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LETTERS

A prospective randomized comparative study of the effects of intranasal and transdermal 17 β-estradiol on postmenopausal symptoms and vaginal cytology

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ABSTRACT

Context: Investigating the adverse effects of oral hormone replacement therapy (HRT), the clinical effectiveness of alternative combinations and route of administrations. **Aim:** To compare the effects of intranasal and transdermal 17β-estradiol combined with vaginal progesterone on vasomotor symptoms and vaginal cytology. **Settings and Design:** A 12-week, prospective, randomized comparative study was conducted between July 2005 and September 2006. **Materials and Methods:** Eighty postmenopausal women aged between 42-57 years, who had scores of ≥1.7 on the menopause rating scale-I (MRS-I) items "1-6", were randomly assigned to receive intranasal (300 µg/day, $n=40$) or transdermal (50 µg/day, $n=40$) 17β-estradiol continuously. All patients also received a vaginal progesterone gel twice weekly. Vasomotor symptoms were evaluated at weeks 0, 4, 8 and 12. Vaginal maturation index (VMI) was evaluated at weeks 0 and 12 of the study. **Statistical Analyses:** The Mann-Whitney *U* and the Wilcoxon tests were used. $P < 0.05$ was regarded as significant. **Results:** Thirty-two women in the intranasal and 29 women in the transdermal group completed the study. The total score of the MRS, the sum-scores of Factor 1 "HOT FLUSHES" and Factor 2 "PSYCHE" significantly decreased in both groups at week 4. Factor 3 "ATROPHY" scores significantly decreased only in the transdermal group at week 12. The VMI showed no changes within and between the two groups at the end of the study. **Conclusion:** Intranasal and transdermal 17β-estradiol combined with vaginal progesterone gel as a continuous HRT caused a similar decrease in vasomotor symptoms but did not have any significant effect on VMI after 12 weeks of treatment in this study population.

KEY WORDS: Intranasal estradiol, menopause rating scale, transdermal estradiol, vaginal maturation index, vaginal progesterone

Perimenopause is a transitional period when vasomotor and urogenital symptoms associated with the postmenopausal period have a major impact on health-related quality of life (HRQoL). Frequent vasomotor symptoms with disturbed sleep and depressive symptoms, experienced by about 70% of women, can be disabling, affecting a woman's social life, psychological health, sense of wellbeing and ability to work.[1] Estrogen deficiency occurring during menopause may affect the whole body. The urogenital symptoms including urgency, urinary tract infections, atrophic vaginitis, dryness and dyspareunia accompanying sexual dysfunction often worsen with time, affecting up to 38% of menopausal women. Reduction of ovarian steroids at menopause is clearly responsible for these problems.[2]

In recent years, there has been a growing awareness of the aspects of HRQoL and aging. Hormone replacement therapy (HRT) has a beneficial effect on HRQoL including sexual functioning in women with climacteric symptoms.[3] Hormone replacement therapy is a widely used and accepted medication for climacteric[4] and urogenital symptoms.[5,6]

However, there has been a suspicion about HRT, especially its oral forms and high doses because of adverse reactions and fear of cancer. For this reason, other routes of administration and low doses have been researched for the best results. It has been shown that oral and transdermal estrogens have several limitations. In fact orally administered estrogen is subjected to significant intestinal and hepatic first-pass metabolism.[7] Oral estrogen formulations cause hypertriglyceridemia[8] and increase the risks of gallbladder disease[9] and thromboembolism.[9,10] Transdermal estrogen patches avoid the first-pass metabolism, but are associated with variable systemic absorption,[11] skin irritation[12] and loss of patches due to poor adhesion.[13] Some progesterones may diminish the beneficial effects of HRT on coronary heart disease and negatively affect mood. Oral and higher doses of progesterones, especially those derived from 19-nortesterone may have metabolic disadvantages as compared to

low doses of transdermal, vaginal or intrauterine progesterone formulations.[14]

