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Impact of Glycyrrhiza glabra (licorice) vaginal cream on vaginal signs and symptoms of vaginal atrophy in postmenopausal women: A randomized double blind controlled trial

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ABSTRACT

Background: Vaginal atrophy is one of the most common menopausal complications affecting women's quality of life. The present study aimed to investigate the impact of Glycyrrhiza glabra (licorice) vaginal cream on vaginal signs and symptoms of vaginal atrophy in postmenopausal women.

Methods: This randomized controlled trial was conducted on 70 menopausal women, referring to health centers of Izeh city, located in the south west of Iran, from May to November 2017. The participants with vaginal atrophy were randomly assigned into two groups of 35. One of the groups received licorice 2% vaginal cream while the other was given placebo over a period of 8 weeks. Data were analyzed using SPSS software at the significance level of 0.05.

Results: The results indicated that at the baseline, none of the subjects (0%) in either groups had a vaginal cells maturation Index within 65–100 in MVI category. However, after 8 weeks of therapy, it improved significantly to 82.9% in Licorice group and 11.4% in the placebo group ($p < 0.001$).

Also, the vaginal mucus cells changed from the baseline cells to intermediate and superficial cells within and between the two groups after the treatment ($p < 0.001$). Finally, the pH level significantly decreased in licorice group over time ($p < 0.001$).

Conclusion: Therapeutic use of licorice vaginal cream can improve the signs and symptoms of vaginal atrophy in postmenopausal women. Accordingly, use of licorice as a natural vaginal cream in vaginal atrophy can be suggested.

1. Introduction

Women experience different reproduction-related stages such as puberty, menstruation, sexual intercourse, pregnancy, childbirth, and finally menopause in their lives.[1] As the last critical stage of women's lives, menopause is not a disease, but is transitioning to a new stage, which can be alleviating, enjoyable, and productive. Menopause is defined as the complete cessation of menstruation for one year, and these events are physiologically related to a decrease in estrogen and thus loss of follicular function and the end of a woman's fertility stage.[2] Changes in a lifetime and increase in life expectancy have caused women to spend over a third of their lives after menopause; therefore, their problems and complications are more tangible in this period. On the eve of the third millennium, menopause has risen from a marginal problem into the locus of attention of the medical and health community such that it has been proposed as a major problem in developed countries, to which high healthcare costs have been allocated.[3]

Low levels of estrogen lead to some undesirable changes in all organs whose functioning and wellbeing depend on the presence of estrogen.[4] Vaginal atrophy refers to thinning, dryness, inflammation of the vaginal walls, where an increase in vaginal pH occurs during menopause and is caused by diminished estrogen levels in

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almost all cases.[5] Also, symptoms of vaginal atrophy include dryness, soreness, and burning or itching of the vagina and dyspareunia.[6,7]

About one-third of women who do not receive hormonal therapy experience symptomatic vaginal atrophy.[8] Vaginal atrophy is a mostly neglected symptom of menopause; however, it is estimated that 90% of women suffer from its symptoms such as vaginal dryness, itching, dyspareunia, postpartum hemorrhage, and urinary frequency and urgency, and it is one of the most important factors affecting sexual function and genitourinary system health. In 2014, International Society for the Study of Women's Sexual Health (ISSWSH) and North American Menopause Society (NAMS) announced Genitourinary Syndrome of Menopause (GMS) as a more precise alternative for vaginal atrophy. Since symptoms of vaginal atrophy are progressive and do not heal spontaneously, failure to treat them can lead to vaginal discomfort and diminished quality of life. Most cases require treatment while only 25% of the patients follow the treatment.[9] With regard to treatment of vaginal atrophy, the results of available studies indicate that estrogen therapy in both topical and systemic forms leads to enhanced collagen level and tissue thickness.

Many women do not use estrogen therapy, which is a standard and effective treatment, due to its complications. One of the alternative therapies is phytoestrogen. They are herbal compounds with estrogenic properties, whose safety have been confirmed for many years.[10,11] Among the herbs, sources of phytoestrogens are soybeans, fenugreek, red clover, and licorice.[12,13] Licorice is one of the plants containing herbal estrogen and is effective in the body's hormonal balance. Its estrogen is of steroidal type and is similar to estrone (E1) and estradiol (E2) which are produced in the body.[14] The estrogen beneficial effects of licorice are attributed to the presence of isoflavones which are the key components of the plant.

