Bioidentical Estradiol Gel for Hormone Therapy in Menopause

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Abstract

More than two-thirds of women experience hot flashes during menopause. Approximately 25% of women during perimenopause and in the first years after menopause experience severe symptoms such as hot flashes, sweating, changes in mood, insomnia, vaginal and skin atrophy and dyspareunia. Hormone therapy is effective in treating menopausal symptoms. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS) I, HERS II, the Women's Health Initiative and the Million Women Study have raised many concerns regarding the safety and usefulness of hormone therapy. Recently, ‘bioidentical’ estradiol therapy at low dosage has been proposed as an alternative to standard hormone therapy. Percutaneous administration of estradiol enables the creation of a hormonal milieu similar to that of the follicular phase. Elestrin™ is a new percutaneous gel that delivers estradiol to the bloodstream evenly over time in a nonirritating, painless and well-accepted manner. Elestrin is administered using a metered dose applicator, thereby allowing precise titration from dose to dose in order to minimize the amount of hormone administered. Notably, Elestrin is currently the drug that delivers the lowest dosage of estradiol approved by the US FDA for treating menopausal symptoms.

Indications for Estrogen Therapy

Indications for estrogens in menopause, although not all approved by the US FDA, include pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery, climacteric complaints, such as hot flashes and night sweating, and lower urogenital tract atrophy, as diagnostic aid in case of a doubtful atrophic cervical smear.

It is estimated that symptoms related to a decline in serum levels of estradiol during the menopause transition may affect the quality of life in up to 75% of postmenopausal women.[1] According to the North American Menopause Society, more than two-thirds of North American women experience hot flashes during menopause.

Approximately 25% of women during perimenopause and in the first years after menopause experience severe symptoms such as hot flashes, sweating, changes in mood, insomnia, vaginal and skin atrophy and dyspareunia.[2] Late consequences of untreated estrogenic deficiency may include osteoporosis and fractures; moreover, observational studies suggest a relationship between menopause and atherosclerosis and Alzheimer’s disease.[3]

Hormone therapy (HT) has been used for many years to treat the symptoms associated with estrogen deficiency. Vasomotor symptoms, particularly hot flashes, have been found to decrease in a linear fashion as estrogen levels are increased by HT.[4] HT, conjugated equine
estrogens (CEEs) 0.625 mg daily, specifically with or without concomitant progestin, can reduce bone loss and reduce risk of hip fracture and other types of clinical fracture.\[^{6,6}\]

**Concerns About Estrogenic Therapy**

In the last few years the publication of data from the Heart and Estrogen/Progestin Replacement Study (HERS) \[^{7}\] and HERS II,\[^{8}\] followed by that from the Women’s Health Initiative (WHI) \[^{9-11}\] and the Million Women Study (MWS) \[^{12}\] have raised many concerns about the safety and usefulness of HT. The WHI study reported an increased risk of stroke and deep vein thrombosis in postmenopausal women (50 - 79 years of age) during 6.8 years of treatment with oral CEEs 0.625 mg/day, compared with placebo.\[^{10,11}\] Moreover, the WHI study also reported an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women (50 - 79 years of age) during 5 years of daily treatment with oral CEEs 0.625 mg combined with medroxyprogesterone acetate 2.5 mg/day.\[^{9}\]

The results of these studies have aroused enormous interest in the media worldwide, with particular emphasis on the potential risks of HT producing considerable confusion and concerns among women, caregivers and the media.

