



A SUPPLEMENT TO

Ob.Gyn. News

CLINICAL PERSPECTIVES ON THE ROLE OF HORMONE THERAPY IN MENOPAUSAL MANAGEMENT



TOPIC HIGHLIGHTS

**Menopause and Hormone Therapy
The Cardiovascular Paradox
Current Recommendations for
Postmenopausal Hormone Therapy
Effective Low-Dose Therapy
Clinical Trial of
Transdermal Estrogen
Other Considerations of Transdermal
Hormone Therapy**

FACULTY

Donna Shoupe, MD
*Professor, Department of
Obstetrics and Gynecology*
Keck School of Medicine
University of Southern California

Steven R. Goldstein, MD
Professor of Obstetrics and Gynecology
New York University School of Medicine

WITH COMMENTS FROM:

Daniel R. Mishell Jr, MD
Keck School of Medicine
University of Southern California

Alfred Moffett Jr, MD, FACOG
University of South Florida
College of Medicine

Lee P. Shulman, MD, FACOG, FACMG
Feinberg School of Medicine
Northwestern University

President, Elsevier/IMNG
Alan J. Imhoff

Program Manager
Jenny R. McMahon

Clinical Editor
Charles Bankhead

National Account Manager
Joe Schuldner

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Lehner & Whyte, Inc.

Production Specialist
Tracy Law

This supplement is based on physician interviews. It was supported by



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CLINICAL PERSPECTIVES ON THE ROLE OF HORMONE THERAPY IN MENOPAUSAL MANAGEMENT

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FACULTY

Donna Shoupe, MD
*Professor, Department of
Obstetrics and Gynecology*
Keck School of Medicine
University of Southern California

Steven R. Goldstein, MD
*Professor of Obstetrics
and Gynecology*
New York University
School of Medicine

WITH COMMENTS FROM:

Daniel R. Mishell Jr, MD
Lyle G. McNiele Professor
Department of Obstetrics/Gynecology
Keck School of Medicine
University of Southern California

Lee P. Shulman, MD, FACOG, FACMG
Professor and Chief
Division of Reproductive Genetics
Department of Obstetrics and Gynecology
Feinberg School of Medicine
Northwestern University

Alfred Moffett Jr, MD, FACOG
Clinical Assistant Professor
Obstetrics and Gynecology
University of South Florida
College of Medicine
OB-GYN Associates of Mid-Florida, P.A.

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CLINICAL PERSPECTIVES ON THE ROLE OF HORMONE THERAPY IN MENOPAUSAL MANAGEMENT

INTRODUCTION

Over the past 50 years, the landscape of demographics in the United States has changed dramatically, resulting in an older population that continues to grow older. Between 1950 and 2005, the US population increased from 151 million to 296 million, representing an annual growth rate of 1.2%.¹ During the same time period, the number of individuals aged 65 years and older increased from 12 million to 37 million, an annual growth rate of 2.0%. The population aged 75 years and older had the most rapid rate of growth, increasing from 4 million to 18 million for an annual rate of 2.8%.² Currently, the fastest-growing segment of the US population is the group of people aged 85 years of age and older.²

The aging of the population has special implications for women. The World Health Organization estimates that the worldwide population of menopausal women will reach 1.2 billion by the year 2030, almost triple the number in 1990.³ Currently, in the United States, about 42 million women are older than 50 years of age, increasing to 52 million by the end of this decade.⁴ For most women, menopause and the postmenopausal period account for a third of their lifespan. The transition to menopause brings with it a multitude of health-related considerations, not the least of which is the issue of hormone therapy (HT).

Since the 1950s, HT has served as the cornerstone for management of postmenopausal symptoms. Data from clinical studies consistently showed that HT effec-

tively minimized or prevented some of menopause's most troublesome symptoms, particularly vasomotor symptoms or hot flashes.^{5,6} The clinical efficacy translated into tremendous growth in the use of HT to manage menopausal symptoms, reaching an apex in the 1990s. From 1995 to 1999, the number of prescriptions for HT increased from 58 million annually to 90 million.⁷

In 2002, the clinical momentum for HT came to an abrupt halt. Long-awaited results of the Women's Health Initiative (WHI) study of HT to reduce the risk of heart disease and cancer in postmenopausal women showed that women taking HT actually had an increased risk of heart disease and heart attack, stroke, and invasive breast cancer compared to women taking placebo.⁸ The impact of the WHI findings on clinical use of estrogen and combined HT was swift and dramatic. By the end of 2003, prescriptions for HT had declined to 57 million.⁶ The decline has continued, and some estimates place current use of HT for menopausal symptoms at less than 20 million prescriptions.⁹

Though greatly diminished compared to years past, use of HT to manage menopausal symptoms has not disappeared. Instead, researchers and clinicians have turned to low-dose therapy and newer formulations that deliver low doses as safer alternatives to conventional high-dose oral therapy. The results have been encouraging, as low-dose therapy does appear to offer improved safety with no loss of efficacy.

