

A comparative study of vaginal estrogen cream and sustained-release estradiol vaginal tablet (Vagifem) in the treatment of atrophic vaginitis in Isfahan, Iran in 2010-2012

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Background: Atrophic vaginitis is a disease, which affects up to 50% of postmenopausal women. This study compared the effectiveness and user-friendliness of Vagifem (an estradiol vaginal tablet) and vaginal estrogen cream in the treatment of atrophic vaginitis. **Materials and Methods:** One hundred and sixty postmenopausal women with symptoms of atrophic vaginitis were randomly divided into two groups of treatment with Vagifem or with vaginal estrogen cream for 12 weeks. Patients used the medication daily for the first 2 weeks of the study, and twice weekly. Severity of vaginal atrophy and four main symptoms of atrophic vaginitis including dysuria, dyspareunia, vaginal itching, and dryness were evaluated and compared before and after treatment. In addition, patients were asked regarding user-friendliness and hygienic issues of medications. **Results:** Both vaginal estrogen cream and Vagifem significantly improved symptoms of atrophic vaginitis but in terms of effectiveness for the treatment symptoms of atrophic vaginitis, there was no significant difference between the two medications. Vagifem compared to estrogen cream resulted in significantly lower rate of hygienic problems (0% versus 23%, $P < 0.001$), and was reported by the patients as a significantly easier method of treatment (90% versus 55%, $P < 0.0001$). **Conclusion:** This investigation showed that Vagifem is an appropriate medication for the treatment of atrophic vaginitis, which is as effective as vaginal estrogen creams and is more user-friendly.

Key words: Atrophic vaginitis, patient acceptability, Vagifem, vaginal estrogen cream

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INTRODUCTION

Postmenopausal decline in estrogen level induces undesirable changes to the female body. Estrogen deficiency affects many organs such as genitourinary system. Genitourinary involvement causes untoward symptoms of atrophic vaginitis including dryness, burning, dyspareunia, vulvar pruritus, and discharge.^[1-5]

These symptoms are localized, affect up to 50% of postmenopausal women, and significantly reduce their

quality of life.^[6-8] For this reason, many investigations have been performed to find out effective, safe, and acceptable therapeutic methods for atrophic vaginitis.

Although systemic administration of estrogen can improve the localized symptoms of atrophic vaginitis, women are often reluctant to use systemic hormone replacement therapy and prefer local administration of estrogen.^[6,7]

Vaginal application of estrogen has been considered as an effective treatment of atrophic vaginitis.^[9,10] Different forms of estrogen have been widely prescribed for the

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local treatment of atrophic vaginitis; however, vaginal estrogen creams has been the most common form of local estrogen therapy.^[6,7]

Patients often consider these preparations to be unhygienic due to vaginal leakage and need for the use of some form of sanitary protection.^[11] These factors cause poor compliance, reduced medication acceptability, and undertreatment, which lead to ineffective symptom control.^[7]

Vagifem is a low dose slow-release small vaginal tablet, which contains 25 µg of 17-β-estradiol. It is placed deep into the vagina by an applicator, adheres to the vaginal mucosa, and has minimal discharge. Vagifem has been reported to be an easy and hygienic method of treatment for atrophic vaginitis.^[6,7,11]

This study was designed to compare the efficacy, acceptability, and safety of Vagifem in a larger sample size with vaginal estrogen cream.

MATERIALS AND METHODS

After approval of the study by the Ethics Committee of Isfahan University of Medical Sciences (research project number 390225) and obtaining informed consent, this randomized clinical trial was performed in a private clinic in Isfahan, Isfahan Province, Iran between 2010 and 2012.

One hundred and sixty postmenopausal women aged 50-70 years with clinical diagnosis of vaginal atrophy who did not need systemic estrogen therapy for the treatment of vasomotor symptoms or prophylaxis of osteoporosis, and had no history of vaginal bleeding over the previous year entered the study.

Women were excluded if they had any history of carcinoma of the breast or endometrium, abnormal genital bleeding, acute thrombophlebitis, or thromboembolic disorders associated with previous estrogen use, or current urinary or vaginal infection. In addition, women who underwent hormone replacement therapy, treated with systemic or vaginal estrogen within 6 months prior to the study, or had any contraindication for estrogen therapy were excluded from the study.

