

# Safety, efficacy, and tolerability of differential treatment to prevent and treat vaginal dryness and vulvovaginitis in diabetic women

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## Summary

**Background:** Problems affecting the vaginal tract in diabetic women are very often neglected. The efficacy and safety of three gynecological treatments in diabetic women have been assessed. **Materials and Methods:** A single-blind randomized progressive trial on 48 diabetic women affected by vaginal dryness, dyspareunia, and recurrent Candida infections was carried out. The ICIQ Vaginal Symptoms (ICIQ-VS) questionnaire was administered. **Results:** The analysis of the parameters of ICIQ-VS questionnaire among the three groups showed significant difference only for "dragging pain" ( $p = 0.019$ ) and "soreness" ( $p = 0.028$ ). In all groups and for all parameters of the questionnaire, improvement of symptoms was observed. In particular, in Group 1 for all symptoms a highly significant difference was observed, to support the already known benefits of the products and of the proposed combination. Significant improvement was also observed in Group 2. **Conclusions:** The proposed treatment with DermoXEN® Ultracalming Special for diabetics and DermoXEN® Vitexyl vaginal gel exert effective moisturizing and soothing action. Indeed, the aforementioned products have been proven effective for the main gynecological problems of diabetic women.

**Key words:** Diabetes; vulvovaginal discharge; vaginal dryness; DermoXen®; Candida Albicans.

## Introduction

Diabetes mellitus (DM) is one of the most popular non-communicable diseases all over the world, affecting approximately 346 million people. In many developing countries and in newly industrial countries, the epidemic is growing fast [1, 2]. Data from the Centers for Disease Control and Prevention (CDC) and from the National Center for Health Statistics in the United States indicate that the number of people affected by DM has increased considerably from 1980 and 2010, passing from around 5.6 to 20.9 million people [3, 4]. Today, the main problems for diabetic people are no longer problems related to survival, but those related to chronic complications of diabetes, both microangiopathic (retinopathy, nephropathy, neuropathy) and macroangiopathic (ischemic heart disease, arteriopathy of the lower limbs, arteriopathy of the supra-aortic trunks) [5]. Patients affected by DM are more susceptible to bacterial and fungal infections [6]. Numerous studies have proven a close correlation between hyperglycaemia and candidiasis [7, 8]. Diabetic women are more predisposed to a high risk

of recurrent vaginitis caused by *Candida* spp, leading to inflammations that result in pain during sexual intercourse (dyspareunia) and cystitis, especially caused by *Escherichia coli*. These problems are often associated with vaginal dryness, redness, burning and itching during sexual intercourse. Problems of female sexual dysfunction (FSD) affect from 30% up to 78% women [9]. It is estimated that the prevalence in diabetic women ranges between 20% and 80% [9, 10]. Indeed, diabetic women are more predisposed to develop a decline in sexual desire, dyspareunia, reduction in sexual arousal, and poor lubrication [11, 12]. Furthermore, a recent study underlines that vaginal dryness is more common in diabetic women compared to non-diabetic women [13]. DM is also recognised as a predisposing factor to vulvovaginal candidiasis, as well as pregnancy, use of broad spectrum antibiotics, high-dose estrogen oral contraceptives and continuous administration of drugs [14, 15]. Symptomatic vulvovaginal infections caused by *Candida* spp. have higher prevalence in patients with diabetes compared to the general population [16]. Hyperglycaemia is the main cause