Menopause and Hormone Therapy

The primary indication for HT is treatment of vasomotor symptoms, or hot flashes. Irregular ovarian function and fluctuation in circulating estrogen levels lead to climacteric symptoms, particularly hot flashes, which appear to result from small increases in core body temperature.¹⁰ Between two thirds and three fourths of menopausal women have hot flashes.^{11,12} The frequency, severity, and duration vary. Among women who have hot flashes, most report daily episodes lasting between 1 and 5 minutes.¹³ Hot flashes persist for 1 to 5

years, with a tendency toward the upper end of the range.^{11,12}

Especially severe or frequent hot flashes can adversely affect quality of life. Some evidence suggests that women who have severe flushing and sweating are more likely to have other symptoms, including tenseness and tiredness.¹⁴ Numerous randomized, controlled clinical trials have evaluated HT's impact on vasomotor symptoms, and the results have consistently demonstrated a beneficial effect.⁵ A meta-analysis of 14 clinical trials demonstrated a significant reduction in the number of weekly hot flashes

compared to placebo, regardless of whether women received conjugated equine estrogen or 17 β -estradiol.⁶

Potential Adverse Effects

One of the most controversial aspects of HT has been its association with breast cancer. The data have not been uniformly consistent at times. In the WHI, women who received combined HT had a 24% increased relative risk of breast cancer compared to women who received placebo.¹⁵ Women who received only estrogen had an 18% lower risk of invasive breast cancer compared to the placebo

group.¹⁵ A report from the Nurses Health Study also revealed no increased risk of breast cancer in women who had undergone hysterectomy and received unopposed estrogen.¹⁶ Some evidence suggests the risk of breast cancer relates more to the duration of HT rather than to HT *per se*.¹⁷

HT with unopposed estrogen has a well-documented risk of endometrial cancer, ranging from twofold higher with less than 5 years' exposure to more than a sixfold increased risk with longer duration of exposure.¹⁸ Data from multiple studies, including the WHI, have shown no increased risk of endometrial cancer in women treated with combined HT (estrogen and progestin).⁵

An association between HT and thromboembolism emerged from the Heart and Estrogen/Progestin Replacement Study (HERS).¹⁹ The trial, designed to evaluate the cardioprotective effects of HT, showed an early increased risk of adverse events including thromboembolism, which dissipated with increased duration of therapy and actually turned into a reduced risk.

The Cardiovascular Paradox

An abundance of epidemiologic and observational data have demonstrated an apparent cardioprotective effect of female hormones.²⁰ HT continued to produce evidence of cardiovascular benefits in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.²¹ PEPI involved 875 healthy postmenopausal women who were randomized to receive placebo or one of five different hormonal regimens. All five of the intervention groups had favorable changes in lipid levels compared to the placebo group.

Clinical Trial Data

Until recently the promise of cardioprotection with HT began to fade after the PEPI results, as two large clinical trials failed to show an effect of HT on cardiovascular risk. The first of the studies was the previously mentioned HERS trial.¹⁹ The study involved 2,763 postmenopausal women with existing coronary artery disease (CAD). They were randomized to continuous HT or placebo and followed for an average of 4.2

“Initiation of hormone therapy early in the menopause is associated with a good risk-benefit ratio. Use of a transdermal formulation of estrogen removes the single largest adverse event— thromboembolism—from the clinical equation and thus is the preferred route of administration, a fact that many clinicians might not yet recognize or appreciate.”

Alfred Moffett Jr, MD, FACOG

years. The study showed no overall benefit on the risk of CAD events. The event rate actually increased in the HT patients during the first year of the study, and a subsequent decrease in event rates in the HT group did not entirely offset the early increased risk. HT did have a favorable effect on lipid levels, as low-density lipoprotein cholesterol decreased and high-density lipoprotein cholesterol increased in patients who received HT.