On the other hand, in the last few years the HERS and WHI study findings have been extensively debated.\[^{13,14}\] A recent re-analysis of WHI studies showed that women who initiated HT closer to menopause tended to have reduced coronary heart disease (CHD) risk compared with the increase in CHD risk among women starting therapy further from menopause.\[^{15}\] Beyond the characteristics of the population enrolled, another criticism of the results from the HERS and WHI studies was that in all cases HT was performed with CEEs and medroxyprogesterone acetate, a synthetic C21-progestin derivate. With regards to this last issue, although the US FDA and most of the medical society generalize results of HERS and WHI to all forms of HT, in virtue of the differences in metabolism, receptor affinity, potency among different estrogens and progestins, some experts have suggested that the results of the HERS and WHI studies cannot be generalized.\[^{16}\] Although HERS and WHI studies indicate that HT increases the risk of cardiovascular disease, a series of experimental and clinical data consistently support a beneficial effect of estrogens on the arterial wall in terms of endothelial function, compliance and atherosclerosis protection. A unifying hypothesis is that the reproductive stage appears to be the major determinant of the effect of estrogens on atherosclerosis progression, complications and plaque vulnerability. The increase in cardiovascular disease events associated with initiating HT 10 years or more after menopause appears to be related to upregulation of the plaque inflammatory processes and plaque instability.\[^{15,17-19}\]

Additional critical points for risks related to HT are the dosage of hormones administered, the variable response of individual women to the same dosage of hormones, and the individual predisposition to diseases.\[^{20}\]

Regarding the dosage of hormones to be prescribed, the results of HERS and WHI studies have led most expert groups, including the FDA,\[^{21}\] the US Preventive Services Task Force\[^{22}\] and the American College of Obstetrics and Gynecology,\[^{23}\] to suggest that HT be prescribed at the lowest effective dose for the shortest possible time. Consequently, in the last few years the interest in ultra-low dosages of estrogens has undergone a significant increase. It was demonstrated that ultra-low dosage estrogens (conjugated estrogens 0.3 mg) are effective in preventing osteoporosis\[^{24}\] and most likely exert better effects on the cardiovascular system; oral CEE at a dosage of 0.3125 mg in postmenopausal women eliminated the adverse effects of
high-dosage oral CEE on vascular inflammatory markers in addition to preserving the favorable effects of estrogen on cell adhesion molecules and endothelial function.\textsuperscript{[25]} However, current studies have not had sufficient power to completely reassure users that lower doses are safe and the WHI study clearly showed that intermediate markers can be misleading.

An additional advantage of ultra-low dosage estrogens is that the daily or monthly association of progestin might not be necessary for preventing endometrial hyperplasia.\textsuperscript{[26,27]} Some adverse effects associated with combination HT are probably related to adding progestin to the estrogenic regimen,\textsuperscript{[11,13]} but women with a uterus who are using a standard dose of estrogens need progestin therapy to prevent uterine hyperplasia and cancer.\textsuperscript{[28]}

Regarding the variable response of women to the same dosage of hormones and predisposition to diseases, it is now known that due to polymorphisms in p-glycoprotein and cytochrome P450 isoenzymes, some people metabolize certain drugs differently than others, and this makes people susceptible to concentration-dependent adverse effects, or drug - drug interactions.\textsuperscript{[29,30]} On the other hand, it is known that genetic predisposition to pathologies (osteoporosis, cardiovascular diseases) may significantly affect the effectiveness and incidence of complications and side effects of HT.\textsuperscript{[31]} However, at present there is no useful way to determine such susceptibility.

Yet, due to concerns regarding the safety of HT generated by WHI, many women already taking HT or those contemplating starting treatment have increasingly turned to phytoestrogens and other natural products (e.g., black cohosh, red clover, primrose oil and herbal and homeopathic products) as safer alternatives to pharmaceutical dosage forms of estrogens and/or progestogens.

However, ‘natural’ does not mean ‘physiological’ and this is the issue of phytoestrogens which are natural, as they are extracted from plants but are not physiological as they are not normally present in the woman’s body. Moreover, metabolic pathways of different phytoestrogens as well as long-term effects of their administration are at the moment poorly understood.\textsuperscript{[32]}

In recent years, a HT based on ‘bioidentical’ estradiol has been proposed as an alternative to conventional HT. This therapy consists of the administration of 17β-estradiol, the bioidentical estrogen produced by the ovaries, at the lowest effective dose. As the hormone administered is the same as the one produced by ovaries and the serum levels are similar to those observed in premenopausal women, this kind of therapy can be truly considered a physiological estrogenic therapy.