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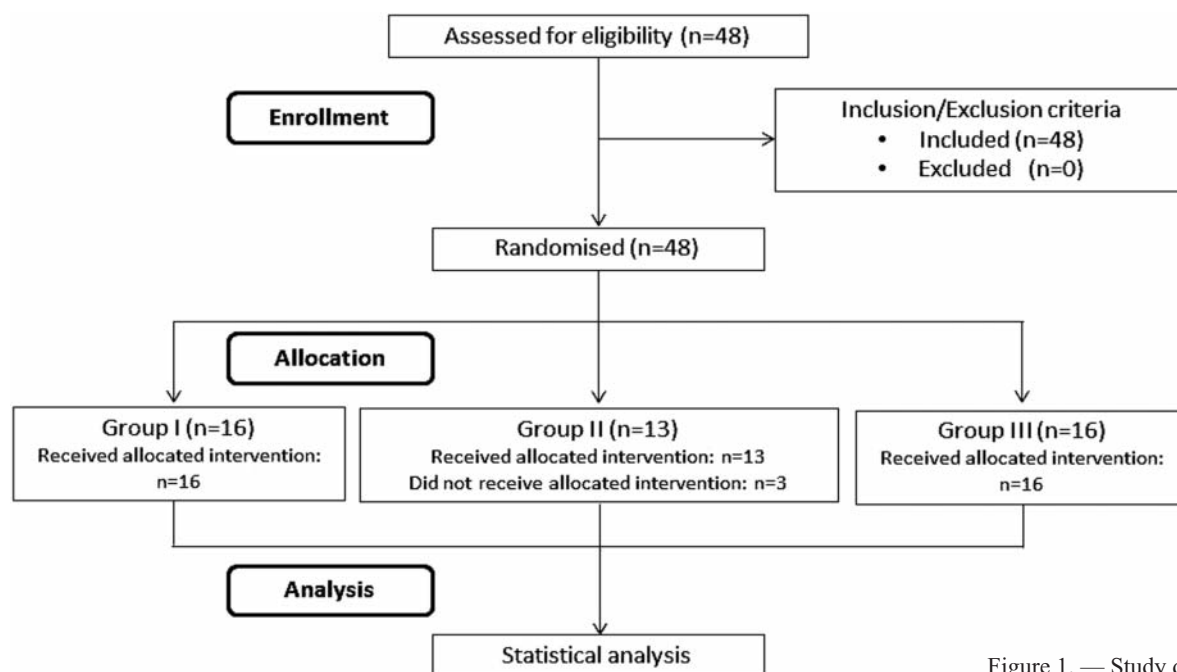


Figure 1. — Study design.

of increased susceptibility to vulvovaginal candidiasis in diabetic patients. High blood glucose level in the genital tissues enhances yeast adhesion and growth. *Candida albicans* binds to epithelial cells more easily in diabetic women, independently if they are premenopausal, post-menopausal or pregnant women [17]. Moreover, hyperglycaemia can influence the humoral response, causing a reduction in neutrophils, chemotaxis, and phagocytosis [18].

The aim of study is to evaluate the efficacy of different gynecological treatments for vaginal dryness, itching, burning, dyspareunia, and recurrent *Candida* infections in diabetic women. In particular, in this randomized study was compared efficacy, safety and tolerability of DermoXEN® Ultracalming Special for Diabetics and DermoXEN® Vitexyl gel used in combination with DermoXEN® Vitexyl gel and another gel based on mineral oil.

## Materials and Methods

Forty-eight diabetic women afferent to the Operative Unit (O.U.) of Diabetology of the Local Health Unit (LHU) of Lecce affected by vaginal dryness, dyspareunia, and recurrent *Candida* infections, were selected for this single-blind, randomized, progressive study in the period between August 2013 and March 2014.

Ethical approval was granted by the Ethics Committee of LHU of Lecce (Protocol n. 1394, August 8, 2013) and written informed consent was obtained for each enrolled women. Three women, belonging to Group 2 dropped out. Women were divided as follows (Figure 1): Group 1: 16 women used daily (for 14 days) DermoXEN® Ultracalming SD for intimate cleansing in the morning and they applied DermoXEN® Vitexyl gel before going to bed; Group 2: 13 women used daily (for 14 days) DermoXEN® Vi-

texyl gel before going to bed; Group 3: 16 women used daily (for 14 days) a common commercially available gel containing mineral oil (Replens gel) before going to bed. Eligible patients were randomized to one of the three treatment at the enrolling time using a 1:1:1 allocation ratio.

Women over 18 years and under 65 years of age affected by diabetes type I and/or II with problems of vaginal dryness and dyspareunia, women did not take the contraceptive pill for at least six months, women did not take corticosteroids and/or antihistamines for at least six months were included in the study.