HERS was followed several years later by the WHI, which was 10 times larger.⁸ More than 27,000 healthy women participated in the study, which examined the issue of whether combination HT could prevent CAD in women who were free of the disease at enrollment. After more than 5 years of follow-up, the trial failed to show a beneficial effect of HT on cardiovascular risk. In fact, the investigators concluded that the risks of HT exceeded the benefits and that combination HT has no role in the prevention of heart disease.

However, the announcement of the principal findings from WHI did not end the cardiovascular chapter in the HT clinical story. Follow-up in the WHI will continue through 2010 and include periodic analyses of the data. One such analysis showed that patients who began HT soon after the onset of menopause appeared to have a reduced risk of cardiovascular disease.²² Women who began HT after they were well into menopause had an increased risk,²² similar to the HERS population whose mean age was about 65 years.

Most recently, another report from WHI investigators provided more

evidence of a beneficial effect of HT in younger women.²³ The analysis showed that women taking estrogen had a significantly lower coronary calcium score compared to women in the placebo group ($P=0.02$). Moreover, the data revealed a significant advantage for estrogen compared to placebo with respect to the odds for having a coronary calcium score >0 , >10 , and >100 . Women who had the highest adherence rates for estrogen derived even greater benefit with respect to coronary calcification ($P=0.01$ to $P<0.001$).

Impact of Clinical Trials

Several members of organized medicine have taken a special interest in issues surrounding the use of HT, and several have weighed in with opinions and position statements. In November 2005, the American Society of Reproductive Medicine sponsored a workshop to bring together authorities in HT to evaluate and discuss the current status of HT. Members of 18 different organizations were invited to participate, representing themselves and not the various organizations. After reviewing the evidence, the participants concluded that healthy, symptomatic women should be offered HT for menopausal symptoms.⁵ For many younger patients, they further agreed, the benefits of menopausal symptom relief outweigh the risks. Participants in the workshop emphasized that HT is not effective for prevention of heart disease. They also agreed that the increased cardiovascular risk observed in some studies primarily involves older patients.⁵

Current Recommendations for Postmenopausal Hormone Therapy

As data emerged from the WHI and other studies, clinical recommendations have been developed and revised in accordance with the data. Many of the recommendations, including updates, are available through the National Guidelines Clearinghouse (available online at <http://www.guideline.gov>). Organizations that have weighed in on the issue of postmenopausal HT include:

- **North American Menopause Society.** Treatment of moderate-to-severe vasomotor symptoms remains the primary indication for HT.²⁴

- **American Society for Reproductive Medicine.** Current indications include treatment of moderate to severe vasomotor symptoms. Neither estrogen nor combined hormonal therapy should be used for prevention of cardiovascular disease or associated events.²⁵
- **American Association of Clinical Endocrinologists.** HT is prescribed during early menopause for relief of menopausal symptoms. Consideration should be given to use of transdermal formulations whenever possible for treatment of vasomotor symptoms. HT is not indicated for cardiovascular prevention. The guiding principle of therapy, regardless of indication, is to use the lowest possible dose for the shortest possible duration.²⁶
- **American Heart Association.** A panel of experts representing a dozen different medical and scientific organizations developed guidelines for cardiovascular prevention in women. Among its recommendations, the panel stated that neither estrogen nor combined hormonal therapy should be used to prevent cardiovascular disease in postmenopausal women.²⁷
- **US Preventive Services Task Force.** No form of HT should be used to prevent chronic diseases in postmenopausal women.²⁸
- **American College of Obstetricians and Gynecologists.** HT is appropriate for relief of menopausal symptoms, including hot flashes, as long as a woman has discussed the risks and benefits with her physician. HT should not be used to prevent disease, including heart disease. When a woman chooses to use HT, she should take the smallest effective dose for the shortest possible time and review her decision annually with her physician.²⁹

Effective Low-Dose Therapy

Even before the WHI results became available, a trend toward low-dose HT had begun. The unsettling findings from the study accelerated that trend. In January 2003, just 6 months after publication of the WHI findings, the US Food and Drug Administration (FDA) released a Fact Sheet that affirmed HT as the most effective treatment for postmenopausal symptoms. However, the