Glycyrrhiza glabra (licorice) belongs to leguminosae family and is native to Mediterranean regions. It grows in most parts of Iran such as Kerman, Arak, Kermanshah, and Khorasan. Iran produces a large portion of export licorice.[15,16] Hajirahimkhan et al. in their study entitled “Evaluation of estrogenic activity of licorice species in comparison with hops used in botanicals for menopausal symptoms” found that licorice is effective in controlling menopausal symptoms thanks to its high estrogenic characteristics and its safety compared to other herbs.[14] However, excessive use of licorice or its other products has been prohibited due to the excessive secretion of the aldosterone hormone which culminates in high blood pressure.[17]

The aim of the present study was to determine the effect of licorice vaginal cream on vaginal atrophy in postmenopausal women. If the effectiveness of the licorice vaginal cream in treating vaginal atrophy is confirmed, it can be recommended as a suitable and safe method to treat vaginal atrophy among postmenopausal women who cannot use hormonal therapy due to its numerous complications, particularly those who have a contraindication of hormonal therapy.

2. Materials and methods

The present study was a double-blind, placebo-controlled trial that was conducted in the selected health centers of Izeh city affiliated with Ahvaz Jundishapur University of Medical Sciences in May to November 2017. To the goal was to examine the effect of licorice vaginal cream on vaginal atrophy in postmenopausal women.

The inclusion criteria were as follows: postmenopausal for at least 1 year, having symptoms of vaginal atrophy (dryness, soreness, and burning or itching of the vagina and dyspareunia), gynecology examination, vaginal pH>5, and the percentage of cellular maturation of 0–49 in vaginal smear, engaging in sexual activity and being monogamous, and having normal blood pressure (<140/90). The exclusion criteria were genital tract disorders (abnormal secretion, infection, sexually transmitted diseases, and cancers confirmed by taking medical history and vaginal examination), vaginal infection which needed to be treated, uterine bleeding with unknown causes, undergoing hormonal therapy or hormonal use during 2 months prior to the study, breast diseases with unknown causes, high use of phytoestrogens such as soybean, red clover, flaxseed, and fenugreek during the last month, cholestatic liver disorders, kidney failure, and BMI>30.

2.1. Participants

The study population comprised postmenopausal women who referred to health centers of Izeh city for health screening and had signs and symptoms of vaginal atrophy.

2.2. Randomization

Eligible women were randomly assigned to intervention (n = 35) or control groups (n = 35) using six random blocks by a ratio of 1:1. In order to reduce the probability of selection bias, allocation was concealed using unique codes to each treatment group. The random block list was designed by a statistics consultant. Then, each block was replaced with a three-digit proprietary code by the supervisor which was custom-made. Note that three digits should have not been selected sequentially. The drugs were coded using the mentioned list. The researcher and participants were completely unaware whether the creams were therapeutic or placebo, with the tubes filled with vaginal cream by a pharmacist. The researcher who distributed the vaginal creams was unaware of these codes.

2.3. Measurements

The required data were collected using a demographic information questionnaire, a checklist, clinical examinations, and laboratory tests.

Vaginal atrophy signs including maturation vaginal index and pH were measured by vaginal smears at the baseline and 8 weeks after the intervention. Maturation vaginal index is defined as the percentage of the three major cell types in the vaginal covering tissue including basal cells, intermediate, and superficial in vaginal smear. The thickness of the lower layer (basal) of vaginal cells increases due to the lack of estrogen in menopause. On the other hand, the thickness of the layer between the basal and surface layer decreases due to low estrogen in menopause. Finally, the superficial layer of vaginal cells plays a role in regulating the vaginal pH, whose thickness shrinks in menopause due to estrogen deficiency.

The score within the range of 0–49 indicates the absence or lack of estrogen effect, between 50 and 64 moderate effects, and 65 to 100 a great effect of estrogen.[18] In clinical examination, vaginal atrophy symptoms including vaginal dryness, soreness, burning or itching, and dyspareunia were measured using a 4-point scale (none = 0, mild = 1, moderate = 2, and severe = 3) at baseline as well as 2, 4, and 8 weeks post-intervention.

