

Comparing Two Treatment Methods of Vitamin E Suppository and Conjugated Estrogen Vaginal Cream on the Quality of Life in Menopausal Women with Vaginal Atrophy

Aazam Parnan Emamverdikhan(MSc)¹, Nahid Golmakani (MSc)^{2*}, Noorieh SharifiSistani (PhD)³, Mohammad Taghi Shakeri (PhD)⁴, Malihe Hasanzade Mofrad(MD)⁵, Abolghasem Sajadi Tabassi (PhD)⁶

¹ Graduate, MSC in Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran

² Assistant Professor, Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran

³ Professor, Solid Tumor Treatment Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

⁴ Professor, Department of Biostatistics and Epidemiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

⁵ Associate Professor, Department of Obstetrics and Gynecology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

⁶ Professor, Department of pharmaceuticals, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO	ABSTRACT
<i>Article type:</i> Original article	Background & aim: Menopause is one of the most critical stages in a woman's life. Special attention needs to be paid to the quality of life of menopausal women. Symptoms of genitourinary atrophy can affect women's comfort and quality of life. The aim of this study was to compare two treatment methods of vitamin E suppository and conjugated estrogens vaginal cream on the quality of life of menopausal women with vaginal atrophy.
<i>Article History:</i> Received: 29-Apr-2014 Accepted: 28-Jul-2014	Methods: This clinical trial was performed on 52 menopausal women (40-65 years old), referring to the gynecology clinic of Ghaem Hospital, Mashhad, Iran in 2013. Women were randomly assigned to two groups to use either conjugated estrogens vaginal cream or vitamin E suppository for 12 weeks. Women's quality of life was measured in both groups before the study and 4, 8 and 12 weeks after the interventions. Data collection tools included a demographic questionnaire and Menopause-Specific Quality of Life (MENQOL) questionnaire. Fisher's exact test, repeated measures ANOVA, Mann-Whitney and t-test were performed to analyze data, using SPSS version 11.5.
<i>Key words:</i> Conjugated estrogens Menopause Quality of life Vitamin E	Results: The mean scores of quality of life before intervention and after 4, 8 and 12 weeks of therapy were 70.03±26.34, 53.96±23.75, 43.03±20.62 and 33±18.26 in vitamin E suppository group, respectively. These values in the estrogen cream group were 64±27.83, 50.76±21.51, 37.23±20.96 and 29.53±18.65, respectively. Comparison of quality of life scores between the two groups did not show a statistically significant difference (P>0.05).
	Conclusion: The two groups were not significantly different in terms of the effectiveness of two methods of therapy. Therefore, it seems that vitamin E suppository could be used as an effective method for the improvement of quality of life in patients with vaginal atrophy.

► Please cite this paper as:

Parnan Emamverdikhan A, Golmakani N, SharifiSistani N, Shakeri MT, Hasanzade Mofrad M, Sajadi Tabassi A. Comparing Two Treatment Methods of Vitamin E Suppository and Conjugated Estrogen Vaginal Cream on the Quality of Life in Menopausal Women with Vaginal Atrophy. Journal of Midwifery and Reproductive Health. 2014;2(4): 253-260.

Introduction

Menopause is defined as the permanent

cessation of menstruation for 12 consecutive months (1, 2). During this period, women

* Corresponding author: Nahid Golmakani, Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran. Email: GolmakaniN@mums.ac.ir

experience long-lasting endocrinal, somatic and psychological changes (2).

Despite the increased life expectancy, age of menopause onset or menstruation cessation has not changed and women spend about 30 years or more (over a third) of their lives in menopausal or pre-menopausal period (3).

Vaginal atrophy, secondary to estrogen deficiency, is a common disease during the post-menopausal period (4). Symptoms of vaginal atrophy include vaginal itching, burning, tightness, dryness and bleeding after intercourse; in advanced cases, scarring and intrauterine adhesions may be seen (1, 5, 6). Approximately 75% of women suffer from this condition in the menopausal period (7). As Palacios has stated, prevalence of symptoms due to vaginal atrophy is 15% during the pre-menopausal period and 40-57% in the post-menopausal period (8).