FDA also emphasized that HT “should be used at the lowest doses for the shortest duration to reach treatment goals”³⁰ A year later, the FDA issued updated information for women about postmenopausal HT, as well as suggested product labeling changes to reflect the WHI findings. The agency reaffirmed its support of using the lowest effective dose of HT for the shortest duration needed to treat the symptoms.³¹

The FDA has acknowledged that the most appropriate dose or doses of HT remain undefined. Few direct comparisons of low- and high-dose therapies have been reported. However, the data that are available suggest low-dose HT is safe and effective. A review of randomized, controlled trials comparing low-dose HT with placebo showed that low-dose formulations improved menopausal symptoms compared to placebo and caused fewer adverse effects, such as irregular bleeding and breast tenderness. When compared to standard-dose therapy, low-dose HT had a comparable effect on menopausal symptoms.³² Another review of randomized, controlled trials showed that low-dose HT reduced the frequency and intensity of vasomotor symptoms for as long as 24 months and had an adverse event profile similar to that of placebo.³³

Other recent reports have bolstered the safety and effectiveness of low-dose HT. Data from the Estrogen and Thromboembolism Risk (ESTHER) study group suggested that the risk of thromboembolism associated with HT is limited to higher-dose oral formulations.³⁴ ESTHER was a multicenter, case-control study of venous thromboembolism (VTE) in postmenopausal women in France. Investigators compared 271 women with documented VTE and 610 age-matched controls. The results showed that women using higher-dose oral estrogen had an odds ratio for VTE of 4.2 compared to women who were not using estrogen. In contrast, women using transdermal estrogen had the same VTE risk as women who were not using estrogen.

Recent reviews of HT have revealed additional evidence that low-dose and transdermal formulations control vasomotor symptoms as well as oral HT but with fewer adverse effects. In particular, transdermal

estrogen preparations appear to be associated with a reduced risk of VTE compared to oral therapy.^{35,36}

A question that has been raised in clinical practice: Why is transdermal HT for postmenopausal symptoms associated with a reduced risk of VTE, but transdermal formulations of contraceptives are not? The contraceptive patch releases substantial levels of ethinyl estradiol, which is much more potent than the estradiol in low- and very low-dose transdermal HT for the menopause. With the contraceptive patch, substantial levels of ethinyl estradiol enter the circulation and stimulate the clotting system. Transdermal HT releases much lower doses of the less potent estradiol, and the amount of hormone introduced into circulation is too low to have a significant effect on clotting factors.

Clinical Trial of Transdermal Estrogen

Development of a transdermal delivery system for HT provided new means for investigating the safety and efficacy of low-dose therapy. A recent clinical evaluation of 0.06% 17 β -estradiol in a hydroalcoholic gel base (marketed as ElestrinTM) demonstrated beneficial effects with one of the lowest-dose formulations developed to date.³⁷

“The estradiol gel recently approved by the Food and Drug Administration delivers only 0.0125 mg of estradiol systemically, an effective low dose of estradiol approved for treatment of postmenopausal vasomotor symptoms. It was encouraging to see that the data presented in the study conducted by Simon et al demonstrated that this low dose showed no evidence of endometrial hyperplasia at 12 weeks. Thus, the beneficial effects of estrogen on vasomotor symptoms in women with a uterus can be obtained without the deleterious effects of systemic progestins on the risk of coronary heart disease and breast cancer.”

Daniel R. Mishell Jr, MD

The compound delivers a nominal daily dose of 0.0125 mg of 17β-estradiol. A major objective of the study was to determine the lowest effective dose for treatment of vasomotor symptoms in postmenopausal women, keeping with the principles set forth by the FDA.

Simon et al³⁷ conducted a randomized controlled trial involving 484 postmenopausal women who reported having at least 60 episodes of hot flashes weekly (Tables 1-3). The phase III trial was conducted at 28 sites in the United States and two in Canada. The study population consisted of women at least 18 years of age who had undergone natural or surgical menopause. Natural menopause was

defined as amenorrhea for at least 12 months prior to screening for the trial. Surgical menopause included women who had bilateral oophorectomy with or without hysterectomy at least 6 months before screening.

All patients had laboratory confirmation of menopausal status. Inclusion criteria for the trial included serum estradiol level <20 pg/ml, follicle stimulating hormone level >40 mIU/ml, and a body mass index of 18 to 35. Women recorded the frequency, timing, and severity of hot flashes over the first 14 days of a 3- to 4-week screening period. Only those women with at least 60 episodes a week were eligible for the trial.