2.4. Preparation of vaginal cream

Licorice vaginal cream was formulated in the laboratory of the Faculty of Pharmacy at Ahvaz Jundishapur University of Medical Sciences. The components and amounts used for producing vaginal cream were as follows. Oil phase: Vaseline (17% w/w), mineral oil (10% w/w), acetyl alcohol (13% w/w). Aqueous phase: water (30% w/

w) and benzyl alcohol (30%w/w). First, the oil component of the cream mixture was melted in gentle heat in Bain Marie (up to a temperature of approximately 70 °C). Then, benzyl alcohol, monobasic sodium phosphate, and sodium dihydrogen phosphate were dissolved in water and heated in a separate container on Bain Marie to 70 °C. Then, the hydroalcoholic extract of licorice was mixed and completely dissolved in the aqueous phase. During the stirring, it was cooled until it was completely formed, indicating the formation of the cream. At the end, 50 g of cream was stored in laboratory tubes and kept at 15 °C for clinical tests.

The prepared vaginal creams were tested under appropriate physical and chemical analyses. These studies included the study of cream stability, releasing rate (determination of viscosity using a Brookfield Viscometer), and determination of the acidity of the cream (pH), followed by the microbial stability study. Finally, licorice vaginal cream tubes were packed under clean conditions. Safety evaluation was tested in a previous study in the university laboratory.[19]

Placebo cream was also made with the same compounds without adding hydroalcoholic extract.

2.5. Intervention

Seventy postmenopausal women with vaginal atrophy were randomly allocated into two groups after completing the personal-social characteristics questionnaire and written consent letter. The first researcher (MS) who was blind asked participants to take the licorice vaginal cream 2% or placebo as a full applicator over a period of 8 weeks at bedtime. The researcher and the participants were completely unaware whether the creams were therapeutic or placebo with the tubes filled with vaginal cream by a pharmacist. Every participant received a phone call weekly regarding correct consumption of licorice or placebo vaginal cream. If the subjects did not want to continue the study, had sensitivity to the drug, and forget to use the drug than one night, they were excluded from the study.

2.6. Outcome measurements

The participants referred back to the centers 2, 4, and 8 weeks after the start of the study to be reexamined and followed up. Vaginal smear and pH measurement were conducted in the first referral visit, before the intervention, and in the last referral visit; however, other symptoms were measured at each visit (at baseline, 2, 4, and 8 weeks after intervention). In the referral visits, the post-treatment checklist was completed, necessary clinical and laboratory tests were repeated, and the results were compared.

2.7. Statistical analysis

Data analysis was performed using SPSS 22.0 at the significance level of 0.05. In order to compare the two groups in terms of quantitative changes before and after the intervention, T-test was utilized. One-way analysis of variance was employed to compare quantitative changes before and after the therapy between the two groups and the basic values. Also, the chi-square test was utilized to compare the qualitative variables.

Further, repeated measures of analysis of variance was used. Data were tested for normality, where the Mauchly test was applied for sphericity. As the Mauchly test was significant, and indicated a violation of the assumption of sphericity, we used the Greenhouse-Geisser adjustment, which showed a significant difference between the changes over time. Also, using F test, a significant difference was found between the changes in the two groups.

The sample size was calculated as 28 women, according to the results of the study by Yaralizadeh et al.[20] and using the formula for comparing two independent means when $P_1 = 0.36$ and $P_2 = 0.033$ plus using 90% power. Considering the attrition risk of about 20% during the study and $\alpha = 0.05$, the final sample size was calculated 35 in each group (total 70 women).

$$n = \frac{(1.96 + 0.78)^2_{0.36(1-0.36)+0.033(1-0.033)}}{(1-0.033)^2} = 28$$

3. Results

The mean age of women in the licorice group was 56.40 ± 4.29 and in the placebo group were 56.17 ± 4.73 years old. The results indicated that the two groups were similar at baseline in terms of age, menopausal duration, age of menarche, sexual intercourse frequency per month, body mass index, economic status, level of education (Table 1).

As evident in Table 2, at baseline, none of the subjects (0%) in either groups had a vaginal cells maturation index with 65–100 in MVI category. This improved significantly to 82.9% in licorice group and 11.4% in placebo group after 8 weeks of therapy ($p < 0.001$).

As a primary outcome, the vaginal dryness, vaginal itching, vaginal soreness, and dyspareunia were improved after 2 weeks of treatment in licorice group compared to the placebo group, which continued in 4 and 8 weeks after the treatment. Also, the average of vaginal mucus cells changed from the baseline cells to intermediate and superficial cells within and between the two groups after treatment. Specifically, after the treatment, the mean of baseline cells in licorice group was (7.3 ± 6.24) significantly lower than that in the placebo group (23.4 ± 36.2) ($p < 0.001$) (Table 3). Further, Table 4 presents descending pH levels over time where such changes were significantly different across treatment groups ($p < 0.001$).