**Bioidentical Hormones**

In general, bioidentical hormone therapy is based on two concepts: the employment of the hormone physiologically produced in the woman’s body and the tailoring of the dosage to the individual’s need.\textsuperscript{[33,34]}

Thus, bioidentical HT provides one or more of these hormones as the active ingredient. The woman’s body can produce various estrogens (such as 17β-estradiol, estrone and estriol) as well as progesterone, testosterone and other hormones. In other words, hormones have been produced commercially to replicate some of these naturally occurring hormones. These hormones are made available in well-tested, government-approved, brand-name prescription drugs.
It is worth underlining that the formulation not only contains the active hormone (or hormones), but also other ingredients that either holds everything together (in the case of a rectal suppository, an under-the-tongue tablet or an under-the-skin pellet) or provides a vehicle for applying the product onto the skin (such as a cream or gel) or into the body (such as a liquid for a nasal spray).

Bioidentical hormones are different from a custom-mixed (‘custom-compounded’) formulation containing one or more various hormones in differing amounts, depending on an individual prescriber’s order. These compounds do not have government approval because individually mixed formulations have not been tested to prove that they are absorbed appropriately or provide predictable levels in blood and tissue. Moreover, there is no scientific evidence concerning the effects of these hormones and as the preparation methods vary from one pharmacist to another, and from one pharmacy to another, patients may not receive consistent amounts of medication.

Another aspect that characterizes therapy with bioidentical hormones is that hormone treatment is not performed with standard dosages but it may be personalized, with the ultimate objective of minimizing the administered amount of hormones. Salivary or serum hormone levels have been proposed to monitor estradiol dosage. Because saliva is similar to a blood ultrafiltrate, salivary hormone concentrations should correlate with free/unbound serum concentrations. However, saliva testing to know if the estrogen dosage is suitable has not been proven accurate or reliable; in practice, these correlations vary, depending on the time of day, diet, the specific hormone tested and other variables. Even blood testing of hormone levels has the drawback that levels vary throughout the day as well as from day to day. More importantly, the desired levels in postmenopausal women have not been established. In addition, an individual woman’s physical comfort may not even be related to her absolute hormone levels and in most reported cases the dosage adjustments are, in fact, made on the basis of symptoms.

It may be argued that the term bioidentical was coined by proponents of the idea that natural hormones are superior to synthetic hormones or that this could be the implicit message in using this term. In fact, even natural estrogens and progesterone in women, and testosterone in men, may have adverse effects on breast and testicular cancer. In the present paper the term bioidentical is used not to suggest a superiority of natural hormones over synthetic ones but simply to indicate that by using bioidentical hormones we can administer the natural estrogen to premenopausal women, thereby avoiding metabolic effects of synthetic molecules.

**Different Formulations of Estradiol**

Several drugs containing bioidentical 17β-estradiol are currently on the market in the form of oral tablets, vaginal cream, rings, nasal spray skin patches and percutaneous gels.

Estradiol can be administered orally. Micronized estradiol is rapidly absorbed in the first part of the intestine; however, circulating levels of estradiol after oral administration exhibit wide fluctuations, and as liver impact is not completely avoided, with consequent conversion of the majority of E2 to E1, high doses are necessary to achieve therapeutic tissue levels. This can be bypassed with transdermal or intravaginal administration. Transdermal delivery via patches or gel is the most employed nonoral route for administering estradiol worldwide. Commercial preparations of transdermal HT are slow-release dosage forms ensuring a sustained release of estradiol for 3 - 7 days.
The main pharmacokinetic characteristic of the transdermal route is that the hepatic first-pass effect is minimized. During oral estrogen administration, the concentration of estradiol in the liver sinusoids is four- to five-times higher than that in the systemic circulation. This supraphysiologic concentration of estrogens in the liver can stimulate the expression of many hepatic-derived proteins, which are not observed in premenopausal women. By contrast, transdermal estrogen delivers the hormone directly into the systemic circulation and, thus, avoids the first-pass hepatic effect.