Symptoms of genitourinary atrophy can affect women's comfort and quality of life (5, 9). In a study that examined the effects of menopause on vagina and vulva, negative effects on sexual life, confidence, marital relationship and social life were 40%, 17%, 13% and 7%, respectively (10).

As many subjects stated (32%), vaginal discomfort was related to women's negative attitude towards aging; also, 14% of the subjects associated vaginal discomfort with low quality of life (10).

In menopausal women, quality of life incorporates menopausal signs such as hot flashes, night sweats and vaginal mucosa dryness. Surely, these symptoms affect women's quality of life. In addition, other aspects of quality of life such as health status, life satisfaction and psychological function are of great importance (3).

Nowadays, evaluation of quality of life is a controversial issue in clinical research and includes people's feelings about their physical, emotional and social functioning. World Health Organization (WHO) defines quality of life as a person's perception of his/her life in the culture and value system in which he/she lives and in relation to his/her goals, standards, expectations and priorities (11).

Although no hormones have been associated with increased quality of life, hormonal therapy for symptomatic menopausal women can

improve their quality of life (12). In vaginal atrophy treatment, hormonal and non-hormonal methods including topical and systemic estrogens are used (13). Estrogen increases the content of skin collagens, maintains skin thickness and increases mucopolysaccharides and hyaluronic acids to improve skin moisture and genitourinary symptoms (14).

Huber et al. (2002) aimed to evaluate the effects of tibolone and hormone replacement therapy on the bleeding rate, quality of life and tolerance of menopausal women. Both treatment methods improved women's quality of life, health status, climacteric signs and urinary symptoms (15).

Hormone replacement therapy may improve women's quality of life and lead to decreased symptoms and signs, caused by menopause (16). However, due to several reasons, especially women's fear of the effects of estrogen, only 20-25% of women with symptoms of vaginal atrophy use this treatment modality (17, 18). Therefore, considering the inefficiency of hormonal therapy (as the confirmed treatment for vaginal atrophy) for some people and the associated side-effects, use of medications with fewer side-effects and therapeutic effects on vaginal atrophy is necessary.

Use of non-hormonal methods as first-line therapy for vaginal atrophy has been recommended by some researchers (6, 19). Use of vitamins, as a non-hormonal method, is relatively harmless and highly acceptable (14, 20, 21). In fact, some vitamins such as vitamin A, D and E have been used for the treatment of menopausal disorders and vaginal atrophy (14, 20).

Vitamin E, as an antioxidant, is used to limit oxidative damages and inflammatory diseases (22). This vitamin increases immune responses and improves disease resistance (23). Most effects of vitamin E are due to its antioxidant properties, which improve the function of respiratory system, blood circulation, reproduction, nervous system, and immune system (24). These vitamins keep arteries flexible and elastic, allowing blood to flow freely (25). They also inhibit prostaglandin production and show analgesic effects through stimulating the secretion of morphine-like substances in the nervous system (24).

According to Lark, vitamin E can be an alternative to estrogen (26). In some studies, use of vitamin E oil before intercourse has been reported to be useful (19). Capuron and colleagues (2009) conducted a study entitled, "Vitamin E status and quality of life in elderly people: influence of inflammatory processes". Results of this study showed that people with higher plasma vitamin E concentration (alpha-tocopherol) obtained higher scores in questionnaires related to health status and physical/mental aspects of quality of life (27).

Almost all women experience menopause. Thus, maintaining women's physical and mental health during this period and eradicating problems such as vaginal atrophy due to menopause will improve their quality of life. Given the limited number of studies on non-hormonal treatment of vaginal atrophy and its effect on the quality of life of menopausal women in Iran, this study was performed to compare the efficacy of vitamin E vaginal suppository and conjugated estrogen vaginal cream on the quality of life of menopausal women with vaginal atrophy, referring to the gynecology clinic of Mashhad Ghaem Hospital in 2013.

