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Allam M. Abdelmonem, Salah M. Rasheed & Abeer Sh Mohamed

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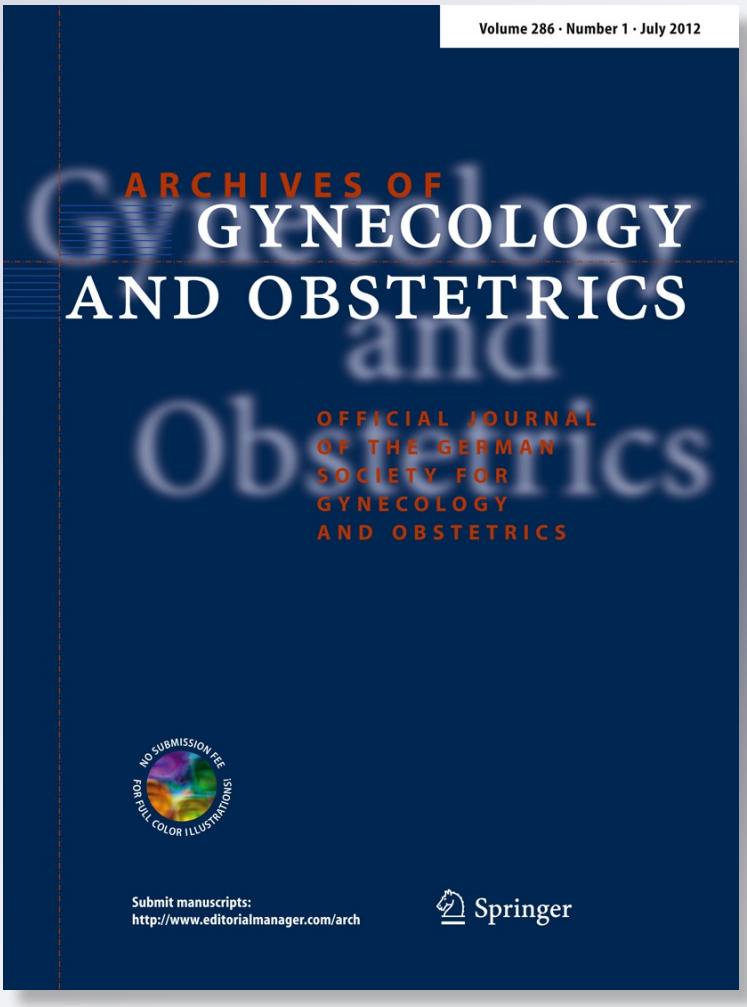

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GENERAL GYNECOLOGY

Bee-honey and yogurt: a novel mixture for treating patients with vulvovaginal candidiasis during pregnancy

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Abstract
Objective To evaluate the clinical and mycological cure rates of a novel mixture consisting of Bee-honey and yogurt compared to local antifungal agents for treating patients with vulvo-vaginal candidiasis (VVC) during pregnancy.
Materials and methods This is a prospective comparative study which included 129 patients with VVC during pregnancy. The participants were allocated into study group ($n = 82$) who received a mixture of Bee-honey and yogurt vaginally and control group ($n = 47$) who received local anti-fungal agents. The Chi-square test was used to evaluate the clinical and mycological cure rates and the side-effects of both modes of therapy.
Results The clinical cure rate was significantly higher in the study than the control group (87.8 vs. 72.3%, respectively) while the mycological cure rate was higher in the control than the study group (91.5 vs. 76.9%, respectively). Both types of therapy were favorably tolerated by most of the patients. Side effects were reported only in 24.3 and 29.7% of patients in group I and II, respectively ($p < 0.05$).
Conclusions The mixture of Bee-honey and yogurt produced a high clinical cure rate and a reasonable mycological cure rate. It can be used as a complementary or an alternative to antifungal agents especially in patients with VVC during pregnancy.

A. M. Abdelmonem (✉) · S. M. Rasheed
Department of Obstetrics and Gynecology,
Sohag Faculty of Medicine, Sohag University, Sohag, Egypt
e-mail: allam30@yahoo.com

A. S. Mohamed
Department of Medical Microbiology and Immunology,
Sohag Faculty of Medicine, Sohag University, Sohag, Egypt

Keywords Bee-honey · Yogurt · Antifungal agents · Vulvo-vaginal candidiasis

Introduction

Vulvovaginal candidiasis (VVC) is one of the most common gynecologic problems affecting the women. It was reported that about 75.0% of all females develop this type of infection at least once during their life; 90.0% of which are caused by *Candida albicans* while the remaining are caused by non-albican species [1]. Moreover, about 5.0% of all women with VVC may develop recurrence [2, 3].