All participants in the control group continued their cooperation to the end of the study course. On the other hand, in the case group two women were excluded in the first week because of adverse effects of drug; one woman because of vulvovaginal itching and burning sensation and the other due to face skin erythema (Fig. 1). However, there was not any significant difference between the two groups with regards to side effects ($p = 0.49$). According to the results, 94.3% of the women in the licorice group compared to only 57.1% of the women in the placebo group were satisfied with using

Table 1
Comparison of the socio-demographic characteristics in the study groups.

Characteristics	Licorice (n = 35) M±SD	Placebo (n = 35) M±SD	p-value*
Age (year)	56.40 ± 4.29	56.17 ± 4.73	0.83
The first day of the last menstruation (year)	5.62 ± 3.22	6.45 ± 3.47	0.30
Age of menarche (year)	11.97 ± 1.40	12.20 ± 1.58	0.52
Number of intercourse per month	3.02 ± 1.12	3.28 ± 1.15	0.34
BMI	26.71 ± 2.54	26.67 ± 2.89	0.95
Education, n (%)			0.94
Illiterate	12 (34.3)	14 (40)	
Under diploma	19 (54.3)	17 (48.6)	
Diploma	4 (11.4)	4 (11.4)	
Economic status, n (%)			0.86
Poor	18 (51.4)	20 (57.1)	
Average	12 (34.3)	10 (28.6)	
Good	5 (14.3)	5 (14.3)	

Table 2
Comparison of mean MVI and PH change in the licorice and placebo groups before and 8 weeks after the treatment.

	Licorice (n = 35)	Placebo (n = 35)	p-value*
	n (%)	**n (%)**	
MVI			
Before therapy			
0-49	35 (100)	35 (100)	0.31
50-64	0 (0%)	0 (0%)	
65-100	0 (0%)	0 (0%)	
MVI, M (SD)	17.70 (10.03)	20.11 (9.88)	
8 weeks after therapy			
0-49	2 (5.7)	21 (0.60)	0.001
50-64	2 (5.7)	10 (28.6)	
65-100	29 (82.9)	4 (11.4)	
MVI, M (SD)	85.18 (15.75)	45.77 (21.39)	
P-value**	0.001	0.001	
pH			
Before therapy			
<5	0 (0%)	0 (0%)	0.38
5–5.49	6 (17.1)	5 (14.3)	
5.5–6.49	19 (54.3)	16 (45.7)	
<6.49	10 (28.6)	14 (40.0)	
8 weeks after therapy			
<5	31 (88.6)	5 (14.3)	0.001
5–5.49	2 (5.7)	8 (22.9)	
5.5–6.49	0 (0)	13 (37.1)	
<6.49	0 (0)	9 (25.7)	
P-value**	0.001	0.001	

* Between the groups.
** Within the groups.

Table 3
Comparison of the mean percentage of vaginal mucus cells in the licorice and placebo groups before and after the treatment.

Vaginal mucus cells	Group Follow-up time	Licorice n = 35 M±SD	Placebo n = 35 M±SD	p-value
Surface cells	Before therapy	7.9 ± 9.12	6.2 ± 9.14	0.80
	After therapy	23.9 ± 67.81	24.9 ± 32.7	0.001
	P-value	0.001	0.001	
Intermediate cells	Before therapy	11.87 ± 18.39	14.4 ± 21.5	0.26
	After therapy	30.2 ± 32.9	15.7 ± 27.8	0.001
	P-value	0.01	0.03	
Base cells	Before therapy	14.6 ± 73.12	16.33 ± 69.28	0.21
	After therapy	7.3 ± 6.24	23.4 ± 36.2	0.001
	P-value	0.001	0.001	

the drug ($p < 0.001$).

4. Discussion

This study aimed to evaluate the effect of the licorice vaginal cream for vaginal atrophy in postmenopausal women. The equal baseline characteristics such as mean age, the menopausal duration, age of menarche, intercourse times/month, body mass index, economic status, and level of education emanated from a precise randomization.

The results of this study showed that licorice could increase the maturation vaginal index and decrease the vaginal pH. This reduction of pH and elevation of MVI may due to the fact that licorice has isoflavones as herbal estrogens. Hajirahimi et al.'s study indicated that licorice compared to other herbs could significantly control the menopausal symptoms.[14] Asgari et al. (2016) conducted

Table 4
Comparison of vaginal dryness, soreness, itching, and dyspareunia in the licorice and placebo groups at 2, 4, and 8 weeks post-treatment (68 patients).

