

# Are All Estrogens Created Equal? A Review of Oral vs. Transdermal Therapy

Michael P. Goodman M.D.

## Abstract

**Background:** To compare oral and transdermal delivery systems in domains of lipid effects; cardiovascular, inflammatory, and thrombotic effects; effect on insulin-like growth factor, insulin resistance, and metabolic syndrome; sexual effects; metabolic effects including weight; and effects on target organs bone, breast, and uterus.

**Methods:** Review of the literature 1990–2010. Studies selected on basis of applicability, quality of data, and relationship to topic.

**Results:** Data applicable to the comparisons of oral versus transdermal delivery systems for postmenopausal estrogen therapy were utilized to perform a review and formulate conclusions.

**Conclusions:** Significant differences appear to exist between oral and transdermal estrogens in terms of hormonal bioavailability and metabolism, with implications for clinical efficacy, potential side effects, and risk profile of different hormone therapy options, but neither results nor study designs are uniform. Bypassing hepatic metabolism appears to result in more stable serum estradiol levels without supraphysiologic concentrations in the liver. By avoiding first-pass metabolism, transdermal hormone therapy may have less pronounced effects on hepatic protein synthesis, such as inflammatory markers, markers of coagulation and fibrinolysis, and steroid binding proteins, while oral hormone therapy has more pronounced hyper-coagulant effects and increases synthesis of C-reactive protein and fibrinolytic markers. Both oral and transdermal delivery systems have beneficial effects on high-density lipoprotein cholesterol to low-density lipoprotein cholesterol ratios (oral > transdermal), while the transdermal system has more favorable effects on triglycerides. Incidence of metabolic syndrome and weight gain appears to be slightly lower with a transdermal delivery system. Oral estrogen's significant increase in hepatic sex hormone binding globulin production lowers testosterone availability compared with transdermal delivery, with clinically relevant effects on sexual vigor.

## Introduction

ESTROGEN HAS BEEN CONSIDERED BY SOME to be an anti-aging modality capable of reducing health consequences of aging in many different tissues. It may be hypothesized that ongoing hormonal exposure could cumulatively change aging tissue, thus allowing for greater responsiveness at older ages. Tissue differences, characteristics of the hormone therapy (HT) regimen, and variations among patients may influence estrogen's effects. Characteristics that have an impact on estrogen function and risk include specific estrogen type, dose, and route of administration and certain patient risk factors. One striking illustration of these differences is oral vs. transdermal (TD) and transmucosal routes of administration. For the sake of simplicity, transmucosal products will hereafter be included under the umbrella of TD preparations.

Estrogen type and route of administration appear to matter. The skin metabolizes estradiol (E2) only to a small extent. Therefore, TD administration produces therapeutic plasma levels of E2 with lower circulating levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy.<sup>1,2</sup>

The Women's Health Initiative (WHI) and virtually all earlier studies (including Heart and Estrogen/Progestin Replacement Study) used only orally administered conjugated equine estrogens (CEE) with the potent oral progestin medroxyprogesterone acetate (MPA), aka PremPro™. The most physiologic form of estrogen is estradiol-17 $\beta$ , the estrogen available in some oral preparations and all patch, cream, gel, vaginal, and spray applications. TD delivery avoids the first-pass effect, resulting in more stable serum E2 levels without supraphysiologic concentrations in the liver. First-pass

metabolism by the liver may alter therapeutic effects of hormonal and other pharmacologic agents. Some drugs are so extensively metabolized that little remains unchanged or bioavailable. The estimated bioavailability of orally administered estrogens may be as low as 2% to 10%.<sup>3</sup> This first-pass effect is additionally responsible for greater variability in serum estrogen levels both between individuals and in the same person over the course of treatment.<sup>4,5</sup>

Many studies suggest that patient age regulates hormone responsiveness. Older individuals respond differently to HT, possibly secondary to the increased degree of atherosclerosis with aging, resulting in less protective benefit and greater risk. Younger patients (50–59 years) do not appear to experience this added risk potential.<sup>6–15</sup>

Recent epidemiological data note an altered risk/benefit ratio with TD, compared with oral therapy. These may be broken down into effects on lipids; cardiovascular, inflammatory, and thrombotic effects; sexual effects; effects on insulin resistance (IR), insulin-like growth factor, and metabolic syndrome (MeS); and effects on weight, among others. Many of these effects are secondary to oral estrogen's "first-pass" effect on the liver, releasing increased amounts of C-reactive protein (CRP), insulin-like growth factor (IGF)-1, clotting factors, and the hormone binding proteins sex hormone binding globulin (SHBG), thyroid binding globulin, and cortisol binding globulin, resulting in significantly lower levels of free testosterone and, to a lesser extent, free triiodothyronine (T<sub>3</sub>)/thyroxine (T<sub>4</sub>) and free cortisol because of competitive binding.<sup>16</sup>

Compared with oral estrogens, TD E2 exerts minimal effects on total and free concentrations of testosterone, T<sub>3</sub>/T<sub>4</sub>, cortisol, and their binding proteins.<sup>17</sup>

## Methods

### Sources

A review of the available English language literature was undertaken, utilizing existing articles and references culled from reviews and editorials in publications available to the author, as well as a database-directed search as means for detecting literature relating to both effects of estrogen therapy (ET) on the health of menopause-aged women, and the comparison of oral vs. TD administration. Search terms utilized included "transdermal vs. oral hormone therapy," and "transdermal vs. oral estrogen therapy." All articles in indexed, English language peer-reviewed publications were considered, and their data were utilized if they contained material referable to the point(s) being addressed and were powered highly enough to provide meaningful data. No attempt was made to judge study validity dependent on methods of data collection or collation. No "combining" of data was undertaken. Articles accessed were from a broad spectrum of investigators across multiple disciplines and journals. Subgroup and secondary analyses were not performed. Areas of comparison include absorption and bioavailability of oral and TD products; metabolic routes and their sequelae; cardiovascular, inflammatory and thrombotic effects; differential effects on lipids, bioavailable testosterone, thyroid proteins, and cortisol; and effects on weight, IR, and other metabolic factors, as well as differential effects on the breast, bones, and uterus.