Using simple randomization, women were randomly divided into Vagifem (from Novo Nordisk) or vaginal estrogen cream (Equin from Actoverco) treatment groups (80 women in each group).

Patients of the first group were commenced on vaginal estrogen cream of Actoverco company, one tube every night for 14 nights; then, one tube 2 nights in 1 week (two tubes

every week) for 10 weeks. In the second group, vaginal estrogen cream from Novo Nordisk was replaced with Vagifem 25 mcg; however, the treatment plan was similar to the first group.

In addition to recording demographic data, four main symptoms of atrophic vaginitis including dysuria, dyspareunia, vaginal itching, and dryness were evaluated by patients' self-report, and vaginal atrophy was assessed by the gynecologist.

At the beginning of the study, all patients were asked to answer a check list to record pretreatment symptom severity. Patients were asked to report whether they had no symptom or had mild, moderate, or severe symptoms.

Then, the women were examined by a single gynecologist, and the degree of vaginal atrophy was determined and recorded. Patients were followed up for 12 weeks. Follow-up sessions were arranged at 2 weeks, 4 weeks, 8 weeks, and 12 weeks after the beginning of the treatment.

Women were reexamined by the gynecologist to reevaluate the severity of vaginal atrophy. The gynecologist who examined the women was unaware of the treatment group. At the end of the study, patients answered regarding their satisfaction of the treatment, and posttreatment symptom severity.

Effectiveness means effectiveness for the relief of vulvovaginal atrophy (VVA) symptoms. This is just confined to the response of the patients to the questions included in the checklist.

Medication acceptability was checked after 2 weeks of the treatment and at the end of the study. Patients were asked about the presence and degree of pain [using visual analog scale (VAS)] during application of the medication, vaginal leakage of the medication, need to use sanitary towels to clean leakage, and user-friendliness.

A 3-point scale (very easy, easy, or difficult) was used to evaluate user-friendliness of the treatment method.

Women were also asked about whether they had experienced vaginal bleeding, recurrent vaginal discharge, stress, or urge incontinence.

Any adverse events were also recorded at the follow-up sessions. Data were analyzed by Statistical Package for the Social Sciences (SPSS) 16 software (Equine cream Manufactured by ALDO-UNION, S.A, Barcelona, Spain). Chi-square and independent *t*-test were used when appropriate. *P* values less than 0.05 were considered to be statistically significant.

RESULTS

For demographic data, no significant difference was found between the two groups in baseline data [Table 1].

The rate of pre- and posttreatment symptoms showed that there was no significant difference between the two groups and they had the same rate of response.

Comparison of pre- and posttreatment within the groups showed a significant improvement of all the symptoms; however, there was no significant difference between the two groups in posttreatment frequency of patients with a different intensity of symptoms. Details of the results are

Table 1: Demographic characteristics of the two groups

Variables	Vaginal estrogen cream (n:80)	Vagifem (n:80)	P value
Age (years)	56.55±8.63	55.28±6.12	0.50
Parity	2.93±1.31	3.11±1.42	0.41
Body mass index (kg/m ²)	23.21±3.25	22.48±2.56	0.66
Age at menopause (years)	49.65±3.43	48.27±1.12	0.75
Years since menopause (years)	6.91±4.21	7.02±3.55	0.83

Data are presented as mean ± SD; n = Number of patients

presented in Tables 2-6. These tables show the rate of each symptom between the two groups.

In contrast to the Vagifem treatment group, most women receiving vaginal estrogen cream experienced discharge of medication following application.

Throughout the 12-week treatment period [Figure 1].

After 2 weeks of treatment, only 13% of the Vagifem-treated women reported leakage of medication from the vagina compared with 53 (66%) of those who had received vaginal estrogen cream. The difference between the treatment groups was highly significant ($P < 0.0001$). At the end of the study, only 6% women in the Vagifem treatment group reported leakage compared with 68% in the vaginal estrogen cream group ($P < 0.0001$).

The need for using sanitary towels was also significantly higher in the vaginal estrogen cream treatment group throughout the trial. After 2 weeks of treatment, vaginal leakage of the medication necessitated the use of sanitary towels by only 7 (9%) of the women receiving Vagifem compared with 35 (44%) of those in the vaginal estrogen cream treatment group ($P < 0.0001$).