	Licorice (n = 35) **n(%)**	Placebo (n = 35) **n(%)**	p-value*
Vaginal dryness			
Before therapy	2.65 ± 0.59	2.68 ± 0.63	0.84
2 weeks	1.8 ± 0.71	2.28 ± 0.62	0.004
4 weeks	0.74 ± 0.50	2.14 ± 0.77	<0.001
8 weeks	0.58 ± 0.28	1.97 ± 0.95	<0.001
*P − Value	<0.001	<0.001	
**P −Value	>0.001		
Itching			
Before therapy	1.54 ± 1.06	1.28 ± 1.07	0.26
2 weeks	0.37 ± 0.59	1.20 ± 1.05	<0.001
4 weeks	0.02 ± 0.16	1.08 ± 1.06	<0.001
8 weeks	0.00 ± 0.00	1.02 ± 1.09	<0.001
*P − Value	<0.001	<0.001	
**P −Value	>0.001		
Vaginal soreness			
Before therapy	1.34 ± 0.05	1.28 ± 1.01	0.75
2 weeks	0.57 ± 0.69	1.20 ± 1.02	0.003
4 weeks	0.05 ± 0.23	1.14 ± 1.06	<0.001
8 weeks	0.00 ± 0.00	1.14 ± 1.06	<0.001
*P − Value	<0.001	<0.001	
**P −Value	>0.001		
Dyspareunia			
Before therapy	2.74 ± 0.61	2.77 ± 0.54	0.75
2 weeks	1.82 ± 0.70	2.17 ± 0.78	0.003
4 weeks	0.60 ± 0.73	2.11 ± 0.83	>0.001
8 weeks	0.05 ± 0.23	1.85 ± 0.97	>0.001
*P − Value	<0.001	<0.001	
**P −Value	>0.001		

* Greenhouse test shows a significant difference between changes over the time in both groups.
** The F test shows a significant difference between the two groups over time.

a study in which 380 mg licorice extract, three times per day or placebo were used for two groups of menopausal women. They found that the level of quality of life increased significantly.[15] In a study by Menati et al., 60 postmenopausal women were randomized into two groups, where 380 mg licorice extract, and 0.625 mg conjugated Estrogen with 2.5 mg medroxyprogesterone, two times per day for three months were used. The results suggested that the average frequency, duration, and severity of hot flushes in licorice group were the same as hormonal therapy.[16]

Also, the results revealed that the average variation of MVI after the intervention was 66.08 and 25.65 in the licorice and placebo groups, respectively. In this regard, there was a significant difference between the two groups ($p < 0.001$).

The maturation vaginal index reflects the percentage of three types of major vaginal mucus cells, including base, intermediate, and superficial cells. This index, ranging from 0 to 100, indicates the effects of estrogen on the vaginal wall. The range of 0–49 shows shortage or lack of estrogen, 50–64 average effect of estrogen, and 65–100 great effect of estrogen.[21]

With regard to changes in MVI, the results of the present study were in agreement with the results found by Shah et al.,[22] who studied the effect of vaginal estrogen cream on vaginal atrophy in menopausal Indian women. In their study, 50 postmenopausal women aging 40–80 years with symptoms of vaginal atrophy were selected and were treated using 0.5 g of vaginal estrogen cream twice a week over a period of 12 weeks. Every month, the clinical scores of genital health and MVI were checked and compared to the baseline data. The results indicated that the average numbers of superficial and base cells in the beginning were 7.70 ± 10.45 and 45.80 ± 31.35 respectively, which reached 36.84 ± 27.48 and 2.36 ± 5.32 post intervention. In the present study, it was concluded