Women under 18 years of age, over 65 years of age, pregnant, took the contraceptive pill, took corticosteroids and/or antihistamines, with serious chronic-degenerative pathologies, with serious infectious diseases, and that used different cleaning vaginal products were excluded from the study.

Information on general characteristics (age, body mass index, parity, DM type, and glycemia) were collected. The ICIQ Vaginal Symptoms (ICIQ-VS) questionnaire in order to collect information on dryness, burning, itching, dyspareunia, vaginal symptoms, sexual matter and quality of life before (T0) and after (T1) the use of selected medical devices was administered [16]. Furthermore, data on pH value and frequency and species of *Candida* before and after treatment were collected. The yeast isolation were detected in the analysis laboratory of LHU by the commercial kit.

## Medical devices

DermoXEN® Ultracalming Special for Diabetics contains high molecular weight hyaluronic acid which moisturizes and protects internal and external mucous membrane, lactic acid which exerts a rebalancing effect of vaginal pH, Fucus vesiculosus extract which provides moisturization and protection of the mucous membrane and dihydro-avenanthramide, a biotechnological byproduct exerting a soothing and calming action against irritations. DermoXEN® Vitexyl vaginal gel is a medical device essentially composed of water and glycerin, with high molecular weight hyaluronic acid and panthenol. It exerts an intense moisturizing action inside the

Table 1. — General characteristics of study participants variable.

	Group 1 (n = 16)	Group 2 (n = 13)	Group 3 (n = 16)	p
Age (years $\pm$ SD)	49.5 $\pm$ 10.5	49.8 $\pm$ 14.3	55.8 $\pm$ 9.7	0.243*
BMI (kg/m <sup>2</sup> $\pm$ SD)	28.9 $\pm$ 5.4	26.9 $\pm$ 3.1	26.2 $\pm$ 4.4	0.230*
Parity (n $\pm$ SD)	2.2 $\pm$ 1.3	2.3 $\pm$ 1.1	2.4 $\pm$ 1.5	0.925*
Diabetes mellitus				
Type 1 (n, %)	5 (31.2)	7 (53.8)	8 (50.0)	
Type 2 (n, %)	11 (68.8)	6 (46.2)	8 (50.0)	0.408**
Glycemia (mg/dl $\pm$ SD)	135.3 $\pm$ 30.5	142.3 $\pm$ 36.8	119.4 $\pm$ 25.2	0.127*

SD: standard deviation; \* Statistical analysis was performed by two-way ANOVA.

\*\* Statistical analysis was performed by  $\chi^2$ .

vaginal tract. Replens vaginal gel contains mineral oil, mucoadhesive substances, glycerin and sodium hydroxide especially designed to moisturize and lubricate the vaginal tract and take care of irritation and itching related to vaginal dryness.

#### Statistical analysis

For the statistical analysis, one goal of the proposed study was to test the null hypothesis that the proportion positive is identical in the two populations. The criterion for significance ( $\alpha$ ) was set at 0.05. The test was two-tailed, which means that an effect in either direction was interpreted. The sample size was calculated by a 95% prerequisite confidence interval (CI) and an estimated error rate exceeding  $\pm 20\%$ . With 80% power, 16 women in each group were needed.

The statistical analysis of all collected data was performed using the SPSS software package (version 18.0). Continuous variables were expressed as mean and standard deviation (SD), while categorical variables in absolute values. Homogeneity of general characteristic data at baseline was verified by analysis of variance (ANOVA) for continuous variables and by a Chi-square test for categorical variables. Intragroup changes were evaluated with the paired Student *t*-test. A *p*-value of  $<0.05$  was considered to be significant.

#### Results

The average age of enrolled women was  $49.5 \pm 10.5$  years in Group 1,  $49.8 \pm 14.3$  years in Group 2, and  $55.8 \pm 9.7$  years in Group 3 ( $p = 0.243$ ). The analysis of the other general characteristics (BMI, parity, glycaemia, and diabetes type) did not show any differences among the study groups (Table 1).