However, intranasal administration of 17β-estradiol (E_2) is at least as effective as oral administration of 2 mg/day E_2 in alleviating postmenopausal symptoms, with less frequent mastalgia and uterine bleeding and without the metabolic consequences of the first-pass effect.[15] Also, it is well-tolerated and provides a reproducible, easily adjustable dosing mechanism.[16] Sustained-release vaginal progesterone gel ensures high endometrial protection and avoids the side-effects and possible risks linked to oral progesterones.[17,18]

We aimed to compare the effects of intranasal and transdermal 17β-E_2 combined with vaginal progesterone gel as a continuous HRT on postmenopausal symptoms measured by the menopause rating scale-I (MRS-I), one of the modern scales for menopausal complaints with high levels of reliability[19,20] and on vaginal cytology in postmenopausal women in this prospective randomized study.

Materials and Methods

Eighty healthy and symptomatic postmenopausal women with an intact uterus, aged 42-57 years old, were eligible to participate in this prospective and randomized study performed in a university hospital between July 2005 and September 2006.

Patients eligible for inclusion had at least six months amenorrhea and elevated follicle-stimulating hormone levels (FSH > 40 mIU/mL), low E_2 (E_2 < 20 pg/ml), scores of ≥1.7 on the MRS Items 1-6 or scores of ≥ 0.3 on MRS Item 1(hot flushes) before treatment. Normal results of mammography, cervical cytology and biochemical tests at enrolment were prerequisites for inclusion. None of the patients had used HRT for at least six months before the study enrolment. Patients with a history of severe allergic rhinitis, intolerance to nasal or transdermal delivery systems or general contraindications to HRT were excluded. Concomitant therapy with agents used for the symptomatic relief of hot flushes and any nasal treatment or medicinal products capable of altering nasal mucosa were prohibited.

All patients gave written informed consent before participation in the trial, which was conducted in accordance with the Declaration of Helsinki and with the approval of the local ethics committee.

Eighty postmenopausal women were randomly assigned to one of two treatments: intranasal 17β-E_2 300 μg/day (Aerodiol®; Servier Laboratories, Courbevoie, France) one spray in each nostril every morning (n=40) or transdermal 17β-E_2 50 μg/day (Climara®; Berlex Laboratories, Inc. Schering AG, Germany) once a week (n=40) continuously for 12 weeks. All patients received a sustained-release vaginal progesterone gel (Crinone® 8%; Ares-Serono International S.A, Switzerland) twice weekly.

There were five clinical visits: two pre-treatment visits (screening at week -2 and screening at baseline -week 0) and three treatment visits (at weeks 4, 8 and 12). Menopausal symptoms were evaluated before the treatment (at week 0) and at weeks 4, 8 and 12. Vaginal cytology was evaluated at the beginning (at week 0) and the end of the treatment (at week 12).

Menopausal symptoms were evaluated by using the MRS-I which comprises 10 items about symptom severities ranging from 0.0 (no symptoms) to 1.0 (very severe symptoms) and provides an individual symptom profile for each patient. The severity of each symptom was defined as mild (0.1-0.3), moderate (0.4-0.5), severe (0.6-0.7) and very severe (0.8-1.0)[21] [Table 1].

According to a factor analytical study MRS items are not independent and can be combined.[22] The MRS items loaded on three main factors. In this three-factorial system, MRS Items 1-3 (hot flushes/sweating, heart complaints, sleep disorders) loaded on Factor 1 "HOT FLUSHES". Items 4-6 (depressive moods, nervousness/irritability and impaired performance/memory) loaded on Factor 2 "PSYCHE". Items 7-10 (disorders of sexuality, urinary symptoms, vaginal dryness, joint and muscle symptoms) loaded on Factor 3 "ATROPHY"[22] [Table 2].

The severity of menopausal symptoms was recorded according to the MRS questionnaire [Table 1] by the patients themselves for seven days preceding weeks 0, 4, 8 and 12. The mean values were calculated for each MRS item. The composite score for each of the three subscales was based on adding up the scores of the items of the respective dimensions. The "total score" was the sum of the sum-scores of the three subscales.