More than 40% of affected women will have a history of two or more episodes of VVC, and infection occurs more frequently during pregnancy. It is believed that higher estrogen levels and higher glycogen content in vaginal secretions during pregnancy increase a woman's risk of developing VVC [4].

Although the pathogenesis of VVC remains controversial, it seems that disruption of the normal vaginal ecosystem may facilitate the overgrowth of Candida species. Antibiotic and steroid therapies, oral contraceptive pills, diabetes mellitus, pregnancy, and immune-suppression were reported to increase the risk for the development of VVC [5]. Women with VVC usually complain of thick white caseous (curd-like) vaginal discharge and itching in addition to dyspareunia, vulval redness, and edema [6].

Antifungal agents that are used for treatment of VVC include imidazole antifungals (e.g., butoconazole, clotrimazole, and miconazole), and polyene antifungals (e.g., nystatin). The topical formulations of imidazole and triazole antifungals, collectively known as azole antifungals, are considered the therapy of choice during pregnancy according to the safety data collected from animals and

humans [4]. Prospective and observational studies involving the use of topical antifungals did not reveal an increased risk of major malformations when mothers were exposed any time during pregnancy. Systemic absorption of these topical medications is minimal, posing little risk of transfer to the fetus [7]. Azole therapy during pregnancy should be recommended for 7 days instead of a shorter duration of therapy because of improved treatment success [8].

Oral fluconazole is considered as a second line of therapy to treat VVC. However, it is not recommended to be used during pregnancy. There have been case reports in which fluconazole has been associated with major malformations, but only at higher doses (≥400 mg/day) [9, 10].

Bee-honey was reported to have an effective antimicrobial activity and was prescribed to be used as a liquid broth or a component of vaginal tablets for treating vaginal candidiasis [1, 11]. The antimicrobial activity of Bee-honey could be attributed to its high osmolarity and acidity [12]. Moreover, the continuous elaboration of hydrogen peroxide from the honey through the glucose oxidase action is an additional factor [13].

Honey has been used since ancient times for the treatment of several diseases. Although several in vitro studies have demonstrated the antibacterial activity of honey [14, 15], limited number of studies have examined the activity of honey against fungi. Sissons et al. [16] reported that Manuka honey may be of benefit in oral infections where *C. albicans* is prominent. Boukraa et al. [17] found that the MIC of five varieties of honey against *C. albicans* ranged between 40 and 50% (v/v). According to Al-Waili [18], the minimum concentration of honey in nutrient agar media required to inhibit *C. albicans* was 66% (v/v). Irish et al. [1] also reported that honey has significant antifungal activity against clinical isolates of *C. albicans*, *C. glabrata* and *C. dubliniensis*. Koc et al. [19] assessed the in vitro antifungal activity of four Turkish honey samples from different botanical origin against *Trichosporon* spp. and *Candida* spp. and concluded that multifloral honey had the highest antifungal activity and it probably contains the highest total phenolic content.

Yogurt is a good source of Lactobacilli which was shown to inhibit the growth of yeast in women with VVC when applied directly into the vagina [20]. Although the traditional yogurt is an inexpensive and a relatively effective therapy for candidiasis, it seems that the plain, soy-based, or organic yogurt may produce better therapeutic effects [21].

Depending upon these foundations, the addition of Bee-honey to yogurt is assumed by the authors of the present study to produce a synergistic antifungal activity and subsequently will enhance their individual therapeutic efficacy against *Candida albicans*, particularly in women with VVC during pregnancy.

Systemic antifungal agents had its contraindications and may be associated with significant health problems [22]. Moreover, the emergence of some mycological resistance secondary to its repeated or long lasting use was reported [23]. These limitations made the authors thinking about the use of a novel mixture consisting of Bee-honey and yogurt and comparing its safety and effectiveness with conventional antifungal agents for treating women with VVC during pregnancy.

Materials and methods

The present prospective non-randomized comparative study was conducted at the outpatient's clinic of the department of obstetrics and gynecology of Sohag University hospital, Egypt in collaboration with the department of medical microbiology and immunology of Sohag faculty of medicine, Egypt, during a 2 years' period from 1 July 2009 till 1 July 2011. Local ethical committee provided approval to the study, and a written consent was obtained from all participants in advance.