The pH value and vaginal symptoms (dryness, burning, itching, and dyspareunia) showed significant differences among the three groups only for “dryness” ( $p = 0.024$ ) and “dyspareunia” ( $p = 0.011$ ) at T0 and for pH ( $p = 0.017$ ) and “dyspareunia” ( $p = 0.013$ ) at T1 (Table 2).

Intragroup comparison at T0 and T1 showed significant reduction for pH and vaginal symptoms, except for “burning” and “itching” in Group 3. In Group 1, a highly significant difference was observed for all symptoms (Table 2). The analysis of the parameters described in ICIQ-VS questionnaire, showed significant difference only for “dragging

Table 2. — Vaginal symptoms in the three groups of diabetic women, after enrollment (T0) and after 14 days (T1).

	Group 1			Group 2			Group 3			G1vsG2vsG3	
	T0	T1	p*	T0	T1	p*	T0	T1	p*	p (T0)**	p (T1)**
pH	5.9 $\pm$ 0.8	5.2 $\pm$ 0.8	<0.0001	5.9 $\pm$ 1.0	5.6 $\pm$ 0.9	0.0019	6.3 $\pm$ 0.9	6.1 $\pm$ 0.8	0.0188	0.334	0.017
Dryness	6.1 $\pm$ 3.1	3.3 $\pm$ 2.3	<0.0001	3.5 $\pm$ 3.2	1.7 $\pm$ 1.9	0.0012	3.2 $\pm$ 3.0	2.1 $\pm$ 2.3	0.0005	0.024	0.127
Burning	1.3 $\pm$ 1.7	0.6 $\pm$ 1.1	0.0066	1.1 $\pm$ 1.0	0.5 $\pm$ 0.2	0.0136	0.9 $\pm$ 1.1	0.8 $\pm$ 1.0	0.3332	0.728	0.609
Itching	2.4 $\pm$ 1.6	0.7 $\pm$ 0.9	<0.0001	2.1 $\pm$ 1.3	0.9 $\pm$ 0.9	0.0025	1.3 $\pm$ 1.4	1.0 $\pm$ 1.3	0.0555	0.103	0.697
Dyspareunia	2.4 $\pm$ 1.7	1.3 $\pm$ 1.2	0.0004	0.7 $\pm$ 0.9	0.2 $\pm$ 0.6	0.0124	1.3 $\pm$ 1.4	0.7 $\pm$ 0.9	0.0011	0.011	0.013
<i>ICIQ Questionnaire Vaginal symptom</i>											
Dragging pain	0.6 $\pm$ 0.9	0.1 $\pm$ 0.2	0.0235	0.2 $\pm$ 0.6	0.0 $\pm$ 0.0	0.1902	0.8 $\pm$ 0.9	0.5 $\pm$ 0.8	0.0962	0.173	0.019
Soreness	0.2 $\pm$ 0.8	0.0 $\pm$ 0.0	0.2162	0.2 $\pm$ 0.4	0.0 $\pm$ 0.0	0.0821	0.6 $\pm$ 1.0	0.3 $\pm$ 0.6	0.0197	0.290	0.028
Reduced sensation	0.4 $\pm$ 0.8	0.2 $\pm$ 0.5	0.1881	0.1 $\pm$ 0.6	0.1 $\pm$ 0.6	-	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	-	0.452	0.936
Loose vagina	0.2 $\pm$ 0.4	0.1 $\pm$ 0.2	0.0825	0.3 $\pm$ 0.5	0.1 $\pm$ 0.3	0.0821	0.3 $\pm$ 0.8	0.0 $\pm$ 0.0	0.1359	0.949	0.570
Lump felt inside	0.1 $\pm$ 0.3	0.1 $\pm$ 0.2	0.3332	0.1 $\pm$ 0.3	0.1 $\pm$ 0.3	-	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	0.378	0.570
Lump seen outside	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	-	-
Dry vagina	2.5 $\pm$ 1.9	0.4 $\pm$ 0.6	0.0002	1.3 $\pm$ 1.3	0.5 $\pm$ 0.7	0.0060	1.5 $\pm$ 1.3	0.0 $\pm$ 0.0	0.0002	0.079	0.674
Faecal evacuation	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	-	-	-
<i>Sexual matter</i>											
Worries about vagina interfere with sex-life	1.1 $\pm$ 1.1	0.3 $\pm$ 0.6	0.0014	0.5 $\pm$ 0.7	0.3 $\pm$ 0.5	0.1902	0.6 $\pm$ 0.7	0.5 $\pm$ 0.7	0.1639	0.154	0.622
Relationship affected	0.9 $\pm$ 1.0	0.2 $\pm$ 0.4	0.0066	0.7 $\pm$ 0.7	0.2 $\pm$ 0.4	0.0075	0.7 $\pm$ 0.9	0.5 $\pm$ 0.8	0.0410	0.851	0.288
Sex life spoilt	3.6 $\pm$ 3.6	1.3 $\pm$ 1.6	0.0009	3.1 $\pm$ 3.2	2.3 $\pm$ 2.2	0.0145	2.7 $\pm$ 2.2	2.1 $\pm$ 1.8	0.0011	0.723	0.305
<i>Quality of life</i>											
Quality of life affected	5.1 $\pm$ 3.2	2.5 $\pm$ 2.1	<0.0001	2.9 $\pm$ 2.6	1.9 $\pm$ 1.6	0.0207	3.5 $\pm$ 2.5	2.7 $\pm$ 2.2	0.0103	0.099	0.575