Vaginal smears for hormonal evaluation were taken from the right and left lateral vaginal walls (midway between the fornix and introitus). Cytology assessments were performed by three

Table 1: Menopause rating scale questionnaire

Item number	Item
1	Ascending feeling of heat, outbreaks of sweating (frequency, severity)
2	Palpitations, racing heart, galloping heart, feeling of being stifled
3	Difficulty falling asleep, difficulty staying asleep, waking up too early
4	Despondency, sadness, weepiness, lack of drive, mood swings
5	Nervousness, inner tension, aggressiveness
6	Physical and mental fatigue, difficulty concentrating, forgetfulness
7	Decrease in sexual desire, sexual activity and satisfaction
8	Complaints on urination, frequency to urinate, involuntary urination
9	Feeling of dryness in the vagina, difficulties with sexual intercourse
10	Pain mainly in the finger joints, rheumatic-like pains, tingling

Please answer all ten questions by crossing the vertical line as in the example below:

Complaints

none mild moderate severe very severe

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

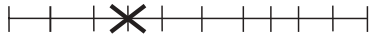

Table 2: Menopause rating scale-I

Subscales	Item	Symptom group	Climacteric symptoms
Factor I	1	Hot flushes, sweating	Sensation of rising heat, outbreaks of sweating (frequency / intensity per 24h)
"HOT FLUSHES"	2	Cardiac symptoms	Palpitations, racing heartbeat, irregular beats, tightness in chest
	3	Sleep disorders	Difficulty in falling asleep, difficulty in remaining asleep through the night, waking too early
Factor II	4	Depressive moods	Despondency, sadness, tearfulness, lack of drive, mood fluctuations
"PSYCHE"	5	Nervousness, irritability	Nervousness, inner tension, aggressivity
	6	Impaired performance/memory	Susceptibility to physical and mental exhaustion, poor concentration, forgetfulness
Factor III	7	Disorders of sexuality	Reduced libido, sexual activity and satisfaction
"ATROPHY"	8	Urinary symptoms	Symptoms during urination, frequent need to pass urine, accidental incontinence
	9	Vaginal dryness	Feeling of dryness of the vagina, symptoms during sexual intercourse
	10	Joint and muscle symptoms	Pain predominantly affecting the finger joints, rheumatic symptoms, itching

cytopathologists blinded to the treatment. Vaginal maturity index (VMI) was defined as the percentage of parabasal, intermediate and superficial cells. Parabasal, intermediate and superficial cells were counted and the percentage of each cell type was calculated.

Values were expressed as mean±standard deviation (SD). Intergroup comparisons of data were made with Mann-Whitney *U* test. The Wilcoxon test was used to compare data within groups. $P < 0.05$ was regarded as significant**.** For VMI analysis, the mean percentages of each cell type of the intranasal 17β-E_2 group were compared with the counterpart data of the transdermal 17β-E_2 group. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 9.0 for Windows (SPSS Inc.; Chicago, Ill, USA).

Results

Sixty-one patients completed the study (32 women in the intranasal group and 29 women in the transdermal group) [Figure 1]. A total of 19 patients were lost to follow-up. At baseline, there was no significant difference in demographic characteristics (age, age at menopause, duration of menopause, weight, height and body mass index) and variables (total score of MRS item hot flushes, sum scores of Factor 1, 2 and 3) between the two groups [Table 3].

Compared to baseline values, the total score of the MRS-I, the sum-scores of Factor 1 "HOT FLUSHES" and Factor 2 "PSYCHE" significantly decreased four weeks after the initiation of therapy and the sum-score of MRS Item 1 (hot flushes) significantly decreased eight weeks after the initiation of therapy in both groups.

Compared to baseline values, the significant decrease in the mean total MRS score at the fourth, eighth and 12th weeks of therapy in the intranasal E_2 group [P =0.043 (CI, 0.040-0.054); P =0.003 (CI, 0.002-0.004) and P =0.001 (CI, 0.00-0.001), respectively] was comparable to the decrease observed in the transdermal E_2 group [P = 0.008 (CI, 0.006-0.009); P =0.006 (CI, 0.005-0.008) and P =0.015 (CI, 0.013-0.017), respectively].