### Study selection

One hundred twenty-five citations were reviewed. Those written in languages other than English, redundant to material already referenced, or with a very small sample size were not utilized. Included were randomized controlled trials (single, multi-centered, blinded, placebo-controlled, crossover), systematic reviews with and without meta-analysis, randomized primary and secondary prevention trials, cohort studies, prospective comparative studies, and observational (including multi-center and cross-sectional) studies. In consideration of space limitations, the areas of gallstone formation, comparisons involving the oral product tibione and selective estrogen receptor modulators, continuation issues involving different delivery systems, effects on homocysteine and dimethylarginine reduction, and differential effects on serum amyloid-a, as well as other more peripheral matters were not analyzed for this review.

### Definition: TD estradiol products

It is important to note that all TD (and transmucosal) preparations contain the same active ingredient, molecularly identical (or "bioidentical") E2, synthesized from plant sterols, most commonly soybeans or wild Mexican yam. All TD products are bioidentical (bioidentical hormone replacement therapy [BHRT]), whether U.S. Food and Drug Administration (FDA)-approved pharmaceuticals or individually compounded preparations, although only FDA-approved medications were included in studies accessed. By definition, TD products involve skin application, whether via patches applied once or twice weekly to the lower abdominal area or daily products sprayed or massaged into the skin of the thigh, upper arm, or forearm. An estradiol-containing slow-release vaginal ring is also available; it is speculated that its metabolic effects are similar to transdermal products.

## Results

### Lipid profile

It is well known that menopause has adverse effects on lipids and lipoprotein serum concentrations, increasing low-density lipoprotein cholesterol (LDL-C) and triglycerides and decreasing high-density lipoprotein cholesterol (HDL-C) concentrations.<sup>5,18</sup> Studies have shown that oral HT beneficially affects lipid profiles of postmenopausal women, resulting in increases in HDL-C and decreases in LDL-C to a degree greater than transdermals,<sup>19</sup> while at the same time increasing triglyceride levels, an independent risk factor for stroke.<sup>20,21</sup> TD HT appears to have a favorable effect on triglyceride levels while maintaining, albeit to a slightly lesser degree, oral HT's beneficial effects on LDL-C and HDL-C.<sup>22–24</sup> Additionally, transdermals have been noted to produce larger LDL-C particles ("pattern A"), more resistant to oxidation.<sup>25</sup> A small study found that postmenopausal women whose triglyceride levels rose after therapy with oral estrogen had significantly reduced levels (–51%) after switching to TD E2 administration.<sup>26</sup> TD, but not oral ET significantly decreased the atherogenic index of plasma compared with baseline, making the differences between the therapies statistically significant.<sup>27</sup> Unknown is whether these differential effects translate into cardiovascular events.

*Cardiovascular, inflammatory, and thrombotic effects*

Studies in the 1960s suggested that oral estrogen–progestin combinations appeared to increase blood coagulability.<sup>28,29</sup> In addition to hormone binding globulins, clotting factors are produced by the liver and are stimulated by the high estrogen levels needed to overcome first-pass metabolism. Exogenous oral estrogen appears to affect the activity of platelets and plasma coagulation factors, both key factors in clotting and thrombosis. It has been shown that oral estrogens combined with a progestin leads to an increase in platelet adhesiveness and aggregability and increased plasma fibrinogen and coagulation factor activity, especially factors VII, VIII, and IX, as well as diminishing antithrombin III, an inhibitor of coagulation. Oral contraceptive sex steroid combinations appear to increase venous thromboembolism (VTE) risk by this combination of increased clotting factors and decreased antithrombin activity. It appears that, presumably via hepatic metabolism, these changes apply also to menopausal HT, but whether this applies to estrogen alone, or only oral estrogen–progestin combination, or estrogen combined with progesterone, remains a subject of debate, with conflicting studies in the literature. What roles do the delivery system (oral vs. TD) and the specific progestogen utilized (progestin vs. progesterone) play? A recent study<sup>30</sup> suggests that indeed the progestin MPA utilized in the WHI investigation may play a critical role, noting that after 11 years, women taking CEE alone and starting near to menopause had significantly lower (RR 0.61–0.63) risks of CVD and MI, in contrast with women who took CEE + MPA (RR 1.21–1.23).

Data from the WHI trials suggest that orally administered HT in women 50 to 79 years old was associated with a combined relative risk (RR) of 1.31 for ischemic and hemorrhagic stroke, although the majority (85.2%; RR 1.44) were ischemic strokes; a minority (14.8%; RR 0.82) were hemorrhagic.<sup>9</sup> A large Danish observational study<sup>31</sup> found no increased risk of myocardial infarction with unopposed estrogen, cyclical combined HT, or tibolone, and a significantly lower risk of MI was found with dermal routes of application (RR 0.63; confidence interval [CI] 0.42–0.93). If the method of taking estrogen was via patch or gel on the skin, the risk of MI was reduced by 38%, and for vaginal application, by 44%, compared with oral unopposed ET. Interestingly, this decrease in MI incidence did not hold with combined ET (oral or TD) and progestin (norethisterone acetate, MPA, or levonorgestrel); progesterone was not utilized in any of the study groups. Another study,<sup>32</sup> in which risk was separated by route of administration, reported similar outcomes for oral and TD, with the multivariate odds ratio for MI was 0.66 and 0.75 for oral and TD routes of administration, respectively.

Cardiovascular findings have been generalized to all patients and HT regimens. However, mounting evidence suggests that many factors influence risk. More recently reported WHI findings and other studies<sup>6–13,15,16,30</sup> have demonstrated that, when started near to menopause (within 6–10 years, in patients younger than 60 years), HT acts to prevent cardiovascular disease (hazard ratio [HR] 0.76, CI 0.5–1.16<sup>14</sup>; HR 0.63, CI 0.36–1.08<sup>11</sup>).