Table 2: Comparison of patients with different intensities of vaginal atrophy between the two groups before and after treatment

Variables	Vaginal atrophy											
	Normal			Mild			Moderate			Severe		
	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P
Vaginal estrogen cream (N:80)	1 (1%)	23 (29%)	<0.0001	20 (25%)	31 (39%)	0.04	32 (40%)	16 (20%)	0.03	27 (34%)	10 (12%)	0.01
Vagifem(N:80)	3 (3%)	20 (25%)	<0.0001	18 (22%)	35 (44%)	0.03	35 (44%)	13 (16%)	0.02	24 (31%)	12 (15%)	0.01
P	0.08	0.33		0.74	0.11		0.82	0.09		0.79	0.46	

Data are presented as numbers (%)

Table 3: Comparison of patients with different intensities of vaginal dryness between the two groups before and after treatment

Variables	Vaginal dryness											
	Normal			Mild			Moderate			Severe		
	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P
Vaginal estrogencream (N:80)	10 (13%)	48 (60%)	<0.0001	26 (32%)	20 (25%)	0.08	13 (16%)	5 (6%)	0.001	31 (39%)	7 (9%)	<0.0001
Vagifem (N:80)	7 (9%)	49 (61%)	<0.0001	22 (28%)	16 (20%)	0.06	18 (22%)	6 (8%)	<0.0001	33 (41%)	9 (11%)	<0.0001
P	0.52	0.92		0.26	0.14		0.12	0.87		0.83	0.78	

Table 4: Comparison patients with different intensities of itching between the two groups before and after treatment

Variables	Itching											
	Normal			Mild			Moderate			Severe		
	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P
Vaginal estrogencream (N:80)	16 (20%)	55 (69%)	<0.0001	21 (26%)	11 (14%)	<0.0001	14 (18%)	5 (6%)	0.001	29 (36%)	9 (11%)	0.001
Vagifem (N:80)	19 (24%)	57 (71%)	<0.0001	16 (20%)	10 (12%)	0.06	12 (15%)	7 (9%)	0.04	33 (41%)	6 (8%)	<0.0001
P	0.52	0.73		0.12	0.87		0.88	0.08		0.53	0.89	

Following reduction of drug application frequency to twice-weekly, none of the women treated with Vagifem reported the need for sanitary towels while 23% women receiving vaginal estrogen cream still needed to use them ($P < 0.0001$). Regarding overall user-friendliness, women reported Vagifem to be a significantly more user-friendly medication [Tables 6 and 7].

DISCUSSION

It is well-understood that use of local estrogen in the form of vaginal cream has some limitations for patients.^[6]

These limitations mainly include difficulties in application such as the obligation for usage at bedtime and somehow leakages from the vagina marking the underwear. Patient acceptability and preference is a very important aspect of local estrogen therapy, which significantly affects patients' compliance.^[6] Since long-term therapy is likely to be

necessary for women suffering from atrophic vaginitis, treatment should be easy and convenient.^[12,13]

Despite the well-documented efficacy of treatment with vaginal estrogen creams, compliance with therapy can be poor due to the aforementioned issues.^[14,15]

In November 2009, the Food and Drug Administration (FDA) approved the 10 mcg estradiol vaginal tablet formulation (Vagifem) for the treatment of VVA in menopausal women. Estradiol vaginal tablets previously were approved in a 25 mcg formulation in the United States and the European Union. The company discontinued the sale of Vagifem 25 mcg in the United States on July 30, 2010.^[16]

This poor compliance is mainly caused by vaginal leakage of medication, which usually necessitates the use of sanitary protection.^[6]

This study showed that both Vagifem and vaginal estrogen cream significantly improve the signs and symptoms of atrophic vaginitis.

Although there was no significant difference between these two medications in treating the symptoms, patients were more satisfied with Vagifem regarding user-friendliness and hygienic issues.