Compared to baseline values, the significant decrease in the sum-scores of Factor 1 "HOT FLUSHES" at the fourth, eighth and 12th weeks of the therapy in the intranasal E_2 group [P =0.048 (CI, 0.043-0.052); P =0.001 (CI, 0.000-0.001) and P =0.015 (CI, 0.013-0.018), respectively] was comparable to the decrease observed in the transdermal E_2 group [P = 0.011 (CI, 0.009-0.012); P =0.001 (CI, 0.000-0.001) and P =0.014 (CI, 0.011-0.016), respectively].

Compared to baseline values, the significant decrease in the sum-scores of Factor 2 "PSYCHE" at the fourth, eighth and Twelveth weeks of the therapy in the intranasal E_2 group [P =0.049 (CI, 0.046-0.053); P =.002 (CI, 0.001-0.003) and P =0.036 (CI, 0.029-0.043), respectively] was comparable to the decrease observed in the transdermal E_2 group [P = 0.003 (CI, 0.002-0.004); P =0.001 (CI, 0.000-0.002) and P =0.019 (CI, 0.017-0.022), respectively].

Table 3: Baseline characteristics of participants completing the study (mean±SD)

	INT E_2* (n=32)	TTS E_2† (n=29)	P
Age (years)	49.0±3.8	50.1±2.4	0.342
Age at menopause (years)	45.7±3.9	48.0±2.5	0.089
Duration of menopause (months)	39.4±37.5	25.0±30.0	0.302
Weight (kg)	72.3±9.1	73.9±9.5	0.593
Height (cm)	157.2±5.6	157.6±3.3	0.542
Body mass index (kg/m²)	29.2±3.5	29.4±3.5	0.790
Total score of menopause rating scale	2.88±1.03	3.37±0.71	0.760
Item hot flushes	0.37±0.14	0.50±0.24	0.207
Sumscore of Factor 1 "HOT FLUSHES"	0.95±0.41	1.15±0.38	0.115
Sumscore of Factor 2 "PSYCHE"	0.95±0.28	1.28±0.55	0.051
Sumscore of Factor 3 "ATROPHY"	1.04±0.48	1.22±0.56	0.344

*INT E_2 - Intranasal estradiol; †TTS E_2 - Transdermal estradiol

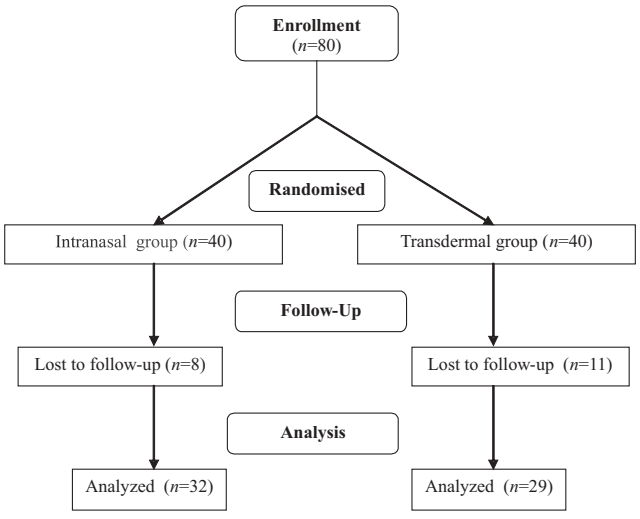

Figure 1: The study protocol

The sum-score of Factor 3 "ATROPHY" reduced in both groups, but reached a significant value only in the transdermal E_2 group 12 weeks after the initiation of therapy [$P = 0.020$ (CI, 0.017-0.022)]. However, there was no significant difference between the groups in terms of changes in vasomotor symptoms ($P > 0.05$).