Transdermally administered estrogen does not appear to be associated with the same short-term cardiovascular risks as oral HT.<sup>33</sup> A large population-based cohort study of >78,800 women showed that, compared with women who used HT for

<6 months, those exposed for >3 years had a hazard ratio for risk of hospitalization for cardiovascular disease of 0.53 if they utilized transdermals and 1.15 with oral HT.<sup>34</sup> However, when adjusted for income, the overall hazard ratio of 0.65 climbed to 0.94, calling into question confounding factors of many studies in the literature. Other cardiovascular risk factors, such as higher body mass index, compounded the VTE risk with oral HT but did not alter the effects of TD HT.<sup>35</sup> Women with a thrombotic mutation who used oral HT had a >25-fold increased risk of VTE, compared with nonusers and TD HT users, both of which had a fourfold increased risk,<sup>14,35</sup> findings confirmed by the earlier study of Scarabin and colleagues.<sup>36</sup> Canonico and her colleagues<sup>37,38</sup> in the Estrogen and Thromboembolism Risk (ESTHER) Study Group in France recruited 206 consecutive hospital admissions for first documented episode of idiopathic VTE, paired with 426 controls. The study, with a population averaging 61.6 years of age (average age at menopause, 49 years), found that in postmenopausal women oral estrogen is associated with an increased thromboembolic risk, especially during the first year of treatment, while TD estrogen may be safer in terms of thrombotic risk. The relative risk with adjusted odds ratio for VTE with use of oral estrogens was 4.2; in contrast, the ratio was 0.9 with TD preparations. Other investigators<sup>39,40</sup> confirm diminished hemostatic activation, thrombosis, and VTE in postmenopausal users of TD ET, when compared with those using oral ET.

In one large retrospective case–control study, oral estrogen was associated with an almost fourfold increased risk of VTE compared to nonuse, whereas transdermals produced no increased risk.<sup>36</sup> TD E2 may also differ from oral estrogen in its ability to lower blood pressure,<sup>41,42</sup> although no “head-to-head” comparison studies exist.

A 1-year study comparing both TD and oral CEE, both combined with MPA, found little differential effect on blood coagulation factors,<sup>43</sup> again calling into question the role of the progestogen in coagulation effects of HT because most studies of oral medications utilized CEE combined with the progestin MPA, distinct from many TD studies, which eschewed the use of MPA. Another study of the effects of unopposed ET on markers of coagulation and inflammation on postmenopausal women showed an increase in plasminogen and CRP, but little difference on other coagulation markers.<sup>44</sup>

Scarabin and colleagues<sup>45</sup> studied cyclic oral and TD E2, both combined with progesterone. Oral, but not transdermal E2 significantly increased prothrombin activation peptide and decreased mean antithrombin activity compared with no treatment. The oral estrogen group was associated with a significant decrease in both plasminogen concentration and plasminogen activation factor and a significant rise in global fibrinolytic capacity, compared with the TD and control groups, with no significant changes in values of fibrinogen, factors VII and VIII, and other clotting factors between the three groups. They concluded that E2/progesterone replacement therapy may result in increased fibrinolytic potential, whereas unopposed TD E2 appears without substantial effects on hemostasis and emphasized that the increased risk of VTE in users of oral postmenopausal estrogen may alter the route of administration, especially those at high risk of VTE.

Biochemical evidence also appears to support the lower cardiovascular risk of TD estrogen. Although estrogen in general reduces levels of inflammatory markers in the blood, there are some exceptions to this general assertion. Oral

estrogen in particular appears to increase inflammatory proteins (namely, CRP and matrix metalloproteinases [MMPs], specifically MMP-9) and suppress their inhibitors, largely a hepatic metabolic effect influenced by the dose and route of administration.<sup>46–56</sup>

Elevated CRP, a strong predictor of adverse cardiovascular events in healthy postmenopausal women, enhances inflammation and promotes tissue damage in acute MI.<sup>57</sup> In a cross-over, placebo-controlled study of postmenopausal women, oral conjugated estrogens caused a statistically significant greater than twofold increase in CRP levels, while transdermals had no effect on CRP levels.<sup>58</sup> In a recent study, Shifren and her colleagues<sup>59</sup> found that TD ET may be preferable to oral ET because it minimizes the hepatic estrogen exposure that increases CRP and levels of coagulation markers and reduces IGF-1. Other investigators have reported similar findings.<sup>60–64</sup> Oral estrogen appears to induce atherosclerotic cardiovascular disease by increasing acute inflammation; TD ET appears to avoid this effect. TD E2 exerts a positive effect on endothelial function similar to oral estrogen; however, TD may be more favorable than oral in terms of vascular disease risk.<sup>65</sup> It must be noted, however, that CRP and IGF-1 are surrogate markers and cannot make a determination of true “risk.”

In a presentation at the 20th Annual Meeting of the North American Menopause Society, October 1, 2009 (unpublished data), Greep and her colleagues from University of California at Los Angeles performed a retrospective study based on the UCLA stroke database of 955 women, finding 127 were postmenopausal. The study found that among these women, the use of oral HT was associated with a significant elevation in ischemic stroke, particularly cryptogenic stroke, in patients with a patent foramen ovale (presumably thus allowing clots to directly access arterial circulation). Of the 25 women in the study who were on HT at the time of their stroke, all were on oral therapy; increased stroke risk was not seen in patients using TD E2.