During the study period, all pregnant women with VVC were invited to participate in the study. Diabetic patients, immuno-compromized patients, and patients who refused to share or dropped out during the follow-up period were excluded. The eligible patients ($n = 129$) were allocated to two groups; study group (group I; $n = 82$) which was treated with the Bee-honey and yogurt mixture vaginally twice daily for 7 days, and control group (group II; $n = 47$) which received local tioconazole (Gynotrosyd, Pfizer) 100 mg vaginal tablet once daily for 7 days.

Thorough history was obtained from all participants followed by complete general and Gynecologic examinations. Transvaginal and/or abdominal ultrasonography and random blood sugar assay were done. VVC was diagnosed both clinically (itching, curd-like discharge, and vulvovaginal redness) and laboratory (Gram staining and culture of the vaginal discharge). Itching, discharge and vulvovaginal redness was assessed by gynecological examination (vulval inspection and speculum examination) to observe any vaginal discharge, redness and any itching marks, in addition to asking the patients about the presence of vaginal discharge and vulval itching before and after therapy.

A sterile non-lubricated vaginal speculum was introduced into the vagina and two cotton-swabs were obtained from the vaginal discharge. The first swab was smeared on a glass slide, left to dry at the room temperature then Gram stained and examined microscopically (1,000× magnification). The slide was examined for detection of *Candida*

albicans (large oval gram positive budding cells) and for the presence of other mixed infections; Streptococci (chained Gram positive cocci), Staphylococci (clustered Gram positive cocci), gonococci (Gram negative intracellular diplococci), and Gram negative bacilli. The other swab was cultured on Sabouraud's agar for the definitive diagnosis of *Candida albicans*. In culture, *Candida albicans* colonies appear as soft and creamy colored. All cultures were examined at least weekly for detection of the fungal growth and were kept for 6 weeks before being considered as negative.

The rational behind the selection of Bee-honey rather than other bee products to be used in the current study was for the reason that it is cheep, available in Egyptian market, and well-known product by the patients in addition to its well-studied antimicrobial properties since ancient times in the literature. Also, the appearance of some recent studies in the literature about its antifungal properties against Candida species encouraged the authors to test this natural product. On the other hand, other bee products such as propolis and pollen which are suggested to have higher antifungal properties than Bee-honey are so expensive and not easily accessible in the market. Furthermore, the addition of yogurt to Bee-honey was assumed by the authors to improve their individual effects against candidiasis.

The mixture of Bee-honey and yogurt was prepared by pouring the native unprocessed multifloral honey into a container having heated distilled water to 40°C and a sterile spoon was used for mixing to make the honey 50% diluted (semi-liquefaction) then honey, yogurt (Nestlé ™) and distilled water were added to each other (v:v:v; 2.5:1.0:0.5, respectively). The three materials were mixed thoroughly till making a homogenous semi-liquid mixture. The mixture contained 62.5% honey, 25.0% yogurt and 12.5% distilled water. The mixture was prepared by the authors themselves and kept in sterile bottles then given to the participants to be used at home. The patients were instructed to use about 30 g (two tablespoon) of the mixture vaginally with the aid of an applicator twice daily for 7 days. The microbiologist tested the novel mixture used in the study for its antifungal activities in culture media before using it clinically by the patients.

Both types of therapy for the two groups were initiated depending upon the clinical diagnosis and the results of Gram stain and without waiting for the results of the cultures. Follow-up visits were scheduled 1 week after treatment, during which the participants were interviewed and inquired about their compliances to both modes of treatment, the presence of any side-effects, and asked about the presence of itching and/or discharge. Vaginal examination was done and two swabs from the vaginal discharge were obtained and evaluated using Gram staining as well as culture on Sabouraud's agar.

The sample size of the study was calculated using a program available at http://www.OpenEpi.com, so as to achieve 80.0% power and 5.0% confidence of significance (type I error). To achieve these levels, 122 participants were required. At the end of the study period, the clinical cure rate which was defined as absence of itching, discharge, and vulvo-vaginal redness and the definitive mycological cure rate which was defined as negative culture for *Candida albicans* were calculated and compared between the two groups using the Chi-square test. The student *t* test was used for comparing the continuous variables. A p value of <0.05 was considered statistically significant.