Two other previous studies also confirmed our findings, and showed that women treated with Vagifem were more likely to remain on therapy than those who were treated with a vaginal cream.^[6,17]

Dugal *et al.* studied 96 women randomly classified them into two equal groups of vaginal estrogen cream and estrogen tablet. Patients were followed up for 24 weeks. Their results

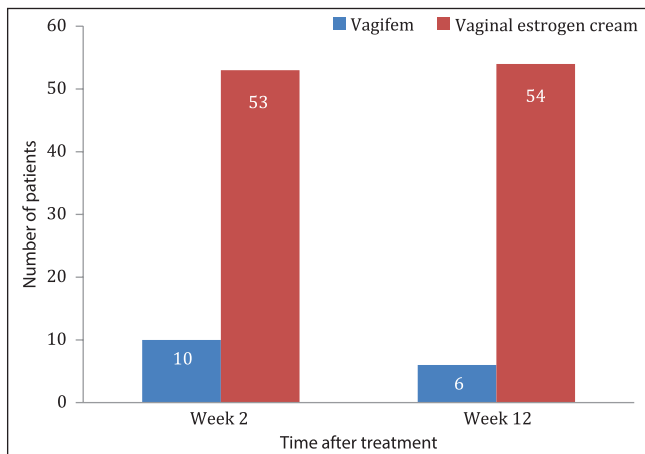


Figure 1: Number of women reporting leakage of medication from the vagina after 2 weeks and 12 weeks of treatment with Vagifem and vaginal estrogen cream

Table 5: Comparison of patients with different intensities of dyspareunia between the two groups before and after treatment

Variables	Dyspareunia											
	Normal			Mild			Moderate			Severe		
	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P
Vaginal estrogencream (N:80)	23 (29%)	47 (59%)	0.01	17 (21%)	13 (16%)	0.15	21 (26%)	10 (12.5%)	0.001	19 (24%)	10 (12.5%)	0.03
Vagifem (N:80)	28 (35%)	53 (66%)	>0.0001	13 (16%)	11 (14%)	0.60	18 (23%)	7 (9%)	0.02	21 (26%)	9 (11%)	0.001
P	0.21	0.14		0.34	0.64		0.73	0.51		0.77	0.87	

Table 6: Comparison of patients with different intensities of dysuria between the two groups before and after treatment

Variables	Dysuria											
	Normal			Mild			Moderate			Severe		
	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P	Pre-	Post-	P
Vaginal estrogencream (N:80)	22 (28%)	47 (59%)	<0.0001	31 (39%)	15 (19%)	0.01	18 (22%)	17 (21%)	0.77	9 (11%)	1 (1%)	<0.0001
Vagifem (N:80)	26 (32%)	45 (56%)	<0.0001	27 (34%)	12 (15%)	0.02	16 (20%)	21 (26%)	0.06	11 (14%)	2 (3%)	0.01
P	0.34	0.65		0.22	0.91		0.76	0.08		0.44	0.71	

Table 7: Comparison of user-friendliness of medications between the two groups according to patients' reported scores

Variables	Very easy	Easy	Difficult
Vaginal estrogen cream	20 (25%)	24 (30%)	36 (45%)
Vagifem	37 (46%)	35 (44%)	8 (10%)
P value	0.02	0.04	<0.0001

showed that vaginal tablets were as effective as estrogen cream; however, patients' acceptance was significantly higher in the tablet-treated group.^[6]

Similarly, Rioux *et al.* Performed a multicenter, open-label, randomized, parallel group study on 159 menopausal women to compare treatment with Vagifem and vaginal estrogen cream. They concluded that treatment with Vagifem and with vaginal estrogen cream was equivalent in relieving symptoms of atrophic vaginitis. In addition, they demonstrated that vaginal tablets have a localized effect with no significant increase in the systemic estradiol level or estrogenic side effects. They also reported greater patient acceptance and lower withdrawal rates in vaginal tablet therapy compared with the vaginal cream group.^[18]

Based on findings of several studies, estradiol vaginal tablets such as Vagifem were found to be an effective alternative to traditional therapeutic methods for atrophic vaginitis in postmenopausal women. This is consistent with the results of previous clinical trials, which treated and followed up patients for up to 2 years.^[6,13,18-20]

It is not a difficult decision to select one treatment from a group of choices when the efficacy is similar. In the presence of similar effectiveness, selection criteria were having fewer adverse effects and more patients' acceptance.

Vagifem is the tablet form of local estrogen preparation and therefore, it has an easier method of application with fewer adverse hygienic effects such as vaginal leakage. This is a very important factor, which affects patient adherence to the treatment in long term.

CONCLUSION

In summary, we conclude that Vagifem is an appropriate medication for the treatment of atrophic vaginitis, which is as effective as vaginal estrogen creams and is more userfriendly.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

All authors contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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