Materials and Methods

This interventional, clinical trial was performed on 52 menopausal women (40-65 years old), referring to the gynecology clinic of Ghaem Hospital and healthcare centers No. 1 and 3 in Mashhad. The sample size was calculated as 30 patients per group, according to the formula for comparing the means of two independent populations (confidence interval=95%, power=80%).

Cluster sampling was applied, i.e., two healthcare centers (healthcare centers No. 1 and 3) were randomly selected from 5 main healthcare centers of Mashhad; four clusters were selected from healthcare centers No. 1 and 3. By employing easy, accessible sampling, the researcher selected the sample size among women, who met the inclusion criteria and referred to these healthcare centers. Afterwards, the patients were randomly divided into vitamin E suppository and estrogen cream groups.

Inclusion criteria were as follows: 1) age range of 40-65 years; 2) experiencing

menstruation cessation for at least 12 months or follicle-stimulating hormone (FSH) level > 40 international units; 3) no removal of bilateral ovaries (with or without uterus removal) over the past six weeks or more; 4) normal Pap smear over the past 3 years; 5) signs of vaginal atrophy (vaginal burning, itching, dryness and pain during intercourse) according to the patient's self-report and examination by the researcher; 6) Vaginal Maturation Value (VMV) ≤ 55 ; 7) PH>5; and 8) non-stressful events within the last 6 months (since such events can decrease one's quality of life, subjects experiencing stressful events were excluded in order to determine the exclusive effect of vaginal atrophy on quality of life).

Exclusion criteria were as follows: 1) failing to answer all the questions in the questionnaire (considering the credit scoring system, in case of failure to completely answer the questionnaire, the scoring system was confounded and the questionnaire lost its scientific validity); 2) known or suspected endometrial or breast cancer; 3) genital tract abnormalities; 4) abnormal vaginal bleeding; 5) diabetes mellitus; 6) chronic renal diseases; 7) arthritis, cardiovascular diseases, or active liver/gallbladder diseases; 8) use of medications lowering blood pressure (due to the effects of these medications on reducing vaginal lubrication); 9) vaginal infection; 10) allergy to estrogen compounds or vitamin E; and 11) hormonal therapy 8 weeks before the study.

Data collection tools included a demographic questionnaire, forms of laboratory results (including data related to VMV and percentages of superficial, intermediate and basal cells), and Menopause-Specific Quality of Life (MENQOL) questionnaire.

MENQOL questionnaire, designed and standardized by Hyldich and colleagues (1996) at University of Toronto, Canada, is a valid tool for evaluation of quality of life. In addition, Falahzadeh et al. (2008) confirmed the reliability of this questionnaire by Cronbach's alpha in Iran ($\alpha=0.85$) (28).

This tool consists of 29 questions regarding the symptoms and signs of menopause. It includes vasomotor (3 questions), psycho-social (7 questions), physical (16 questions), and sexual (3 questions) domains, measured using a Likert scale (score 1 indicating minimum

severity and score 6 denoting maximum severity); the total score is calculated with respect to each question. Higher scores in each domain indicate lower quality of life and lower scores show higher quality of life.

Validity of laboratory result forms in this study was confirmed by content validity and reliability of the demographic questionnaire was evaluated, using internal reliability ($r=0.7$). The reliability of laboratory result forms was determined using equivalent method ($r=0.8$).

If a patient with symptoms of vaginal atrophy was referred to one of the studied clinics and met the inclusion criteria, she was included in the study. A vaginal discharge sample was obtained for determination of Vaginal Maturation Index (VMI) by shaving 1/3 of the upper wall of vagina inside the cervix using a plastic spatula. To ensure the absence of any problems, Pap smear test was performed for each patient by the researcher and the results were sent to the laboratory, along with vaginal wall samples.