Results

During the study period, 198 pregnant patients with VVC were recruited from the outpatient's clinic of obstetrics and gynecology department, Sohag university hospital. In total, 156 patients fulfilled the inclusion criteria of the study and were assigned to the study ($n = 94$) and control ($n = 62$) groups, respectively. The reasons for exclusion were diabetic patients, immuno-compromized patients, and patients refused to participate in the study.

During the follow-up visits, 27 (17.3%) patients (12 in group I and 15 in group II) dropped out and were excluded from the study. The remaining 129 patients (82 patients in group I and 47 patients in group II) constituted the final study group.

There was no statistically significant difference regarding the mean age (34.0 ± 2.8 vs. 35.0 ± 3.1), parity (3.0 ± 1.3 vs. 3.0 ± 1.7) nor the body mass index (26.2 ± 3.2 vs. 25.4 ± 2.1) between the two groups.

The rates of vulvo-vaginal itching, discharge, and vulvo-vaginal redness (clinical diagnosis) were comparable between the two groups before treatment. Marked improvement in these clinical symptoms and signs was noticed after both types of therapy in the two groups of patients. The total clinical cure rate was significantly higher in group I (87.8%) compared to group II (72.3%). Similarly, the mycological cure rate according to the results of Gram staining and culture showed marked improvement after therapy in both groups. The definitive mycological cure rate was significantly higher in group II than in group I (91.5 vs. 76.9%, respectively) (Table 1).

The rates of mixed infections were comparable between the two groups (26.8 vs. 25.5%, respectively) before treatment. Staphylococci were the most commonly found organism while Gonococci were the least encountered organism in the two groups. Following treatment, there was a much more reduction in the rate of this mixed infection in group I (6.1%) than in group II (19.1%) ($p < 0.01$). In both

Table 1 The clinical and mycological data and the results of treatments in the two groups of patients

	Before treatment			After treatment		
	Group I[a] ($n = 82$)	Group II[a] ($n = 47$)	p value	Group I[a] ($n = 82$)	Group II[a] ($n = 47$)	p value
Itching	66 (80.5%)	39 (83.0%)	0.74	3 (3.7%)	7 (14.9%)	0.01
Discharge	61 (74.4%)	35 (74.5%)	0.96	4 (4.9%)	6 (12.8%)	0.04
Vulvo-vaginal redness	53 (64.6%)	32 (68.1%)	0.47	3 (3.7%)	4 (8.5%)	0.04
Clinical cure rate				72 (87.8%)	34 (72.3%)	0.02
Gram +ve hyphae	59 (72.0%)	34 (72.3%)	0.97	6 (7.3%)	3 (6.4%)	0.51
Candida growth on agar	74 (90.2%)	43 (91.5)	0.82	19 (23.1%)	4 (8.5%)	0.001
Mycological cure rate				63 (76.9%)	43 (91.5%)	0.01
Mixed infections (total)	22 (26.8%)	12 (25.5%)	0.84	5 (6.1%)	9 (19.1)	0.001
Staphylococci	16 (19.5%)	9 (19.1%)	0.91	3 (3.7%)	5 (10.6%)	0.04
Streptococci	11 (13.4%)	7 (14.9%)	0.74	2 (2.4%)	7 (14.9%)	0.001
Gram −ve bacilli	5 (6.1%)	1 (2.1%)	0.31	4 (4.9%)	1 (2.1%)	0.98
Gonococci	0 (0.0%)	1 (2.1%)	0.98	0 (0.0%)	1 (2.1%)	NA

All data were expressed as number (percentage), unless otherwise indicated

NA Non applicable for statistical analysis due to the small sample size

[a] The patients may have more than one complaint and the Gram stain may detect more then one organism in the same slide

groups, the rates of Staphylococci and Streptococci significantly decreased while that of gram negative bacilli and Gonococci remained relatively unchanged (Table 1).

Both types of therapy were favorably tolerated by most of the patients. Side effects were reported only in 24.3 and 29.7% of patients in group I and II, respectively ($p < 0.05$). Soiling of underclothes was significantly higher in group I than in group II (17.0 vs. 10.6%, respectively). However, local irritation was significantly higher in group II than in group I (6.4 vs. 1.2%, respectively) (see Table 2).

Discussion

VVC is a distressing problem to women and is associated with great discomfort, inconvenience, and even disruption of their life style. Systemic anti-fungal therapy was considered by many authors unsafe during pregnancy and may be associated with fetal malformations [9, 10]. However, topical formulations of imidazole and triazole antifungals, collectively known as azole antifungals, are considered the therapy of choice during pregnancy owing to the safety data collected from animals as well as humans [4].