Compared to baseline values, the significant decrease in the sum-score of MRS Item 1 (hot flushes) only at the eigth and 12th weeks of the therapy in the intranasal E_2 group [$P = 0.025$ (CI, 0.022-0.028) and $P = 0.029$ (CI, 0.026-0.032), respectively] was comparable to the decrease observed in the transdermal E_2 group [$P = 0.029$ (CI, 0.026-0.033) and $P = 0.033$ (CI, 0.030-0.037), respectively].

The changes in the mean values of all scores of variables are illustrated [Figure 2].

Vaginal cytology, expressed as mean percentage of VMI, did not change significantly in both groups at the end of the treatment and there was no significant difference between the groups [Table 4].

In the intranasal group, the most frequent adverse events were nasal symptoms which were mostly mild in intensity (nose itching in two and rhinorrhea in six patients) and in the transdermal group erythema at the application site in nine patients and poor adhesion of patches in one patient. The incidence of moderate to severe mastalgia in both groups was low (four and two in the intranasal and transdermal groups respectively). The intensity of vaginal bleeding was mild in both groups and did not cause withdrawal of treatments.

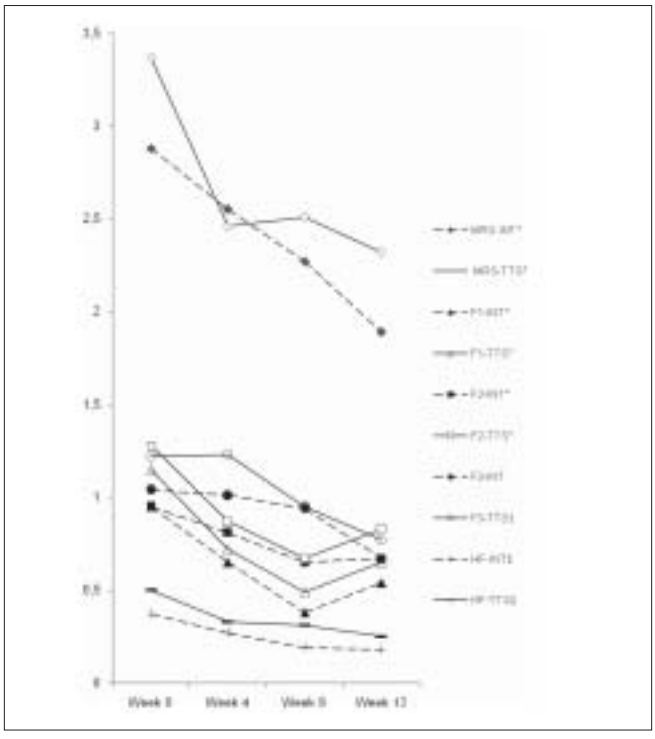

Figure 2: Changes in climacteric symptoms measured by the MRS I and subscores of three factors.
MRS = Total score of MRS, INT = Intranasal estradiol, TTS = Transdermal estradiol, F1 = Factor 1 'hot flush', F2 = Factor 2 'psyche', F3 = Factor 3 'atrophy', HF = MRS Item 1 (hot flushes). Values compared to baseline; *$P < 0.05$ for all measures, †$P < 0.05$ only at the end, and ‡$P < 0.05$ after 8 weeks of the treatment

Discussion

This study showed that intranasal and transdermal estradiol combined with intravaginal progesterone as a continuous HRT reduced vasomotor symptoms to the same degree after 12 weeks of therapy. Both treatment modalities decreased the total score of the MRS, the sum-score of Factor HOT FLUSHES and the sum-score of Factor PSYCHE after four weeks of treatment and the sum-score of the item hot flushes after eight weeks of treatment. The sumscore of Factor 3 "ATROPHY" decreased insignificantly in the intranasal E_2 group and there was no significant difference in Factor 3 "ATROPHY" between intranasal and transdermal estradiol. Both treatment modalities have similar effects on atrophy.