#### *Effects on IGF, IR, and MeS*

Several investigators have sought to determine whether oral or TD E2 treatment would be more beneficial for women with IR and MeS, based on changes in inflammation and coagulation markers. In postmenopausal women with obesity and MeS who have increased cardiovascular risk, TD therapy did not affect the ratio of circulating MMP-9 to tissue inhibitor of metalloproteinase (TIMP)-1, whereas the ratio was increased with oral ET. MMPs, notably MMP-9, belong to a family of enzymes that degrade collagen and have a role in promoting plaque rupture. High levels of MMPs are strongly associated with symptomatic cardiovascular disease and are predictive of cardiovascular risk. These metabolic changes in the presence of significant atherosclerosis may have the ability to cause coronary artery plaque instability and may lead to plaque rupture and coronary occlusion.<sup>66</sup> Chu and her group<sup>66</sup> also found that postmenopausal women with MeS have higher levels of certain coagulation and inflammation markers, facts corroborated by Davis et al.<sup>67</sup> who noted differential effects of the route of administration on IGF-1, IGF binding protein-3, and IR.

#### *Sexual effects*

As noted earlier, SHBG levels are influenced by the first-pass effect of oral estrogen therapy. This sex hormone-specific

plasma transport protein, which is synthesized in the liver, controls hormone activity by binding reversibly but with high affinity to testosterone and E2. Since only the unbound hormone is biologically active, increasing SHBG decreases hormone activity, potentially having a negative effect on energy, mood, sex drive, and sexual responsiveness.<sup>68</sup>

Oral HT of any type has been shown to increase SHBG, frequently by greater than 100%, although production is dose and individual dependent.<sup>20,69</sup> However, studies have verified that lower dose TD E2 has little or no effect on SHBG levels.<sup>5</sup>

In a systematic review on the subject of different types of estrogen therapy in relation to women’s sexual function, Nappi and Polatti<sup>70</sup> also come to the conclusion that the type, dose, and delivery system matter, and further posit that “... Collectively, these data allow us to reasonably state that TD E2 seems to be the more logical choice to treat peri- and postmenopausal women with female sexual dysfunction, because it avoids a further reduction of circulating androgens without significantly affecting vascular homeostasis... (pgs 607, 608)” Their focus was on SHBG, which decreases circulating free and bioavailable testosterone. SHBG is variably effected by ET, strongly increased by CEE at a dose of 0.625 mg/d, moderately increased by oral E2 at a dose of 1 mg/d, and minimally increased by TD ET at a dose of 0.05 mg/d,<sup>71</sup> which was corroborated by a randomized open label cross-over study by Shifren et al.<sup>72</sup>

The authors theorize that TD E2, which avoids first-pass metabolism by liver and enzymatic degradation by the gastrointestinal tract, displayed only a mild effect (12% elevation) on SHBG levels, while CEE 0.625 mg/d increased circulating SHBG by 132.2% after 12 weeks. Shifren et al.<sup>72</sup> found the amount of free E2 was almost double in women treated with TD E2, while free estrone was significantly increased in women taking CEE. Free testosterone was significantly reduced (–32.7%) in women on CEE, while almost unchanged (+1%) in women on TD E2. They refer to Simon and Snabes’s study<sup>73</sup> by stating that TD E2 induces a less pronounced effect on hepatic protein markers of coagulation and fibrinolysis, while oral E2 has more pronounced hyper-coagulant effects on synthesis of CRP and fibrinolytic markers. They quote other epidemiologic data identifying VTE risk differences between oral and TD therapy.<sup>36,74</sup>

#### *Effects on weight*

It has been shown that estrogens, both oral and transdermal, appear to reduce midlife weight gain and have a positive effect on weight and body composition.<sup>75</sup> Several studies have been performed investigating differences in body composition, comparing orally versus transdermally administered estrogen. Although most of these studies show an improved lean/fat mass ratio for TD estrogen, the evidence is indirect, and there is not universal agreement.

Because of its first-pass effect, oral estrogen causes diminished lipid oxidation resulting in more fat accumulation.<sup>76</sup> At the same time, growth hormone and its binding protein are increased, resulting in decreased IGF-1 and reduction in lean mass, with increased fat mass and increases in leptin, changes not found with TD estrogen.<sup>77</sup> Increases in leptin have been statistically associated with IR, contributing to more abdominal fat accumulation.<sup>78</sup> It has been observed that oral estrogen may cause a worsening of IR in postmenopausal women with

obesity and MeS, while TD E2 was neutral.<sup>79</sup> Additionally, oral estrogen led to an increased leptin/adiponectin ratio, while leptin was unchanged with TD therapy.

Intuitively as well, any product that increases, even slightly, thyroid binding globulin and cortisol binding globulin might be expected to have the effect of lowering the basal metabolic rate, resulting in a slightly lowered caloric expenditure and weight gain. These data are suggestive, but not overwhelming; there is certainly room for well-designed studies to add to knowledge in this area.

#### *Breast cancer, uterine cancer, and bone density issues*

In a study directly comparing the bone-sparing effects of TD and oral therapies compared with placebo, Hillard and colleagues<sup>80</sup> found no difference between the two delivery systems. Ettinger and colleagues<sup>81</sup> have shown that a daily TD dose as low as 0.014 mg E2, average serum concentration ( $C_{ave}$ ) = 8.5 pg/mL, effectively maintains bone mineral density in postmenopausal women aged 60 or greater. All of the commercially available FDA-approved TD and oral products, at all available dosages, exceed this serum concentration, with the  $C_{ave}$  for lower-dose TD products in the 8.5- to 31-pg range.<sup>82</sup>