Swab specimens of vaginal wall discharge were taken and evaluated by a pathologist in terms of quality and quantity after staining. Different cellular lines (surface, middle and basal cells) and their percentages were identified and VMV was determined:

$$\text{VMV} = (\text{Percentage of middle cells} \times 0.5) + (\text{percentage of superficial cells})$$

If Pap smear results were normal, PH was > 5 and VMV was ≤ 55 , the person was included in the study.

Before performing the research, study objectives were explained to all subjects and written consents were obtained. Participants in the study were given 12 weeks of treatment

regimen and randomly assigned to either vitamin E vaginal suppository (dosage of 100 IU) or conjugated estrogen vaginal cream (0.625 mg, manufactured by Aboureihan Company) (0.5 g is equivalent to 1.8 of the cream applicator) group.

The patients were advised to use the medications every night during the first two weeks and twice per week for the rest of the intervention (next 10 weeks). In case of any possible side-effects during the treatment, the intervention was interrupted and the MENQOL questionnaire was again completed by the subjects. Among 60 participants in this study, 8 patients (4 cases in vitamin E suppository group and 4 cases in estrogen cream group) were excluded due to improper use or sensitivity to medications.

Fisher's exact test, repeated measures ANOVA, Mann-Whitney and t-test were performed, using SPSS version 11.5.

This study was approved by the ethics committee of Mashhad University of Medical Sciences.

RCT code: IRCT2013060913611N1

Results

The results of this study showed that in the vitamin E suppository group, the mean age of subjects was 52.11 ± 4.70 years, duration of menstruation cessation was 54.46 ± 52.21 months, mean parity was 5 ± 2.78 children, and body mass index (BMI) was 27.25 ± 5.03 kg/m². In the estrogen cream group, the mean age of subjects was 52.88 ± 6.30 years, duration of menstruation cessation was 62.76 ± 59.23 months, mean parity was 5 ± 2.48 children, and BMI was 28.62 ± 4.46 kg/m²; the difference between the two groups

Table 1. Frequency distribution of subjects based on education, occupation, income level and physical exercise

Variables	Estrogen cream group		Vitamin E suppository group		Results of statistical tests	
	N	%	N	%		
Education level	Literate	11	42.3	7	26.9	Mann-Whitney Z= 1.59 P=0.11
	Elementary education	10	38.5	9	34.6	
	Secondary education	2	7.7	3	11.5	
	High school diploma	2	7.7	4	15.4	
Occupation	University degree	1	3.8	3	11.5	Fisher's exact test P>0.99
	Housewife	22	84.6	21	80.8	
Income level	Employed	4	15.4	5	19.2	Mann-Whitney Z= 1.28 P=0.20
	Insufficient	13	50.0	8	30.8	
	Sufficient	10	38.5	14	53.8	
Physical	More than sufficient	3	11.5	4	15.4	Mann-Whitney
	Never	21	80.8	22	84.6	

exercise	Once a week	1	3.8	1	3.8	Z= 0.40
	Twice or three times a week	2	7.7	2	7.7	P=0.68
	More than three times a week	2	7.7	1	3.8	

Table 2. Comparison of the mean scores of quality of life dimensions in subjects after 4, 8 and 12 weeks of treatment in the two groups

Variables	Groups	Baseline	Fourth week	Eighth week	Twelfth week	Repeated measures test results
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Vasomotor	Estrogen cream group	6.88 ± 5.10	4.88 ± 4.78	3.23 ± 3.22	1.73 ± 2.52	P<0.001
	Vitamin E suppository group	9.15 ± 6.43	6.73 ± 5.40	4.80 ± 4.75	3.34 ± 4.48	P<0.001
Psycho-social	Estrogen cream group	14.80 ± 9.02	11.84 ± 7.96	8.92 ± 7.73	6.53 ± 5.81	P =0.002
	Vitamin E suppository group	15.07 ± 8.59	10.76 ± 7.32	8.53 ± 6.46	7.23 ± 6.17	P =0.01
Physical	Estrogen cream group	30.69 ± 16.31	26.42± 12.44	19.42± 11.47	16.23± 11.71	P<0.001
	Vitamin E suppository group	32.42 ± 13.67	26.65 ± 13.10	21.61 ± 11.70	16.50 ± 10.60	P<0.001
Sexual	Estrogen cream group	11.61 ± 4.94	7.61 ± 3.91	5.65 ± 4	5.03 ± 3.52	P<0.001
	Vitamin E suppository group	13.38 ± 3.95	9.80 ± 3.63	8.07 ± 3.48	5.92 ± 3.90	P =0.001