Table 4: The effects of intranasal and transdermal estradiol on vaginal maturation index in terms of mean percentage of parabasal / intermediate / superficial cells

	Baseline		*P*	Week 12		*P*
	INT E_2* (*n*=32)	TTS E_2† (*n*=29)		INT E_2* (*n*=32)	TTS E_2† (*n*=29)	
Index	10/87/3	2/89/9	.052 /.965 /.458	1/89/10	0/85/15	.850 /.930 /.186
Index	10/87/3	-	-	1/89/10	-	.058 /.876 /.067
	-	2/89/9	-	-	0/85/15	.767 /.764 /.653

*INT E_2 - Intranasal estradiol; †TTS E_2 - Transdermal estradiol

Clinical equivalence of intranasal and oral[15,16,23] or transdermal 17β-E_2[24] for menopausal symptoms has been shown previously. Studd *et al*. reported that the Kupperman Index value in the group taking intranasal estradiol 300 μg/day was similar to that achieved by patients receiving estradiol 2 mg.[16] Another study showed that systemic exposure to estradiol was dose-dependent and that the dose of 300 μg gave an estimated 24h systemic exposure to exogenous E_2 close to that of a 50 μg/day reservoir patch or 2 mg tablet.[25] This formulation has been shown to be effective in a dose-dependent manner.[16] The dose of 300 μg in one administration per day offers the optimal efficacy/acceptability ratio and is a suitable dose for initiating estrogen therapy whilst being easily adaptable to each patient's clinical response.[26] In the present study, the initial dose of intranasal estradiol was 300 μg/day and because this dose was sufficient for the relief of climacteric symptoms, the patients did not need a change in the initial dose.

Since it is well known that hypoestrogenism causes vasomotor symptoms and changes vaginal cytology, we decided not to include a placebo comparison group in this trial. Furthermore, our aim was not to evaluate the effects of menopause on these variables. Also, it was demonstrated that intranasal [27] and transdermal E_2[4] reduced the incidence of vasomotor symptoms when compared to placebo.

There is compelling evidence that HRT alleviates climacteric symptoms, especially vasomotor symptoms. Improvement is usually obtained within four weeks.[4] Consistent with the literature, in the present study intranasal E_2 decreased vasomotor symptoms after four weeks of treatment. Lopes *et al*. demonstrated that the Kupperman Index score was markedly and significantly reduced in the intranasal and transdermal E_2 groups of patients who received dydrogesterone 10 or 20 mg/day for 14 days per 28-day cycle on completion of the 12-week randomized treatment period. They found that intranasal and transdermal estrogen delivery systems had equivalent efficacy and similar safety profiles.[24] Rozenbaum *et al*. demonstrated that compared with placebo, intranasal E_2 300 μg/day and 150 μg/day significantly reduced the incidence of moderate to severe vasomotor symptoms after 8-12 weeks of treatment respectively and the mean Kupperman index at weeks 4 and 12 respectively. Furthermore, using visual analogue scales, they observed that intranasal estradiol 300 μg/day significantly reduced urogenital, psychological and vasomotor symptoms at week 4 compared with placebo.[27] Studd *et al*. found in their study on the efficacy of different doses of intranasal E_2, postmenopausal symptoms were alleviated after four weeks of therapy compared with placebo. Oral estradiol and that pair-wise comparisons showed a significant reduction in the Kupperman index score of the groups receiving intranasal E_2 300 μg/day and 400 μg/day compared with placebo. They were administered once daily throughout the study period of weeks 0-12 and then for a further two weeks, supplemented each evening by medroxyprogesterone acetate 5 mg to promote endometrial shedding. The incidence of hot flushes per day was reduced by intranasal therapy at both week 4 ($P<0.05$) and week 12 ($P<0.01$).[16] Pelissier *et al*. showed that climacteric symptoms significantly improved after six weeks of treatment in groups receiving doses ranging from 200 to 900 μg daily for 21 days or 25-30 days per month with one to five-day treatment-free period and progesterone therapy in the form of dydrogesterone, chlormadinone acetate, nomegestrol acetate, medrogestone and micronized progesterone depending on the gynecologist's choice for the last 10-14 days of each cycle of estrogen therapy.[26]