Although oral estrogen exerts a more favorable influence than transdermal estrogen on traditional cardiovascular risk factors such as high- and low-density lipoprotein cholesterol levels, recent studies have indicated that oral estrogens adversely influence many emerging risk factors in ways that are not seen with transdermal estrogen. Oral estrogen significantly increases levels of acute-phase proteins such as C-reactive protein and serum amyloid A, procoagulant factors such as prothrombin fragments 1 and 2; and several key enzymes involved in plaque disruption, while transdermal estrogen does not have these adverse effects. Recent publications suggest that oral estrogen induces atherosclerotic vascular disease risk by increasing acute inflammation; however, transdermal estrogen avoids this untoward effect.

Additionally, transdermal estrogen exerts a positive effect on endothelial function similar to that of oral estrogen. Therefore, the transdermal route might be favorable in terms of atherosclerotic risks.

With regards to the hemostatic system, transdermal E2 has been shown to reduce plasma levels of fibrinogen and Factor VII, both of which are important risk factors for cardiovascular disease. Data in the literature show that the risk of deep vein thrombosis is statistically significantly increased by oral (relative risk: 3.5) but not by transdermal therapy (relative risk: 0.9). In a recent French, multicenter, case-control study of venous thromboembolism among 271 postmenopausal women and 610 controls, after adjustment for potential confounding factors, odds ratios for venous thromboembolism in current users of oral and transdermal estrogen compared with nonusers were 4.2 (95% CI: 1.5 - 11.6) and 0.9 (95% CI: 0.4 - 2.1), respectively.

However, it should be underlined that although data in the literature suggest greater cardiovascular safety of transdermal estradiol compared with oral formulation, the superiority of transdermal or percutaneous over any form of oral route is not currently proven as definitive clinical trials with cardiovascular outcomes have not been performed.

Many reservoir-based and matrix patches are now available on the market that ensure daily estradiol release ranging from 25 to 100 µg. Skin-patch delivery systems are usually called transdermal since the drug reservoir remains outside the skin; steroid-containing gels that are massaged into the skin are often referred to as a percutaneous system, where the skin itself acts as a temporary partial reservoir.

Unfortunately, in up to 15% of cases patches are associated with local skin reactions that may induce women to discontinue therapy. As the adhesive rather than the active content is generally the cause of these reactions, transdermal gel delivery systems have now been developed with better skin tolerance. In general, estradiol absorption with gels appears to be equally effective as with patches. Studies in the literature show that there is no difference between gel and patches with regards to peak concentrations of estradiol and bioavailability;
however, gels seem to ensure more stable serum levels of estradiol as the fluctuations between peak and trough estradiol levels were significantly greater with the patches than with the gel.\textsuperscript{[46]}

Site and area of application, frequency of administration and formulation may heavily influence drug delivery via the transdermal route. Indeed, the smallest application area of a gel is associated with optimal estradiol absorption and bioavailability.\textsuperscript{[47]}

Patch and gel formulations are equally as effective in treating climacteric symptoms and improving bone mineral density and the effects are comparable to those achieved by oral HT.\textsuperscript{[37]}

Another important issue is compliance with HT, which is considered to be rather poor.\textsuperscript{[44]} The main reasons for noncompliance include side effects (such as breast tenderness and perception of weight gain,\textsuperscript{[48]} the return of menstrual bleeding and the fear of cancer. Most side effects, but also bleeding and cancer risk, are related to the dosage employed and may benefit from a reduction in the dosage. HT with gel can be tailored to suit the individual and this can improve compliance. Additional factors for good compliance are the fact that the gel is invisible once applied and that gel is probably considered more similar to a cosmetic product than a drug.

**Elestrin™**

Elestrin™ (transdermal estradiol gel) is a new gel formulation of bioidentical estradiol developed by BioSante Pharmaceuticals, Inc. (IL, USA).

In Elestrin, estradiol is carried in a patent-pending (notice of allowance received) gel formulation that enhances absorption and bioavailability of the hormone, which was coinvented for estradiol by Antares Pharma and BioSante.