The patients were randomized to four different treatment groups:

- 0.87 g/d of estradiol gel (N=136)
- 1.7 g/d (N=142)
- 2.6 g/d (N=69)
- Placebo gel (N=137)

Patients applied the assigned topical treatment daily to a small area of the upper arm for 12 weeks. The primary endpoints of the study included the change from baseline in hot flash frequency and severity, measured after 4 and 12 weeks. The patients recorded daily hot flash episodes in a diary, noting the time, duration, and intensity of each episode.

Between 93% and 97% of women in each treatment group completed the study. Study participants' ages ranged between 28 and 74 years, and time since onset of menopause ranged from 5 months to 43 years. A majority of the patients had a history of hormone therapy for hot flashes. Mean number of hot flashes ranged between 12.9 and 13.5 per day, and severity averaged 2.4 on a scale of 0-3.

Between weeks 3 and 5, all three active-treatment groups had statistically significant decreases in the frequency of hot flashes compared to placebo. At week 3, patients assigned to the 1.7 g/d dose had a statistically significant difference of 2.8 compared to placebo ($P=0.007$), and patients who self-administered 2.6 g/d had a net decrease of 4.1 episodes compared to placebo ($P<0.001$). By week 5, participants receiving 0.87 g/d of estradiol gel had a net decrease of 2.2 episodes compared to the placebo group ($P<0.001$). Statistically significant differences from placebo were maintained through week 12 in all three groups of patients receiving active therapy.

Significantly more patients on active treatment (all groups) had at least a 50% reduction in moderate-to-severe hot flashes by week 4 ($P<0.001$). By week 12, a majority of patients treated with the 0.06% 17β-estradiol gel had at least a 50% reduction in the frequency of hot flashes, whereas fewer than half of the placebo group had reductions of that magnitude ($P<0.001$). Significantly more patients treated with active estradiol gel had 80%, 90%, 95%, and 100% reductions in hot flash episodes.

Table 1. Mean Change From Baseline in Daily Moderate-to-Severe Hot Flush Rate³⁷

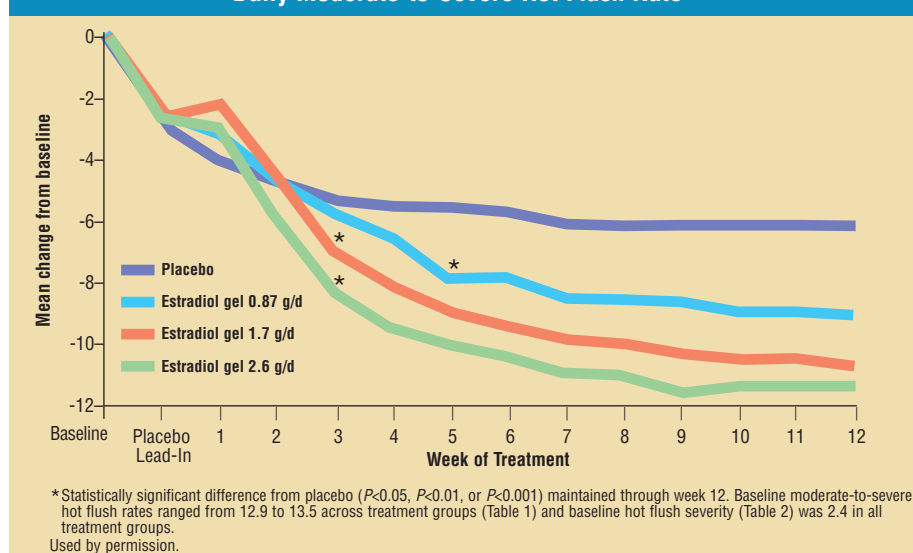
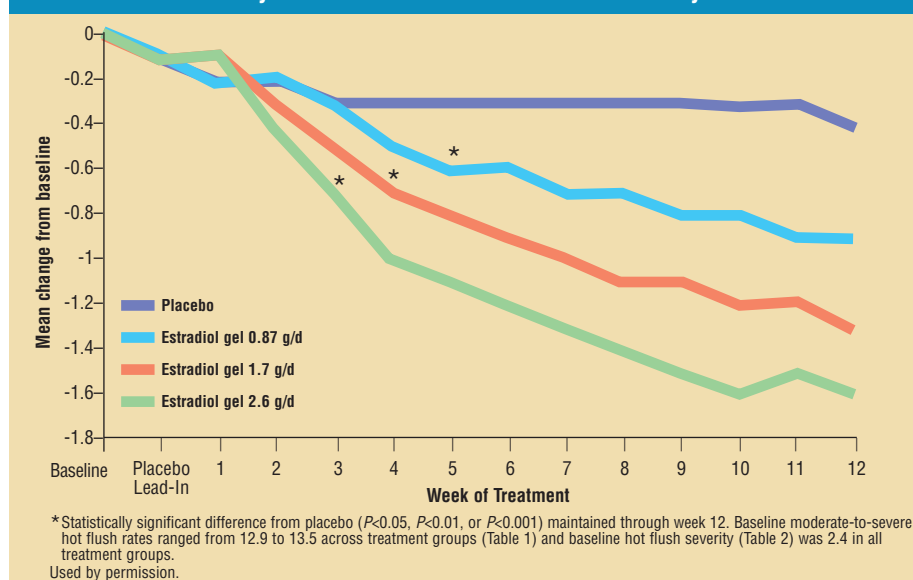