Table 3. Comparison of the mean scores of quality of life after 4, 8 and 12 weeks of treatment between the two groups

Groups	Baseline	Fourth week	Eighth week	Twelfth week
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Vitamin E suppository group	70.03 ± 26.34	53.96 ± 23.75	43.03 ± 20.62	33 ± 18.26
Estrogen cream group	64 ± 27.83	50.76 ± 21.51	37.23 ± 20.96	29.53 ± 18.65
Results of t-test	P =0.42 df=50	P =0.61 df=50	P =0.31 df=50	P =0.50 df=50

was not statistically significant.

Overall, 26.9% of cases in the vitamin E suppository group and 42.3% of subjects in the estrogen cream group were literate; in addition, 80.8% of cases in the vitamin E suppository group and 84.6% of the estrogen cream group were housewives (Table 1).

The obtained results showed that the mean scores of quality of life in vasomotor (P<0.001), psycho-social (P=0.002), physical (P<0.001) and sexual (P<0.001) dimensions after 4, 8 and 12 weeks of treatment significantly decreased in the estrogen cream group. Similarly, the mean scores of quality of life in vasomotor (P<0.001), psycho-social (P=0.01), physical (P<0.001) and sexual (P=0.001) dimensions after 4, 8 and 12 weeks of treatment significantly decreased in vitamin E suppository group (Table 2).

Results showed that the two groups were not

significantly different in terms of quality of life scores after 4, 8 and 12 weeks of treatment (P>0.05) (Table 3).

Discussion

Urogenital atrophy is considered a major health concern in menopausal women (29). This condition is associated with problems such as vaginal dryness, itching, pain during intercourse, bleeding after intercourse, burning and frequent urgent urination (1, 5, 30, 31). These problems have a great impact on the quality of life of menopausal women (5, 9).

In the last two decades, there has been a great deal of concern regarding individuals' quality of life (32). Quality of life is related to mental/personal assessment and is rooted in cultural, social and environmental aspects of one's life. In 1978, WHO reported that receiving psychiatric/physical care and high quality of life

are common human rights (33).

The aim of this study was to evaluate the therapeutic effects of vitamin E suppository and conjugated estrogen vaginal cream on the quality of life of menopausal women with vaginal atrophy. The findings of this study showed that the mean score of quality of life in vasomotor, psycho-social, physical and sexual dimensions significantly decreased in both groups after 4, 8 and 12 weeks of intervention; the score of quality of life in the two groups was not significantly different at the end of treatment period.

Given the function of brain neurotransmitter receptors, estrogen could lead to the perception of sexual pleasure and increase one's quality of life (34). In a study by Huber et al. (2002), effects of tibolone and hormone replacement therapy on bleeding rate, quality of life and tolerance were evaluated on 501 menopausal women under the age of 65 years for 12 months. In this study, Life Enjoyment and Satisfaction Questionnaire was used. The results showed that both treatments improved subjects' quality of life, health status, climacteric signs and urinary symptoms (15).

In a study by Welton et al. (2008), which aimed to determine health-related quality of life after combined hormonal therapy, slight significant improvements were observed in sexual function, sleep problems and vasomotor symptoms (35). Similarly, in a study by Evio and colleagues (2005), use of hormone replacement therapy in menopausal women improved some aspects of quality of life including routine activities and sexual function (36).

In a study by Gautam et al. (2011), performed on Indian women (age range: 45-55 years), three-month (or longer) use of hormone therapy during menopause improved physical, mental, social and environmental parameters; this result was consistent with the findings of the present research and studies by Langdahl and Raymer et al. (37). Similarly, in the study by Mark et al. (2002), hormone therapy improved subjects' quality of life (38). The current findings are similar to previously-mentioned studies, which can be due to similar age range of the subjects and inclusion criteria.