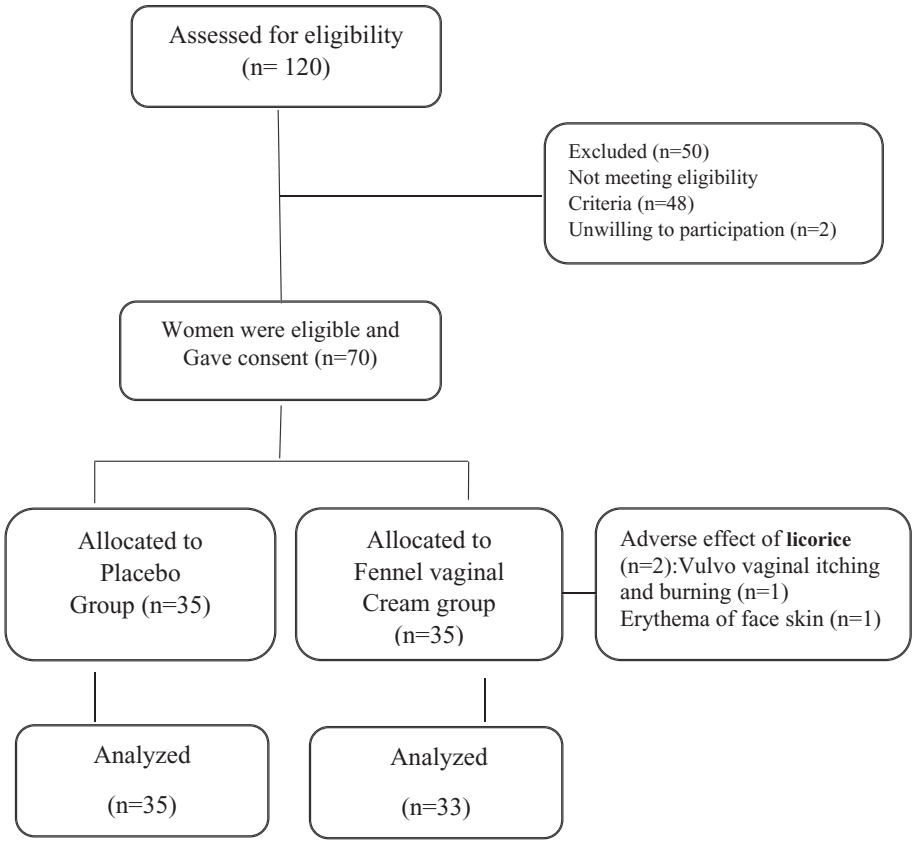

Fig. 1. Flow diagram of recruitment and retention of participants in the study.

that the index of the surface cells in the licorice and placebo groups was 8.71 ± 7.9 and 9.1 ± 6.2, which changed to 74.5 ± 26.5 and 29.5 ± 26.3 respectively after the intervention. Also, the results of the present study were consistent with the study conducted by Yaralizadeh et al.,[20] with regard to MVI. They examined the effect of fennel vaginal cream on MVI in 60 postmenopausal women aging 45–60 in Ahvaz. After 8 weeks of intervention, the results revealed a significant rise in basal cells in the fennel group than in the placebo group. Furthermore, the results of the present study showed that licorice vaginal cream had a significant effect on vaginal pH in postmenopausal women compared to the placebo. In the beginning of the present study, 19 participants (54.3%) in the licorice group and 16 women (45.7%) in the placebo group had vaginal acidity (pH) of over 5 (5.5–6.49). After the intervention, it was observed that vaginal acidity (pH) of 33 licorice women (94.3%) reached below 5 (5.5–6.49) while vaginal acidity (pH) of only 5 placebo women (14.3%) dropped below 5. The results of the present study were well consistent with the study carried out by Tadayon et al., who studied the effect of vitamin D suppository on vaginal atrophy in menopausal women. In their study, they divided 44 menopausal women into two groups. One of the groups employed vaginal vitamin D suppository while the other group received placebo suppository. The mean level of vaginal pH had a significant decrease in the intervention group compared to the placebo group.[23]

Based on this finding, it can be stated that licorice has a positive effect on the growth of superficial cells of the vaginal mucus. Evidence has suggested that elevated pH levels along with decrease in lactobacilli lead to altered natural vaginal flora vaginal vaginal bacterial infections.[23] Specifically, an increase in pH level of vaginal mucus is due to a decline in lactobacilli resulting the formation of bacterial colonies culminating in vaginal infection and inflammation.[24] Although receiving estrogen improves vaginal atrophy and inflammation, it is reported that estrogen enhances the risk of breast and uterine cancer; however, if moisturizers are regularly used, they can have similar effects as steroid hormones in treating dyspareunia, vaginal dryness, and vaginal atrophy.[25]

4.1. Strengths and limitations of the study

This clinical trial study was conducted for the first time for determining the impact of licorice vaginal cream on vaginal cytology. Licorice was made by pharmacology school of Ahvaz Jundishapur University of Medical Sciences itself. One limitation of this study was that we did not follow up patients for the effective duration of licorice.

5. Conclusion

The licorice vaginal cream can improve the signs and symptoms of vaginal atrophy, and maintain the natural vaginal flora in postmenopausal women. Accordingly, licorice vaginal cream is suggested as a natural substance to be used women who have vaginal atrophy and require a drug with a less systemic absorption.

Declaration of interest statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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