Although a significantly smaller segment of the female population eventually succumbs to breast carcinoma than to cardiovascular disease, for which ET appears to generously diminish risk (HR 0.63–0.76) if started near to menopause,<sup>6–15,83</sup> the former is of immense concern to our patients. Adequate evidence exists that an individual's development of this disease relates to ongoing levels of estrogen and progestogenic substances circulating through breast tissue, and may be dose dependent, although the data to substantiate this are not robust. No prospective head-to-head reports yet grace the literature regarding this important consideration, although one might posit that TD products, with their generally lower average serum concentrations, may be associated with mildly diminished rates of carcinoma, when compared with average oral doses for which  $C_{ave}$  levels are harder to calculate secondary to individual absorption differences exceeding that of TD products. The  $C_{ave}$  for oral conjugated equine estrogens 0.625 mg has been calculated at ~87 pg/mL, and for oral E2 1 mg, 50 pg/mL plus estrone levels in the 150–300 mg/mL range.<sup>63</sup> Data are not available for the lower dose formulations of oral products (i.e., conjugated equine estrogen 0.3 and 0.45 mg, oral E2 0.5 mg), but the lower dose TD formulations (e.g., E2 patch 0.025 and 0.0375 mg, aerosolized E2 one to two sprays, E2 gel 0.25–0.5 mg of 0.1% gel) produce average serum concentrations of 10–31 pg/mL, with mid-dose products (E2 patch 0.05 to 0.075 mg, higher dose E2 gels, E2 aerosol three sprays) in the 40–60 pg/mL range.<sup>82</sup> Several investigators<sup>83–86</sup> have found similar risks, although one study<sup>84</sup> of 73,500 Italian women noted a hazard ratio for ever developing breast cancer to be 1.34 (1.27 with TD and 2.14 with oral), suggesting, at least in this group, that oral therapy may increase risk. Nothing is noted about dosages utilized.

Additionally, increased risk of breast cancer is more likely related to concentrations of estrogen locally in breast tissue rather than the serum levels. Oral products providing higher levels of estrone in breast tissue than TD products may have impact.

Of great importance, whether ET is administered via oral or TD route, is the role of the accompanying progestogen in

breast cancer development. Even before the analysis by LaCroix et al.<sup>30</sup> of the ongoing WHI investigation provided evidence of the lack of breast cancer increase in women taking CEE without concomitant MPA, Ross et al.<sup>83</sup> in a landmark study showed a very small increase in breast cancer risk for women consuming ET (CEE) alone, but a very considerable increase in risk for women on estrogen/progestin therapy with MPA as the progestogen. Additionally, they concluded that "... for each incident case of breast cancer, 6 cardiovascular deaths would be prevented.... (p. 331)" These findings have also been confirmed by Stefanick et al.<sup>87</sup> in their original analysis of data from the WHI ET (CEE)-only arm of the WHI, finding a relative risk of 0.8 compared with control for women on CEE (no progestin) for 7.1 years.

Clinicians must also consider that individual uterine responsiveness to estrogen varies widely and that for uterine protection, even when using a low-dose TD product, continuous or cyclic progestogen treatment remains the standard of care, while at the same time understanding that present data suggest that, certainly if that progestin is MPA, the incidence of breast carcinoma will rise.

#### **Discussion**

Estradiol-17 $\beta$  is the estrogen produced in greatest quantity by the premenopausal ovary, filtering from cells of the developing ovarian follicles into capillaries and thus directly into the vascular system for distribution and metabolism.

Exogenous estrogen for supplementation or replacement has been administered in a multitude of delivery systems and estrogenic compounds, but the compound utilized by the overwhelming majority of scientific studies, certainly in the United States, has been CEE, frequently combined with the unique progestin, MPA, in an oral delivery system. Certain adverse effects (incidence of breast cancer, cardiovascular effects, cognitive effects, and others) have been reported in some studies, but not in others. Results from European studies, where the predominant estrogen utilized is estradiol, frequently administered transdermally, differ from U.S. studies. Additionally, those studies that directly compare cardiovascular, cognitive, sexual, and disease risks of oral vs. TD delivery either show little difference or report beneficial advantage of TD delivery.

TD estrogen has a less pronounced effect on hepatic protein synthesis, such as markers of coagulation and fibrinolysis, while oral estrogen has more pronounced hyper-coagulant effects and increased release of inflammatory proteins and hormone binding globulins. Oral products have a slightly more favorable effect on HDL-C and LDL-C, while TD delivery has greater beneficial effects on triglycerides. These differences vary in degree related to dosage of oral products, with newer, low-dose oral formulations promising to carry less risk in selected domains.

By avoiding first-pass hepatic metabolism, dermal administration may maintain its effectiveness, even at lower doses, with greater tolerability because side effects such as breast tenderness, vaginal bleeding, etc., are generally dose related. Both oral and TD estrogen have direct effects on adipose tissue through estrogen receptor alpha, decreasing abdominal fat mass and diminishing IR. Lobo<sup>88</sup> concluded in his review that TD estrogen appears to result in better body composition

changes when compared with oral estrogens, while admitting that results are mixed.

While the described advantages of TD delivery may apply to the low-risk consumer, hard data are less than robust, and at the present time cautious interpretation of the mostly observational data at hand would favor TD delivery specifically for high-risk individuals, including those at increased risk for thromboembolism, those with MeS and/or IR, individuals with elevated triglycerides, women at increased cardiovascular risk, especially with elevated CRP, and women with symptomatic hypoactive sexual desire.

It would appear that women with pre-existing CVD fare more poorly on oral vs. TD preparations and that while there may be less difference in risk/benefit ratio during the menopause transition when oral therapy, with its modestly greater beneficial effects on LDL-C and HDL-C may be warranted, TD administration would appear to be especially appropriate in women more distant from menopause or with risk factors for VTE, triglyceridemia, MeS, hypertension, and coronary vascular disease.

Disadvantages of oral estrogen include the need for daily dosing, relatively higher dosages compared with TD estrogen, intestinal absorption variability, altered hepatic proteins, and increased plasma triglyceride levels. Disadvantages of TD delivery include daily dosing (gels, spray), possible skin allergy, and increased price compared with generic orals.

Many FDA-approved TD molecularly identical (bioidentical) E2 products, dosages, and delivery systems, including patches, sprays, gels, vaginal rings, and, in the near future, possibly an intranasal spray,<sup>89</sup> are available. All TD products, despite different delivery systems, contain the exact same ingredient: bioidentical E2. FDA-approved TD estradiol is "BHRT" every bit as much as the compounded product. However, because generic oral products are cheaper than TD products, there is pressure from third party payers to prescribe oral preparations since cost plays an ever-increasing role in health care.