Elestrin is quickly absorbed through the skin after topical application on the upper arm, delivering estradiol to the bloodstream evenly over time at minimal dosage and in a fast-drying, painless manner.\textsuperscript{[34]}

In December 2006, the FDA approved the marketing of Elestrin (estradiol gel) in the USA to treat moderate-to-severe vasomotor symptoms (hot flashes) associated with menopause. Two doses of Elestrin 0.87 and 1.7 g/day, were approved.

Estradiol gel formulations available on the market are reported in Table 1. Notably, Elestrin 0.87 g/day is the lowest dose of estradiol approved by the FDA for the treatment of moderate-to-severe vasomotor symptoms.

In contrast to conventional estrogen therapy based on standard dosage of different kinds of estrogens, treatment with Elestrin, according to the principles of therapy with bioidentical hormones, allows the administration of the natural hormone at very low doses and the individualization of dosage.

**Pharmacokinetics**

Elestrin is administered using a metered dose applicator that delivers 0.87 g of gel per actuation, which delivers 12.5 µg of estradiol, thereby allowing precise titration from dose to dose. The gel dries quickly in 1 - 2 min.
Absorption of Elestrin is controlled by the patent-pending formulation that was coinvented for estradiol by Antares and BioSante. This formulation consists of a hydroalcoholic gel containing a combination of ingredients. The gel is totally invisible with excellent cosmetic characteristics. The gel is designed to be absorbed quickly through the skin after application on the arms, shoulders or abdomen. The formulation does not cause irritation or occlusion of the skin after application. The formulation is nontoxic and all excipients used in the formulation are classified and generally recognized as safe.

The gel contains a combination of permeation enhancers that create a reservoir of the drug in the skin. This particular property achieves a sustained plasmatic profile of the active agent.

The percutaneous gel technology controls the active agent for 24 h of delivery. The extent of the controlled-release window enables once-daily application. The same technology has been used in formulations containing testosterone, different progestins and also for contraception.

Estradiol is transported across intact skin into systemic blood circulation by passive diffusion. The rate of diffusion across the stratum corneum is the rate-limiting factor.

Steady-state serum concentrations of estradiol are achieved in approximately 3 days following daily application of Elestrin to the upper arm. Pharmacokinetic parameters for estradiol on day 14 following daily application of 0.87 or 1.7 g/day of Elestrin are summarized in Table 2. At steady state, the unadjusted mean average estradiol concentrations for Elestrin 0.87 and 1.7 g/day were 15.4 and 39.2 pg/ml, respectively.[49]

Clinical Studies

The FDA submission included data from the pivotal Phase III clinical trial as well as data from three additional clinical trials, a transfer study, a sunscreen study and a pharmacokinetic study.

A 12-week, double-blind, placebo-controlled Phase III study of 484 symptomatic menopausal women was designed to identify the lowest effective dose to allow estrogen treatment in the safest possible manner. The women in the study were randomly assigned to one of four treatment arms: low-dose (0.87 g), mid-dose (1.7 g) or high-dose (2.6 g), or matching placebo. The FDA-defined end points were a significant decrease over placebo in both the number and severity of hot flashes at week 4 and 12 of treatment. The most effective Elestrin dose decreased the number of hot flashes by 88%, from 12.9 per day at baseline to 1.6 per day after treatment (p < 0.0001). The decrease was also significant versus placebo, with a mean decrease of 11.3 hot flashes per day with Elestrin versus a decrease of 6.1 with placebo (p < 0.0001).

The lowest dose of Elestrin was also effective and produced low estradiol blood levels with a safety profile similar to that observed in the placebo group. Notably, Elestrin was shown to be effective at a daily dose of 12.5 µg of estradiol, which is 50% lower than the lowest dose currently available for the treatment of hot flashes (25 µg/day).