Data are expressed mean score  $\pm$  SD.\* Statistical analysis was performed by paired Student's *t*-test (two-tailed). \*\* Statistical analysis was performed by two-way ANOVA.

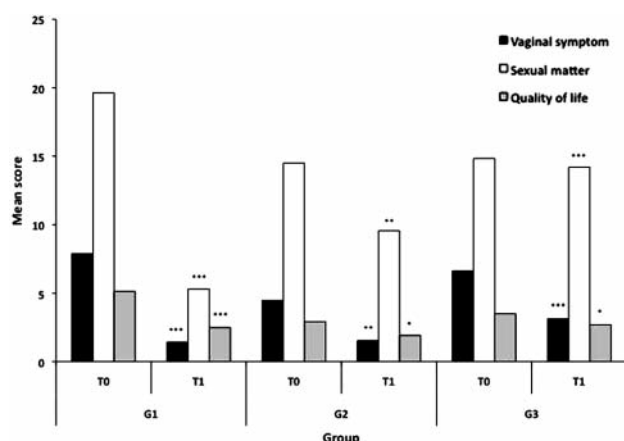


Figure 2. — Mean scores for 3 domains of the ICIQ-VS questionnaire (vaginal symptoms, sexual matters and quality of life), in the three groups of diabetic women, after enrollment (T0) and after 14 days (T1). Asterisks identify statistical intra-group comparisons with paired t test (\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.0001$ ).

pain” ( $p = 0.019$ ) and “soreness” ( $p = 0.028$ ) among the three groups. Improvement in symptoms was observed in all groups and for all parameters of the questionnaire. No enrolled patients had “lump seen outside” and “faecal evacuation” at T0 and T1. In Group 1, sexual matters and quality of life showed a significant improvement for all parameters, while the “worries about vagina interfere with sex-life” was not improved significantly in Group 2 and 3 (Table 2). The score analysis at T0 and T1 was carried out using the validated ICIQ-VS questionnaire [19]. Analysis of score data underlined highly significant improvement ( $p < 0.0001$ ) in Group 1 for all domains. A similar trend was observed in Group 3, with exception of the quality of life, because the perceived improvement was lower compared to Group 1 ( $p < 0.05$ ). Significant improvement was observed in Group 2 for the domains related to vaginal symptoms ( $p < 0.01$ ), sexual matters ( $p < 0.01$ ), and quality of life ( $p < 0.05$ ) (Figure 2). All *Candida* species isolated by vaginal mucous membrane at T0 were found negative after the treatment period (T1) in all groups (Table 3).