Additionally confounding is the fact that oral estrogens are a heterogeneous group, and most statistics gathered (and referenced) here are based on experience with CEE, often combined with the potent progestin MPA, and may not fully apply to other oral products, or as a recent publication shows,<sup>30</sup> to that particular estrogen utilized alone without the addition (and possibly additive risk) of the progestin.

To understand the data presented, authors may find it appropriate to distinguish between delivery systems when interpreting and discussing the ongoing data of the WHI and when presenting evidence-based conclusions in the literature.

Evidence from a majority of studies that compared oral with TD delivery show minimal differences in some endpoints, while giving the edge in safety and effectiveness to TD delivery in others. In the end, much of the data is only marginally convincing secondary to the mixture of study design and endpoints. A large, randomized clinical trial, utilizing different doses and different oral and TD preparations combined with different progestogens, could provide a more robust clinical conclusion.

## Conclusion

There are many differences between oral and TD estrogens. The data at this point in time, although mostly observational in

nature, appear to point to an increased safety profile for TD when compared with oral preparations in the domains of lipid, cardiovascular, inflammatory, thrombotic, and sexual effects, and more arguably in the areas of IR, MeS, and weight. TD products generally are clinically effective in a low serum E2 range, and incidence of breast cancer may be dependent upon ongoing serum estrogen concentrations among other factors.

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## References

1. Tuomikoski P, Ebert P, Groop PH, et al. Effect of hot flashes on vascular function: a randomized controlled trial. *Obstet Gynecol* 2009;114:777–785.
2. Slater CC, Hodis HN, Mack WJ, Shoupe D, Paulson RJ, Stanczyk FZ. Markedly elevated levels of estrone sulfate after long-term oral, but not transdermal, administration of estradiol in postmenopausal women. *Menopause* 2001;8:200–203.
3. O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol* 1995;35(suppl):18S–24S.
4. AACE Menopause Guidelines Revision Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. *Endocr Pract* 2006;12:315–337.
5. Minkin MJ. Considerations in the choice of oral vs. transdermal hormone therapy; a review. *J Reprod Med* 2004;49:311–320.
6. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–1712.
7. Manson JAE, Hsia J, Johnson KC, et al; Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523–534.
8. Cheblowski RT, Hendrix SL, Langer RD, et al; WHI Investigators. Effect of estrogen on breast cancer and mammography in healthy postmenopausal women; the Women's Health Initiative randomized trial. *JAMA* 2003;289:3243–3253.
9. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al; WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women; the Women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673–2684.
10. Cushman M, Kuller LH, Prentice R, et al; Womens Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;292:1573–1580.
11. Hsia J, Langer RD, Manson JE, et al; Women's Health Initiative Investigators. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006;166:357–365.
12. Hendrix SL, Wassertheil-Smoller S, Johnson KC, et al; WHI Investigators. Effects of conjugated equine estrogen on

- stroke in the Women's Health Initiative. *Circulation* 2006;113:2425–2434.
13. Curb JD, Prentice RL, Bray PF, Langer RD, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med* 2006;166:772–780.
  14. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–1477.
  15. Manson JE, Bassuk S, Harman M, et al. Postmenopausal hormone therapy: new questions and the case for new clinical trials. *Menopause* 2006;13:139–147.
  16. Altman AM. Bioidentical hormones: what's fact and what's fable? *Sexuality, Reproduction and Menopause* 2007;5:13–16.
  17. Shrifrin JL, Desindes S, McIlwain M, Doros G, Mazer NA. A randomized, open-label crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. *Menopause* 2007;14:985–994.
  18. Stevenson JC, Crook D, Godtsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis* 1993;98:83–90.
  19. Clarkston TB, Karas RH. Do the cardiovascular risks and benefits of oral vs transdermal estrogen therapy differ between perimenopausal and postmenopausal women? *Menopause* 2007;14:963–967.
  20. The Writing Group for the PEPi Trial. Effects of estrogen or progesterin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progesterin Interventions (PEPi) Trial. *JAMA* 1995;273:199–208.
  21. Hully S, Grady D, Bush T, et al. Randomized trial of estrogen plus progesterin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–613.
  22. Godtsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000. *Fertil Steril* 2001;75:898–915.
  23. Sanada M, Tsuda M, Kodama I, Sakashita T, Nakagawa H, Ohama K. Substitution of transdermal estradiol during oral estrogen-progesterin therapy in postmenopausal women: effects on hypertriglyceridemia. *Menopause* 2004;11:331–336.
  24. Chen F, Lee N, Soong Y, Huang, K. Comparison of transdermal and oral estrogen-progesterin replacement therapy: effects on cardiovascular risk factors. *Menopause* 2001;8:347–352.
  25. Nabhan ZM, DiMeglio LA, Qi R, Perkins SM, Eugster EA. Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study. *J Clin Endocrinol Metab* 2009;94:2009–2014.
  26. Strandberg TE, Ylikorkala O, Tikkanen MJ. Differing effects of oral and transdermal hormone replacement therapy on cardiovascular risk factors in healthy postmenopausal women. *Am J Cardiol* 2003;92:212–14.
  27. Kurtay G, Ozmen B. A comparison of the effects of sequential transdermal versus continuous orally administered hormone replacement therapies on plasma total homocysteine levels in postmenopausal women: a randomized, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol* 2006;130:206–211.
  28. Hodges RM. The effects of oral estrogen-progesterin compounds on blood coagulation factors. *Int J Fertil* 1968;13:349–353.
  29. Hougie C, Rutherford RN, Banks L, Coburn RN. Effect of a progesterin-estrogen oral contraceptive on blood coagulation factors. *Metabolism* 1965;14:411–417.
  30. LaCroix AZ, Chlebowski RJ, Manson JE, et al: WHI Investigators. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy. *JAMA* 2011;205:1305–1314.
  31. Lokkegaard E, Andreassen AH, Jacobsen AK, Nielsen LH, Agger C, Lidegaard O. Hormone therapy and risk of myocardial infarction: a national registry study. *Eur Heart J* 2008;29:2660–2668.
  32. Varas-Lorenzo C, Garcia-Rodriguez LA, Perez-Gutthann S, Duque-Oliart A. Hormone replacement therapy and incidence of acute myocardial infarction. *Circulation* 2000;101:2572–2578.
  33. Carrao G, Zambon A, Nicotra F, et al. Persistence with oral and transdermal hormone replacement therapy and hospitalization for cardiovascular outcomes. *Maturitas* 2007;57:315–324.
  34. Sumino H, Ichikawa S, Kasama S, et al. Different effects of oral conjugated estrogen and transdermal estradiol on arterial stiffness and vascular inflammatory markers in postmenopausal women. *Atherosclerosis* 2006;189:436–442.
  35. Straczek C, Oger E, Yon de Jonage-Canonico MB, et al. Estrogen and thromboembolism risk (ESTHER) Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. *Circulation* 2005;112:3495–3500.
  36. Scarabin PY, Oger E, Plu-Bureau G; Estrogen and Thromboembolism Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428–432.
  37. Canonico M, Oger E, Conard J, Meyer G, et al. Obesity and risk of venous thromboembolism among postmenopausal women: different impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;4:1259–1265.
  38. Canonico M, Plu-Bureau G, Lowe GD, Scarabin Y. Hormone replacement therapy and the risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;336:1227–1231.
  39. Brosnan JF, Sheppard BL, Norris LA. Haemostatic activation in post-menopausal women taking low-dose hormone therapy: less effect with transdermal administration? *Thromb Haemost* 2007;97:558–565.
  40. Flaumenhaft R, Nachtigall M, Lowenstein J, Nachtigall L, Nachtigall R, Nachtigall L. Association of oral but not transdermal estrogen therapy with enhanced platelet reactivity in a subset of postmenopausal women. *Menopause* 2009;16:407–412.
  41. Vongpatanasin W, Tuncel M, Mansour Y, Arbiqque D, Victor RG. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation* 2001;103:2903–2908.
  42. Ichikawa J, Sumino H, Ichikawa S, Ozaki M. Different effects of transdermal and oral hormone replacement therapy on the renin-angiotensin system, plasma bradykinin level, and blood pressure of normotensive postmenopausal women. *Am J Hypertens* 2006;19:744–749.
  43. Boschetti C, Cortellaro M, Nencioni T, Bertolli V, Della Volpe A, Zanussi C. Short and long-term effects of hormone replacement therapy (transdermal estradiol vs oral conjugated equine estrogens, combined with medroxyprogesterone