Physiological decline in estrogen and androgen levels during menopause leads to

decreased blood flow to vagina and vulva; as a result, decreased arousal and vaginal dryness lead to decreased genital sensory threshold, dyspareunia and loss of libido. Gonadal hormones typically improve blood flow and sensation in the genital area, improve autonomic sensual responses and cause arousal. It appears that estrogen with direct effects on mood and indirect effects on sexual function and libido has a positive effect on the quality of life of menopausal women (34).

Veerus et al. (2008) conducted a study to report subjects' quality of life after hormone therapy among Estonian postmenopausal women. Quality of Life Questionnaire (EQ-5D) was used in this study. The results showed that hormone therapy reduces vasomotor symptoms and sleep problems, although it does not affect subjects' quality of life (39). The observed discrepancy with the current results may be related to differences in study tools, duration of subjects' follow-up (3.6 years) and cultural backgrounds.

Capuron and colleagues (2009) conducted a study with the aim to determine the relationship between vitamin E status and quality of life in the elderly. Short Form-36 (SF-36) questionnaire was used and 69 subjects were included. Results showed that participants with higher plasma vitamin E concentration (alpha-tocopherol) had a better health status and obtained higher scores in physical and mental aspects of quality of life (27). Although the tools, methods and study population of the mentioned study were different from the current research, results of these two studies were consistent.

Nutritional factors are most likely to affect one's health and mood. Regarding the properties of antioxidants, alpha-tocopherol is able to modulate the function of immune system and regulate inflammatory responses. Recent data indicate that alpha-tocopherol can suppress the destruction of tryptophan in blood mononuclear cells. With regard to the role of tryptophan in mood regulation, the positive relation between plasma vitamin E concentration, health status and quality of life can be explained (27).

Vitamin E in recommended doses is non-toxic and free of side-effects; it can also improve one's quality of life. Therefore, it is hoped that the results of this research promote the application of vitamin E suppositories for relieving

symptoms associated with menopause, especially for those who are not able to use hormone therapy or do not accept its side-effects; in fact, use of these vitamins can improve the quality of life of menopausal women.

In this study, rather than focusing solely on the treatment of vaginal atrophy, consequences and effects of this condition on menopausal women's life were evaluated and women's quality of life was assessed before and after the treatments. Therefore, during treatment, unpleasant consequences of vaginal atrophy on the quality of life should be considered.

One of the limitations of this study was that researchers trusted patients' self-reports about medication use, since they were unable to control the process. Also, cultural differences could affect subjects' answers to the quality of life questionnaire.

Conclusion

In this study, four dimensions of quality of life significantly changed in both groups after the treatments and there was no statistically significant difference in the score of quality of life between the groups at the end of the treatment period. Treatments could reduce menopausal problems, mitigate their severity and improve quality of life. Since quality of life constitutes the basis of healthcare services, researchers hope that the results of this study can be used as background information for future research. Therefore, for patients who cannot use hormonal treatments due to medical conditions, vitamin E suppository is an appropriate option for relieving the symptoms of vaginal atrophy and improving quality of life.

Acknowledgment

This study was extracted from a thesis paper (code: 911186) by Azam Parnan Emamverdikhan, MSc. student of midwifery. This study was funded by the research faculty of Mashhad University of Medical Sciences. Hereby, we appreciate the council of research, laboratory personnel of Mashhad School of Pharmacy and all personnel in the gynecology clinic of Ghaem Hospital and Mashhad healthcare centers (No. 1 and 3).