Intranasal E_2, in combination with continuous or sequential progestogens, also exhibits good endometrial safety and patient acceptability in postmenopausal women.[28] In general, side-effects due to estrogen combined with progestagen are mild although they may be severe in a small percentage of women. Known adverse reactions caused by progestagen alone include edema, breast effects (e.g. mastalgia, increased breast size), skin and hair effects (e.g. rash, melasma, acne, hirsutism and alopecia), headache and psychological effects (e.g. mood swings, irritability, fatigue and depression). Uterine bleeding is the primary adverse effect associated with HRT. Some progestogens may diminish the beneficial effects of estrogen on coronary heart disease and negatively affect mood.[15] Because of the side-effects and possible risks of oral synthetic progestins, we preferred to use vaginal progesterone gel to prevent endometrial hyperplasia. Currently, sustained-release vaginal progesterone gel is used twice weekly as a continuous combined HRT and ensures high endometrial protection and avoids the side-effects and possible risks linked to synthetic progestins.[17,18]

The HRQoL refers to the effects of an individual's physical state on all aspects of psychosocial functioning. There are many different ways of assessing the quality of life during menopause. In the last 40 years, a number of researches have used the Kupperman Index or the Blatt-Kupperman index[5] for the characterization and quantification of menopausal symptoms.[29] In the previous studies which evaluated the effects of intranasal E_2, Kupperman Index was used for assessing the menopausal symptoms.[15,16,23,24,26,27] The Kupperman Index does not meet accepted standards of psychometrics today and it now needs to be reassessed. The scale combined physician and patient assessments, but the relative contributions of each are unclear. The index does not include two frequently described climacteric symptoms: vaginal dryness and loss of libido. The terms included in the index are not defined and some are no longer in common use.[29] Since the MRS is a HRQoL scale and was developed in response to lack of standardized scales to measure the severity of aging-symptoms and their impact on the HRQoL,[30] it was successfully used in the present study to compare efficacy of intranasal and transdermal E_2.

The 'gold standard' for diagnosing atrophic vaginitis is still cytohormonal analysis of the vaginal epithelium. Several ratios are used –karyopyknotic index, maturation value and the maturation index—all of which are expressed as numeric values.[31] Estrogen therapy relieves hot flushes and treats urogenital atrophy by restoring urogenital health. With estrogen use, women report less vaginal irritation, pain, dryness or burning during intercourse. Increased libido, when linked to dyspareunia,

may also be noted with estrogen use. This contributes to an improved HRQoL for many women.[32]

It was suggested previously that 300 μg/day intranasal estradiol and 2 mg oral micronized E_2 increased the karyopyknotic index in 90% and 92% of the patients respectively, with no significant difference between the two arms at week 14.[15] In the present study, although vaginal superficial cells were slightly stimulated by the two treatment regimens, no significant change was observed within the groups. Also, there were no differences in terms of the changes in the percentage of vaginal cells compared to baseline values between the groups. Although symptoms such as vaginal dryness, soreness, dyspareunia, recurrent vaginitis and cystitis from colonic germs, post coital cystitis, nocturia, urinary frequency and urgency respond well to estrogens, improvement may take several months and in cases of severe atrophy, initial combination of HRT and local therapy may be followed by local therapy alone, which may be given topically. Long-term treatment is often required as symptoms can occur on cessation of therapy.[3]

Factor 3 "ATROPHY" involves not only the variable "atrophy" but also other variables such as joint pain and therefore, scoring "atrophy" can be subjective. In addition, intravaginal progesteron may have exerted its effects on the vaginal epithelium and partly modified the results.

In the present study, treatment was well tolerated and any adverse effect did not lead to treatment withdrawal in both groups.

Conclusion

Intranasal and transdermal 17β-estradiol combined with vaginal progesterone gel as a continuous hormone replacement therapy similarly decreased vasomotor symptoms after 12 weeks of treatment.

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