Table 2. Mean Change From Baseline in Daily Moderate-to-Severe Hot Flush Severity³⁷



On the basis of the reductions in hot flash episodes, the investigators calculated that the number needed to treat (NNT) for benefit for the 0.87 g/d dose would be 3.2, 4.2, 4.5, and 6.3 for reductions of 80%, 90%, 95%, and 100%, respectively. For the 2.6 g/d dose, the NNTs would be 1.7, 1.8, 1.8, and 2.3 for the same reductions at week 12.

Improvement in vasomotor symptoms with the transdermal estrogen therapy correlated with significant improvement in quality of life compared to placebo. Patients on active therapy had statistically significant improvement in the vasomotor, psychosocial, and physical domain scores of the Menopause Quality of Life (QoL) scale.

The incidence of treatment-emergent adverse events increased slightly with the dose of active therapy, from 59% in the 0.87 g/d group to 68% in the 2.6 g/d group. However, the rates were only marginally higher than in the placebo group (56%). Reproductive system and breast disorders were the most common treatment-emergent adverse events that differed significantly between treatment groups ($p < 0.001$). Application-site adverse effects were uncommon in patients on active treatment. Dryness

occurred in 1% to 4% of patients across the three groups receiving active therapy and erythema in 2% to 3% of each group

As discussed in the study conducted by Simon et al, the two higher doses of the 0.06% 17 β -estradiol gel significantly decreased postmenopausal vasomotor symptoms before the pre-defined efficacy landmark time point of 4 weeks, consistent with current FDA guidance for establishing efficacy for this indication.³⁸ The 0.87 g/day dose demonstrated a significant effect compared to placebo at week 5. Given that finding, a dose lower than 0.87 g/day would be unlikely to demonstrate efficacy within 4 weeks in a similar patient population.

The 0.87 g/day dose, which provides a nominal daily delivery of 0.0125 mg of 17 β -estradiol, significantly reduced the frequency and severity of hot flashes through the end of the study. This symptomatic improvement correlated with improved quality of life, as assessed by a validated QoL survey instrument. Of note, only a small proportion of patients treated with this dose reported a 100% reduction in hot flash frequency by week 4, suggesting that the probability that a lower dose of 17 β -estradiol would relieve hot

“The most common problem associated with the onset of menopause is vasomotor instability. Ongoing research has better delineated the physiological changes responsible for menopausal vasomotor symptoms and will hopefully lead to the development of effective therapies. However, the most effective current treatment for “hot flashes” remains estrogen therapy. The recent approval of a daily transdermal gel delivering a low but effective systemic dose of estradiol (0.0125 mg) represents a new and important option for women and clinicians seeking reliable and safe treatment for hot flashes.”

Lee P. Shulman, MD,
FACOG, FACMG

flashes by 100% at 4 weeks is very low.

As Simon and colleagues³⁷ noted, low-dose HT for menopausal symptoms confers a potential for multiple beneficial effects. Compliance with therapy might increase because of a decreased incidence and severity of treatment-related adverse effects. Moreover, use of low-dose therapy might increase the likelihood of patients’ continuing treatment for menopausal symptoms.