Table 2 Side effects of both types of treatment in the two groups of patients

	Group I ($n = 82$)	Group II ($n = 47$)	p value
Side effects (total)	20 (24.3%)	14 (29.7%)	0.009
Non-compliance	5 (6.09%)	3 (6.3%)	0.68
Soiling of underclothes	14 (17.0%)	5 (10.6%)	0.006
Local irritation	1 (1.2%)	6 (6.4%)	0.001

All data were expressed as number (%)

Bee-honey and yogurt were previously tested individually for treating patients with VVC either alone or as complementary therapies. Bee-honey at different concentrations was reported to inhibit the growth of different pathogenic bacteria as well as *candida albicans*. The minimal concentration of Bee-honey required for inhibiting *candida albicans* was reported to range from 30.0 to 50.0% [18]. Attempts were made to increase this efficacy of Bee-honey by its combination with other substance such as starch and olive oil [17, 18].

To the best of our knowledge, a mixture containing both Bee-honey and yogurt was used for the first time in the present study. The mixture produced a relatively high clinical cure rate which was even higher than that produced with the use of anti-fungal therapy (87.8 vs. 72.3%, respectively). On the contrary, the anti-fungal therapy produced a significantly higher definitive mycological cure rate. This paradoxical effect may seem astonishing and even illogic. However, the higher clinical than the mycological cure rate can be attributed to the inhibiting effect of the mixture on other organisms rather than the *Candida albicans* alone. The mixture produced a relatively high therapeutic efficacy against Staphylococci and Streptococci. Moreover, the anti-inflammatory properties of the honey may alleviate the problems of itching and redness thus improving some of the symptoms and signs of vaginal candidiasis.

The higher clinical and mycological cure rates reported in the present study compared to other studies [11, 17, 21] which used Bee-honey alone or in combination with other

substances may support the authors' hypothesis that the addition of Bee-honey to yogurt may have a synergistic effect against different microorganisms. The Bee-honey had potent antifungal and anti-inflammatory activities while yogurt is a good source of lactobacilli and lactic acid making the vaginal milieu unsuitable for candidal growth [20].

The mixture is cheap, easy to be prepared and easy to be used. The mixture contains about 62.5% Bee-honey; a concentration which was higher than the minimal concentration (30.0%) reported for inhibition of the *Candida albicans* [11]. The addition of distilled water to the mixture had the drawback of decreasing the honey concentration and subsequently possibly decreasing its therapeutic efficacy. From the other point of view, adding water had the merit of decreasing both the viscosity of the mixture and the stickiness of Bee-honey to the vagina and vulva. During the pilot phase of the study, the mixture was prepared by mixing Bee-honey to yogurt in a ratio of 3.0:1.0 without adding water. The mixture was much viscid, and its stickiness to the vagina and underclothes of the patients was high and associated with high rates of inconvenience, non-compliance, and discontinuation. Accordingly, the authors used distilled water in order to decrease the viscosity and stickiness of the mixture.

Although side-effects were reported in about one quarter of patients using the novel mixture, yet there were no reported major health problems, and soiling of the underclothes constituted the vast majority of the reported side-effects. However, local irritation was an apparent symptom in patients using local antifungal agents.

The most evident limitation of the present study was the lack of randomization of the patients. Although, during a pilot phase of the study, the original design of the study was randomization, however, most of the patients during counseling selected to use the mixture and not the antifungal therapy. This could be attributed to either the preference of the patients to try a natural new line of therapy or to mysterious fears about their fetus secondary to the use of chemical antifungal agents during pregnancy. Whatsoever, this patient's preference rendered randomization invalid. Another limitation was that the mixed infections were diagnosed by the Gram stain only and not by culture. Although the culture is the gold standard method for diagnosis of any infection, however, the present study was designed mainly for detection of *C. albicans*. A third limitation was the lack of long periods of follow up for the patients in order to detect the rate of recurrence.

Despite these limitations, the present study provided a novel mixture which was natural, available, cheap, easy to be prepared, easy to be used and associated with negligible side-effects. The mixture produced a high clinical cure rate and a reasonable mycological cure rate in patients with VVC during pregnancy. The mixture is of a particular merit either as a complementary or an alternative therapy to antifungal agents if they are ineffective or contraindicated. The authors hope that this mixture may add more to the field of complementary medicine.

Conflict of interest We declare that we have no conflict of interest.

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