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Gharekhani P, Sadatiyan A. Women's diseases CMMD. Tehran: Noordanesh publication; 2000. [Persian]
2. Rayan KJ, Berkowitz RS. Kistner's Gynecology & womens Health. 7th ed. Boston: Mosby; 1999. 634-646
3. Forouhari S, Safari Rad M, Moattari M, Mohit M, Ghaem H. The effect of education on quality of life in menopausal women referring to Shiraz Motahhari clinic in 2004. Journal of Birjand University of Medical Sciences. 2009; 16(1):39-44.
4. Lima SM, Yamada SS, Reis BF, Postigo S, Galvao da Silva MA, Aoki T. Effective treatment of vaginal atrophy with isoflavone vaginal gel. Maturitas. 2013; 71(3):252-258.
5. Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th ed. Lippincott Williams & Wilkins; 2005. P: 552-599.
6. Chism L. Overcoming resistance and barriers to the use of local estrogen therapy for the treatment of vaginal atrophy. International Journal of Women's Health. 2012; 4:551-557.
7. Panjari M, Davis S. Vaginal DHEA to treat menopause related atrophy: A review of the evidence. Maturitas. 2011; 70 (1):22-25.
8. Palacios S. Managing urogenital atrophy. Maturitas. 2009; 63(4):315-318.
9. Huang AJ, Moore EE, Boyko EJ, Scholes D, Lin F, Vittinghoff E, et al. Vaginal symptoms in postmenopausal women: self-reported severity, natural history, and risk factors. Menopaus. 2010; 17(1):121-126.
10. Parish SJ, Nappi RE, Krychman ML, Kellogg-Spadt S, Simon JA, Goldstein JA. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. International Journal of Women's Health. 2013; 47:437-447.
11. Mohaddsi H, Ayatollahi H, Hasanzade G, Yegansangi M. Quality of life in breast cancer patients: Study in the Omid cancer research center- Urmia. Iranian Journal of Breast Disease. 2013; 5(4):35-43.
12. Sanjari N. 2012 Hormone therapy position statement from NAMS: Benefits and Risks of Hormone Therapy. Obstetrician and Gynecologist Journal. 2012; 7:52-66.
13. Ziagham S, Abbaspoor Z, Abbaspoor MR. Effect of hyaluronic acid and vitamin E vaginal tablets on atrophic vaginitis: A randomized controlled trial. African Journal of Pharmacy and Pharmacology. 2012; 6(45): 3124-3129.
14. Castelo-Branco C, Cancelo M, Villero G, Nohales F, Juli M. Management of post-menopausal vaginal

