or other types of fungi, such as *Candida glabrata*, which recently started to appear. The symptoms are characterised by profuse whitish, clotty discharge, redness of vagina and vulva followed by itching [7]. Furthermore, in about 10–25 % of all cases vaginitis is caused by the protozoan parasite *Trichomonas vaginalis*. This sexually transmitted infection increases the risk of preterm rupture of membranes and preterm birth [10]. It is distinguished by the appearance of greenish, profuse vaginal discharge of unpleasant odour, dyspareunia and dysuria in some cases [7].

Various therapy options are available depending on the cause of the vaginal infection, while systemic and local antibiotic therapy is increasingly substituted by antiseptic treatment options due to the potential for development of resistance and high relapse rates [10]. In this context, the application of the antiseptic octenidine dihydrochloride/phenoxyethanol (OHP) has been established as standard therapy in the past years, since it is indicated for all types of vagina infections [7, 10]. Recently, very good results in the treatment of vaginal infections and in the maintenance of vaginal health have also been achieved by strengthening of natural defences via the treatment with Lactobacillaceae preparations [10, 11]. Lactic acid produced by vaginal lactobacilli establishes a pH value of 3.8–4.5, which inhibits the adherence of germs to epithelial cells, and thus helps to protect against reproductive tract infections [18].

The aim of the present study was to compare the effectiveness of OHP treatment in hospitalised pregnant women suffering from different types of vaginitis with antimicrobial conventional therapies. In this context, the main focus was on the time required to achieve cure of patients, i.e. absence of infection. In order to be able to supervise and to control the OHP amount being used during hospitalisation, it was applied via soaked gauze instead of using an OHP spray, which in the past has proven to be more comfortable and easier to apply for the patients [15].

In accordance with available data from the literature, the major causes of vaginitis determined in pregnant women of the present study were bacterial vaginosis and vaginal candidiasis [6–8, 19]. In contrast, the age groups most frequently affected by vaginitis showed inconsistent results among trials [20]. In general, all age groups are affected.

In the present study, the healing process was significantly accelerated in patients suffering from different types of vaginitis when treated with OHP therapy, which was to be expected, as its efficacy against bacteria and fungi has already been verified in previous studies [7, 10, 13]. The differences in average time and number of days needed to obtain negative smear results for patients using antimicrobial therapies compared to women treated with OHP most probably is due to the fact that vaginitis may have multifactorial causes. OHP is advantageous in this context as it is a nonspecific mucosal antiseptic, and thus is indicated for all types of vagina infections, which further has a proven tolerability in pregnancy without side effects and the occurrence of resistances [10]. Compared to this, the effectiveness of common antimicrobial therapies is limited due to the fact that they are directed only to one out of many possible causes.

In conclusion, our study data indicate that treatment with OHP has a great effect in treating vaginitis in pregnant women compared to antimicrobial therapies. Thus, the application of OHP should support the treatment of different types of vaginitis as integral part of standard therapy regimens.

Acknowledgments We thank Nicole Scholtz, Ph.D. and Andrea Rathmann-Schmitz, Ph.D. (Bonn, Germany) for their assistance in preparing the manuscript for publication, and MIOFARM export–import d. o. o., Novi Sad, Serbia for donation of the necessary supply of octenidine dihydrochloride/phenoxyethanol.

Conflict of interest None.

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