Importantly, more than 80% of women who used Elestrin reported ‘great’ or ‘moderate’ results, a highly significant improvement over placebo treatment (p < 0.0001). Results were presented at the 2006 Annual Meeting of the International Society for the Study of Women’s Sexual Health in Lisbon, Portugal and at the 17th Annual Meeting of the North American Menopause Society in TN, USA, October 11 - 14, 2006.
**Side Effects**

In the Phase III study the lowest dose of Elestrin studied (0.87 g) produced very low estradiol blood levels and exhibited a safety profile similar to that observed in the placebo group. There were no significant differences in the safety profile of any dose of Elestrin compared with placebo other than predictable estrogen effects, such as breast tenderness. Furthermore, the application site reactions were minimal and very infrequent, and no subjects discontinued the study due to application site reactions. Almost all subjects (97%) in the lowest dose group completed the Phase III study.

**Expert commentary**

Individualized therapy with dosages of natural hormones based on response to therapy appears to be an attractive alternative to conventional HT. The percutaneous route is an effective and well-accepted administration route for estradiol that allows:

- The administration of estradiol, the main estrogen in premenopausal women
- The creation of a hormonal milieu (estradiol:estrone ratio) similar to that in the follicular phase
- A body distribution of estradiol similar to that of endogenous estradiol
- The avoidance of liver first-pass effect and metabolic induction
- The ability to titrate the dose based on patients’ symptoms and also to minimize the amount administered
- Good acceptance and compliance of therapy

In addition to the advantages of percutaneous administration, Elestrin delivers a very low dose of estradiol that is 50% lower than the next lowest-dose estradiol on the market for the same indication. The once-daily gel is absorbed into the skin without a trace of residue, providing reliable absorption and good compliance. Remarkably, Elestrin releases the lowest dose of estradiol approved by the FDA to treat hot flashes.

In conclusion, although *ad hoc* well-designed clinical trials are needed to demonstrate the safety of ultra-low dose estradiol therapy in general, this kind of HT (i.e., Elestrin), which is based on natural hormones and very low dosages, is an attractive alternative to currently marketed estrogen therapies and may help in removing concerns and doubts of doctors and women about estrogen therapy in menopause.

**Five-year View**

The mean age of the population and the number of women in menopause are continually increasing. The request to maintain or improve the quality of life is an important issue and is a justification for hormonal treatment. We believe that, notwithstanding health concerns, the desire to improve the quality of life, in all its aspects both physical and psychological, will convince a growing number of menopausal women to start a hormonal therapy in the near future.
In the next few years we believe that initiating therapy early during menopause, the employment of natural hormones, nonoral administration routes and low dosages will represent the key points for hormonal therapy in menopause. Individualization of therapy tailored to each patient based on a series of personal and familial risk factors will represent a fascinating and challenging aspect of HT in menopause. Therapy with Elestrin fits all these points and it is therefore reasonable to suggest that the employment of estradiol gel in general and of Elestrin specifically, is destined to increase in the near future.

Table 1. Estradiol Content and Dosage of Different Estradiol Gel Preparations Available on the Market

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Estradiol content (with/water)</th>
<th>Daily dosage/ skin surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandrena®</td>
<td>0.1%</td>
<td>0.5-1.5 g/200-400 cm²</td>
</tr>
<tr>
<td>Estrogel®</td>
<td>0.06%</td>
<td>2.5 g/720 cm²</td>
</tr>
<tr>
<td>Elestrin™</td>
<td>0.0014%</td>
<td>0.87-1.7 g/200-400 cm²</td>
</tr>
</tbody>
</table>

Table 2. Summary of Unadjusted Pharmacokinetic Parameters for Estradiol After 14 Days of Dosing

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Elestrin™ 0.87 g (estradiol 0.52 mg/day) mean</th>
<th>Elestrin™ 1.7 g (estradiol 1.04 mg/day) mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-2₄ (pg.h/ml)</td>
<td>335.2</td>
<td>940.2</td>
</tr>
<tr>
<td>Cₘₐₓ (pg/ml)</td>
<td>21.6</td>
<td>66.7</td>
</tr>
<tr>
<td>Cₐᵥₑ (pg/ml)</td>
<td>15.4</td>
<td>39.2</td>
</tr>
<tr>
<td>Cₘᵢₙ (pg/ml)</td>
<td>9.4</td>
<td>21.1</td>
</tr>
<tr>
<td>Tₘₐₓ (h)*</td>
<td>18 (1-20)</td>
<td>4 (1-20)</td>
</tr>
<tr>
<td>Fluctuation index</td>
<td>0.80</td>
<td>1.16</td>
</tr>
<tr>
<td>E₂:E₁ ratio</td>
<td>0.53</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*Tₘₐₓ shown as median (range).