- atrophy and atrophic vaginitis. *European Menopause Journal*. 2005; 52(1): 46-52.
15. Huber J, Palacios S, Berglund L, Ha`nggi W, Sathanandan SM, Christau S, et al. Effects of tibolone and continuous combined hormone replacement therapy on bleeding rates, quality of life and tolerability in postmenopausal women. *International Journal of Obstetrics and Gynaecology*. 2002; 109(8):886-893.
 16. Maasoumi R, Zieaie S, Faghihzade S. Comparing the effects of tibolone and continuous hormone replacement therapy on the vaginal maturation index and value in menopausal women. *Koomesh Journal*. 2012; 13(4):397-404.
 17. Reiter S. Barriers to effective treatment of vaginal atrophy with local estrogen therapy. *International Journal of General Medicine*. 2013; 6:153-158.
 18. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez G, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Journal of the North American Menopause Society*. 2009; 16 (5):907-922.
 19. Tadayon M, Rad P, Abbaspour MR, Latifi SM, Rashidi I, Barati M, et al. The Effect of Vitamin D Suppository on Atrophic Vaginal Mucosa in Menopausal Women. *Armaghane-danesh, Yasuj University of Medical Sciences Journal (YUMSJ)*. 2012; 17(3): 187-195.
 20. Costantino D, Guaraldi C. Effectiveness and safety of vaginal suppositories for the treatment of the vaginal atrophy in postmenopausal women: an open, non-controlled clinical trial. *European Review for Medical and Pharmacological Sciences*. 2008; 12(6): 411-416.
 21. Rahimi M, Ziaee S, Babaei G, Rabiei M. The Effect of Vitamin E in the Treatment of Menorrhagia in Patient with Dysfunctional Uterine Bleeding. *Medicine Daneshvar Journal*. 2009; 16 (82):59-66.
 22. Cook-Mills JM, McCary CA. Isoforms of vitamin E differentially regulate inflammation. *Endocrine, Metabolic & Immune Disorders Drug Targets*. 2010; 10(4):348-366.
 23. Meydani M. Effect of functional food ingredients: vitamin E modulation of cardiovascular diseases and immune status in the elderly. *American Journal of Clinical Nutrition*. 2000; 71(6): 1665s-1668s.
 24. Seddighi A, Ziei S. Effect of vitamin E on prevention of menstrual Migraine. *Medicine Daneshvar Journal*. 2008; 15(74): 23-30.
 25. Vitamin E (tocopherol). 2005-2006. Available at: <http://www.vitamins-supplements.org> Accessed: Jan 21, 2013.
 26. Feinstein A. Treatment with vitamins. 1st Edition. Translation: Haghbir H. Tehran: Afarinegan Publisher,2000; P: 413-591. [Persian]
 27. Capuron L, Moranis A, Combe N, Cousson-Gélie F, Fuchs D, Smedt-Peyrusse V, et al. Vitamin E status and quality of life in the elderly: influence of inflammatory processes. *British Journal of Nutrition*. 2009; 102(10):1390-1394.
 28. Makvandi S, Bastami A, Shoushtari SZ, Yazdizadeh H, Etemadpour Y, Taghavifar SA. Quality of life and its related factors in postmenopausal women referred to Ahvaz East Health Center, Iran, 2012. *Iranian Journal of Obstetrics, Gynecology and Infertility*. 2013; 16(59): 6-13.
 29. Berek JS, Novak E. Berek and Novak's Gynecology. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. P: 522-529.
 30. Donne M, Caruso C, Mancuso A, Costa G, Lemmo R, Pizzimenti G, et al. The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause *Archives of Gynecology and Obstetrics*. 2011; 283(6): 1319-1323.
 31. Marxa P, Schade G, Wilbourn S, Blank S, Moyer D, Nett R. Low-dose (0.3 mg) synthetic conjugated estrogens A is effective for managing atrophic vaginitis. *Maturitas*. 2004; 47(1): 47-54.
 32. Zlatonovic L. The role of the person's self-concept in quality of life research. *Facta Universitatis-Series Philosophy, Sociology, Psychology and History*. 2000; 2(7):391-397.
 33. Nourani SH, Jonaidy E, Shakeri MT, Mokhber N. Comparison of Quality of life in Fertile and Infertile Women Referred to the Public Clinics in Mashhad. *Iranian Journal of Obstetrics, Gynecology and Infertility*. 2012; 15(7): 24-31.
 34. Eftekhari T, Akhoondzadeh S, Ghanbari Z, Iranshahr R, Haghollahi F. Effect of vaginal estrogen on post menopausal mood & sleep disturbance/ and sexual satisfaction. *Tehran University Medical Journal*. 2009; 67(2): 118-124.
 35. Welton, AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ*. 2008; 337: a1190
 36. Evio S, Pekkarinen T, Sintonen H, Tiitinen A, Valimaki MJ. The effect of hormone therapy on the health-related quality of life in elderly women. *Maturitas*. 2007; 56(2): 122-128.
 37. Sharif niya H, Bahrami N, Saatsaz S, Soleymani MA, Nazari R, Mohamad Tabar R. Assessment of Life Quality of Menopausal Women and Its Relative Factors. *Iranian Journal of Obstetrics, Gynecology and Infertility*. 2012; 15(31):7-12.
 38. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA, HERS Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin

- Replacement Study (HERS) trial. *JAMA*. 2002; 287(5):591-597.
39. Veerus P, Fischer K, Hovi SL, Karro H, Rahu M, Hemminki E. Symptom reporting and quality of life in the Estonian Postmenopausal Hormone Therapy Trial. *BMC Womens Health Journal*. 2008; 8(1): 5.