## Discussion

Problems of the vaginal tract in diabetic women are very often neglected, although they entail a reduced quality of life. Indeed, vaginal dryness, caused by angiopathic and neuropathic complications typical of diabetes, often causes dyspareunia. Moreover, high glucose level in normal secretion, as well as in body fluids (for example in blood), increases the risk of bacterial and fungal infections, especially caused by *Candida* spp. A recent study confirmed that diabetes is associated with *Candida Albicans* and non-*C. Albicans* fungal infections in Brazilian women with incidence

Table 3. — Frequency of *Candida* species isolated from the vaginal mucosa in the three groups of diabetic women, after enrollment (T0) and after 14 days (T1).

Isolated species	G1*		G2		G3	
	T0 n. (%)	T1 n. (%)	T0 n. (%)	T1 n. (%)	T0 n. (%)	T1 n. (%)
<i>C. albicans</i>	2 (12.5)	0	0	0	1 (6.25)	0
<i>C. krusei</i>	2 (12.5)	0	0	0	0	0
<i>C. glabrata</i>	2 (12.5)	0	0	0	0	0
<i>C. sphaerica</i>	0	0	1 (7.7)	0	0	0

\* Statistical analysis was performed by  $\chi^2$ : T0 vs. T1  $p < 0.0001$ .

of isolation of 55.6% and 44.4%, respectively. The high incidence of reported cases underlines that a particular attention and further investigation regarding to *Candida* infections in DM patients are needed [20]. In the study no adverse effects were observed in the three treatments. The medical device DermoXEN® Ultracalming Special for Diabetics was produced to give a daily non-pharmacological treatment to diabetic women in order to tackle effectively the problems of the vaginal tract. This device was tested in association with a vaginal gel. Results obtained as balance of pH level around acidic values (more suitable for the vaginal environment), as treatment of *Candida* spp. and Female Sexual Function Index score (by administering specific questionnaires) demonstrated the efficacy of the device in management of vaginal complications in diabetic women. Indeed, the results of pH analysis, before and after the combined application of DermoXEN® Ultracalming Special for Diabetics and DermoXEN® Vitexyl vaginal gel showed a highly significant improvement ( $p < 0.0001$ ) that was not observed in the remaining two groups. Acid pH values (4.0-5.5) determine a chemico-physical situation conducive to the growth of Doderlein flora inhibiting the growth of pathogenic ones. In particular, *Candida* species are not able to develop hyphae (pathogenic profile) in acidic pH conditions [21]. The analysis of score data showed a highly significant improvement ( $p < 0.0001$ ) in Group 1 for all domains. A similar trend was observed in Group 3, with the exception of the domain related to quality of life, that the perceived improvement was lower than Group 1 ( $p < 0.05$ ). The treatment of Groups 1 and 2 was more effective than that of the Group 3 and no adverse event was observed. *Candida* infections at T0 were observed mainly in Group 1 (6 in 7 women); the combined treatment with DermoXEN® Ultracalming SD and DermoXEN® Vitexyl gel proved to be effective to restore an adequate vaginal pH level, inhibiting the growth of *Candida Albicans*. At the beginning and at the end of the treatment, the intragroup comparison showed significant reduction of pH values and vaginal symptoms, except for “burning” and “itching” in Group 3. In Group 1 a highly significant difference was observed for all symptoms (Table 2), highlighting greater effectiveness of the proposed product combination. Comparing the effects of the proposed



treatments in Groups 1 and 2, the moisturizing and soothing action of DermoXEN® Ultracalming Special for diabetics emerges. Significant improvement was observed in Group 2 for vaginal symptoms ( $p < 0.01$ ), sexual matters ( $p < 0.01$ ) and quality of life ( $p < 0.05$ ), demonstrating the real efficacy of the DermoXEN® Vitexyl vaginal gel. Indeed, it has been especially designed in order to improve lubrication of the vaginal tract and improve sexual intercourse in case of dyspareunia. Therefore, this trial shows that DermoXEN® Ultracalming Special for diabetics and DermoXEN® Vitexyl gel have a safety and efficacy profile suitable for the treatment of the main problems of the vaginal tract in diabetic women. The association with DermoXEN® Vitexyl vaginal gel is recommended in order to improve the symptoms in diabetic women.

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