References
15. Rossouw JE, Prentice RL, Manson JE *et al.* Postmenopausal hormone therapy and risk

   - Women’s Health Initiative study had major design flaws that led to adverse conclusions about the positive effects of hormone therapy (HT). Alternative hormonal regimens, when initiated appropriately in a population of younger, more recently menopausal women, may yield a more favorable risk/benefit outcome.


   - Available evidence points to a number of polymorphisms in a wide variety of genes as strong hereditary determinants of the susceptibility to benign and malignant gynecologic and obstetric conditions.


33. Boothby LA, Doering PL, Kipersztok S. Bioidentical hormone therapy: a review.
• Currently no evidence exists to suggest that individualized therapy with bioidentical hormonal products have proven advantage over conventional HTs.
• Patch and gel formulations are equally as effective in treating climacteric symptoms and improving bone mineral density, and the effects are comparable to those achieved by oral HT.
• Oral but not transdermal estrogen-replacement therapy (ERT) is associated with risk of venous thromboembolism in postmenopausal women. These data suggest that transdermal ERT might be safer than oral ERT with respect to thrombotic risk.
• Oral HT instigated inflammation, but transdermal did not; both oral and transdermal hormone-replacement therapy, however, improved endothelial function and decreased oxidative stress through affecting the cellular redox state.
46. Paoletti AM, Pilia I, Nannipieri F, Biagini C, Melis GB. Comparison of pharmacokinetic profiles of 17β-estradiol gel 0.6 mg/g (Gelestra) with transdermal delivery system (Estraderm TTS 50) in postmenopausal women at steady state. Maturitas 20, 203 - 209 (2001).
48. Bakken K, Eggen AE, Lund E. Side-effects of hormone replacement therapy and
Sidebar: Key Issues

- More than two-thirds of women experience hot flashes during menopause, and approximately 25% of women during perimenopause and in the first years after menopause experience severe symptoms.

- Hormone therapy (HT) has been used for many years to treat the symptoms associated with menopause.

- In recent years the publication of data from the Heart and Estrogen/Progestin Replacement Study (HERS) I, HERS II, Women's Health Initiative and the Million Women Study have raised many concerns about the safety and usefulness of HT.

- The mean age of the population and the number of women in menopause are continually increasing. The aim to maintain or improve the quality of life is an important issue and is a justification for hormonal treatment.

- In recent years, 'bioidentical' estradiol therapy based on administration of 17\(\beta\)-estradiol, the bioidentical estrogen produced by ovaries, at the lowest effective dose has been proposed as an alternative to conventional HT.

- The percutaneous route is an effective and well-accepted administration route for estradiol that allows the reproduction of a hormonal milieu (estradiol:estrone ratio) similar to that of the follicular phase, the avoidance of liver first-pass effect and metabolic induction, the possibility to titrate the dose based on the patient's symptoms and to minimize the amount administered.

- Elestrin™ is a new gel formulation of estradiol that benefits from the technological advantages of transdermal administration. By virtue of its sustained release, Elestrin may be applied once daily. Elestrin is absorbed into the skin without a trace of residue providing reliable absorption and good compliance.

- Elestrin is currently the drug that releases the lowest dose of estradiol approved by the US FDA to treat hot flashes.

- Elestrin conforms to the recommendations directed to physicians by the US FDA, the American College of Obstetricians and Gynecologists and the North American Menopause Society to prescribe the lowest effective dose of estrogen to control menopausal symptoms such as hot flashes.

- It is reasonable to suggest that the popularity of Elestrin is destined to increase in the near future.
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