A transdermal formulation of estradiol that delivers a nominal daily dose of 0.014 mg of 17 β -estradiol, currently approved for treatment of osteoporosis, carries a labeling recommendation for 14 days of progestin treatment every 6 to 12 months and yearly endometrial biopsies.³⁹ In the study conducted by Simon et al, none of the patients treated with the 0.87 g/day dose of estradiol gel developed endometrial hyperplasia or any other suspicious endometrial changes. In contrast, the highest dose of the gel formulation was associated with some cases of hyperplasia, consistent with the recognized dose-dependent effect of 17 β -estradiol on the endometrium, as demonstrated in other 12-week studies.⁶

If low-dose HT formulations, such as the 0.87 g/day dose of estradiol gel, are shown not to cause endometrial

Table 3. Effects of Estradiol Gel on Most Bothersome Moderate-to-Severe Vulvovaginal Atrophy Symptom, Vaginal pH, and Vaginal Maturation Index³⁷

| Evaluation | Placebo | Estradiol Gel Dose | | |
|---|-----------------|--------------------|-----------------|-----------------|
| | | 0.87 g/d | 1.7 g/d | 2.6 g/d |
| Most bothersome moderate-to-severe vulvovaginal atrophy symptom | | | | |
| N (baseline/week 12) | 64/62 | 69/67 | 64/61 | 35/35 |
| Baseline Severity (mean \pm SD) | 2.48 \pm 0.50 | 2.36 \pm 0.48 | 2.23 \pm 0.43 | 2.26 \pm 0.44 |
| Change at week 12 (last visit) | -1.31 | -1.74 | -1.53 | -1.75 |
| P value | | .018 | .378 | .052 |
| Vaginal pH | | | | |
| N (baseline/week 12) | 84/81 | 68/66 | 80/78 | 36/34 |
| Baseline pH (mean \pm SD) | 6.28 \pm 0.71 | 6.31 \pm 0.62 | 6.18 \pm 0.61 | 6.07 \pm 0.62 |
| Change at week 12 (last visit) | -0.17 | -1.21 | -1.20 | -1.31 |
| P value | | <.001 | <.001 | <.001 |
| Vaginal maturation index | | | | |
| N (baseline/week 12) | 123/117 | 119/116 | 117/115 | 57/56 |
| Baseline VMI (mean \pm SD) | 40.6 \pm 11.9 | 40.8 \pm 12.8 | 41.5 \pm 10.5 | 42.3 \pm 10.8 |
| Change at week 12 (last visit) | 1.2 | 17.9 | 25.9 | 28.3 |
| P value | | <.001 | <.001 | <.001 |

SD=standard deviation; VMI=vaginal maturation index. Reprinted with permission.

hyperplasia after extended treatment, less frequent progestin therapy might be possible and might prove to be even more beneficial. Some authors have advocated the use of transvaginal ultrasound as an adjunct to that end.⁴⁰ However, current class labeling requires monthly progestin to prevent endometrial hyperplasia and endometrial cancer, which have been observed in other 12-week studies of unopposed estrogen therapy. Simon and colleagues³⁷ conclude that the study's results support the 0.87 g/day dose of 17 β -estradiol gel as a lowest effective estrogen dose in the patient population studied.

Other Considerations of Transdermal Hormone Therapy

The recently approved 0.06% estradiol in a hydroalcoholic gel base (ElestrinTM) is recommended for application to a small, easy-to-reach area of the upper arm or shoulder. The gel is dispensed from a pump-actuation container, and a single pump releases a precise amount of the estradiol-containing gel. The gel is colorless, odorless, and will not stain or otherwise mar clothing that comes in contact with the treated area. The topical compound dries within a few minutes, and the 17 β -estradiol is readily absorbed through the skin.

One pump actuation releases a 0.87-g dose that provides for systemic delivery of 0.0125 mg of 17 β -estradiol. Two pump actuations result in a 1.7-g dose, which provides systemic delivery of 0.0375 mg of 17 β -estradiol daily.

Summary

Hormone therapy has a long history of safe and effective use to prevent and manage postmenopausal symptoms. That use remains the principal indication for HT. Although epidemiologic data suggest a cardioprotective effect of female hormones, no cardiovascular benefits have been demonstrated in multiple clinical trials. The recent trend in HT is to use the lowest effective dose for the shortest possible duration. Development of a low-dose transdermal formulation of estrogen therapy offers postmenopausal women the opportunity to obtain relief from menopausal symptoms with a reduced risk of adverse events.

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