- acetate) on blood coagulation factors in postmenopausal women. *Thromb Res* 1991;62:1–8.
44. Luyer MDP, Khosla S, Owen WG, Miller VM. Prospective randomized study of effects of unopposed estrogen replacement therapy on markers of coagulation and inflammation in postmenopausal women. *J Clin Endocrinol Metab* 2001;86:3629–3634.
  45. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Alger R, Aich M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. *Arterio Thromb Vasc Biol* 1997;17:3071–3078.
  46. Post MS, Thomassen MC, Van Der Mooren MJ, et al. Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis. *Arterioscler Thromb Vasc Biol* 2003;23:1116–1121.
  47. Vehkavaara S, Silveira A, Hakala-ala-Pietila T, et al. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost* 2001;85:619–625.
  48. Salpeter SR, Walsh JM, Orniston TM, Greyber T, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone replacement therapy on components of metabolic syndrome in postmenopausal women. *Diabetes Obes Metab* 2006;8:538–554.
  49. Sumino H, Ichikawa S, Kasama S, et al. Effect of transdermal hormone replacement on carotid artery wall thickness and levels of vascular inflammatory markers in postmenopausal women. *Hypertens Res* 2005;28:579–584.
  50. Decensi A, Omodei U, Robertson C, et al. Effect of transdermal estradiol and oral conjugated estrogens on C-reactive protein in retinoid-placebo trial in healthy women. *Circulation* 2002;106:1224–1228.
  51. Modena MG, Bursi F, Fantini G, et al. Effects of hormone replacement therapy on C-reactive protein levels in healthy postmenopausal women: comparison between oral and transdermal administration of estrogen. *Am J Med* 2002;113:331–334.
  52. Lewandowski KC, Kamarowski J, Mikhailidis DP, et al. Effects of hormone replacement therapy type and route of administration on plasma matrix metalloproteinases and their tissue inhibitors in postmenopausal women. *J Clin Endocrinol Metab* 2006;91:3123–3130.
  53. Pradham AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA* 2002;288:980–987.
  54. Wakatsuki A, Okatani Y, Ikenoue N, Fukaya T. Effect of medroxyprogesterone acetate on vascular inflammatory markers in postmenopausal women receiving estrogen. *Circulation* 2002;105:1436–1439.
  55. Silvestri A, Gebara O, Vitale C, et al. Increased levels of C-reactive protein after oral hormone replacement therapy may not be related to an increased inflammatory response. *Circulation* 2003;107:3165–3169.
  56. Koh KK, Yoon B-K, Bairney-Merz CN, Sakuma I, Rebar RW. The effects of hormone therapy on inflammatory, hemostatic and fibrinolytic markers in postmenopausal women. *In*: Lobo RA, ed. *Treatment of the Postmenopausal Woman*. 3rd ed. Burlington, MA: Academic Press, 2007:471–480.
  57. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–843.
  58. Vongpatanasin W, Tuncel M, Wang Z, Arbique D, Mehrad B, Jialal I. Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J Am Coll Cardiol* 2003;41:1358–1363.
  59. Shifren JL, Rifai N, Desindes S, McIlwain M, Doros G, Mazer NA. A comparison of the short-term effects of oral conjugated equine estrogens versus transdermal estradiol on C-reactive protein, other serum markers of inflammation, and other hepatic proteins in naturally menopausal women. *J Clin Endocrinol Metab* 2008;93:1702–1710.
  60. Saucedo R, Rico G, Basurto L, Ochoa R, Zarate A. Transdermal estradiol in menopausal women depresses interleukin-6 without affecting other markers of immune response. *Gynecol Obstet Invest* 2002;53:114–117.
  61. Mueck AO, Genazzini AR, Samisoe G, Vukovik-Wysocki I, Seeger H. Low dose continuous combinations of hormone therapy and biochemical surrogate markers for vascular tone and inflammation: transdermal versus oral application. *Menopause* 2007;14:978–984.
  62. Ho JY, Chen MJ, Sheu WH, et al. Differential effects of oral conjugated equine estrogen and transdermal estrogen on atherosclerotic vascular disease risk markers and endothelial function in healthy postmenopausal women. *Hum Reprod* 2006;21:2715–2720.
  63. Yilmazer M, Fenkci V, Fenkci S, et al. Hormone replacement therapy, C-reactive protein, and fibrinogen in healthy postmenopausal women. *Maturitas* 2003;46:245–253.
  64. Bukowska H, Stanosz S, Zochowska E, et al. Does the type of hormone replacement therapy affect lipoprotein (a), homocysteine, and C-reactive protein levels in postmenopausal women? *Metabolism* 2005;54:72–78.
  65. Zanger D, Yang BK, Ardans J, et al. Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. *J Am Coll Cardiol* 2000;36:1797–1802.
  66. Chu MC, Cushman M, Solomon R, Lobo RA. Metabolic syndrome in postmenopausal women: the influence of oral or transdermal estradiol on inflammation and coagulation markers. *Am J Obstet Gynecol* 2008;199:526.e1–7.
  67. Davis SR, Stuckey BG, Norman RJ, Papalia MA, Drillich A, Bell RJ. Effects of the route of estrogen administration on insulin like growth factor-1, IGF binding protein-3, and insulin resistance in healthy postmenopausal women: results from a randomized, controlled study. *Menopause* 2008;15:1065–1069.
  68. Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006;154:1–11.
  69. Nachtigall LE, Raju U, Banerjee S, Wan L, Levitz M. Serum estradiol-binding profiles in postmenopausal women undergoing three common estrogen replacement therapies: associations with sex hormone binding globulin, estradiol, and estrone levels. *Menopause* 2000;7:243–250.
  70. Nappi RE, Polatti F. The use of estrogen therapy in women's sexual functioning. *J Sex Med* 2009;6:603–616.
  71. Nachtigall LE, Raju U, Banerjee S, Wan L, Levitz M. Serum estradiol-binding profiles in postmenopausal women undergoing three common estrogen replacement therapies: Associations with sex hormone-binding globulin, estradiol, and estrone levels. *Menopause* 2000;7:243–250.
  72. Shifren JL, Desindes S, McIlwain M, Doros G, Mazer NA. A randomized, open-label, crossover study comparing the



- effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. *Menopause* 2007;14:985–994.
73. Simon JA, Snabes MC. Menopausal hormone therapy for vasomotor symptoms: Balancing the risks and benefits with ultra-low doses of estrogen. *Expert Opin Investig Drugs* 2007;16:2005–2020.
  74. Smith NL, Heckbert SR, Lemaitre RN, et al. Esterified estrogens and conjugated equine estrogens and the risk of venous thrombosis. *JAMA* 2004;292:1581–1587.
  75. Gambacciarri M, Ciaponi M, Cappagli B, et al. Body weight, body fat distribution, and hormone therapy in early postmenopausal women. *J Clin Endocrin Metab* 1997;82:414–417.
  76. O'Sullivan AJ, Crampton LJ, Freund J, Ho KK. The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. *J Clin Invest* 1998;102:1035–1040.
  77. Di Carlo C, Tommaselli GA, Sammartino A, Bifulco G, Nasti A, Nappi C. Serum leptin levels and body composition in postmenopausal women: effects of hormone therapy. *Menopause* 2004;11:466–473.
  78. Chu MC, Cospers P, Orio F, Carmina E, Lobo RA. Insulin resistance in postmenopausal women with metabolic syndrome and the measurements of adiponectin, leptin, resistin, and ghrelin. *Am J Obstet Gynecol* 2006;194:100–104.
  79. Chu M, Cospers P, Nakhuda GS, Lobo RA. A comparison of oral and transdermal short-term estrogen therapy in postmenopausal women with metabolic syndrome. *Fertil Steril* 2006;86:1669–1675.
  80. Hillard TC, Whitcroft SJ, Marsh MS, et al. Long term effects of transdermal and oral hormone replacement therapy on postmenopausal bone loss. *Osteopor Int* 1994;4:341–348.
  81. Ettinger B, Ensrud KE, Wallace R, et al. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol* 2004;104:443–451.
  82. Physicians Desk Reference. 63rd ed. Montvale NJ: Thomson Healthcare, 2009.
  83. Ross RK, Paganini-Hill A, Wan PC, Rice MC. Effect of hormone replacement therapy on breast cancer risk: estrogen vs. estrogen plus progestogen. *J Natl Cancer Inst* 2000;92:328–332.
  84. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol* 2006;108:1354–1360.
  85. Corrao G, Zambon A, Conti V, et al. Menopause hormone replacement therapy and cancer risk: an Italian record linkage investigation. *Ann Oncol* 2008;19:150–155.
  86. Wong T, Shah NR. Breast cancer from oral and transdermal estradiol: a cohort study of Finnish women. *Womens Health (Lond Engl)* 2007;3:321–324.
  87. Stefanick ML, Anderson GL, Margolis KL, et al., for the WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 2006;295:1647–1657.
  88. Lobo RA. Adiposity after menopause and the effects of hormones. *Menopause Management* 2009;18:27–31.
  89. Hemelaar M, Kenemans P, Huck CE, Klipping C, van der Mooren MJ. Hemostatic markers in healthy postmenopausal women during intranasal and oral hormone therapy; a randomized trial. *Menopause* 2008;15:248–255.

Address correspondence to:

*Michael P. Goodman, M.D.*

*Caring For Women Wellness Center*

*635 Anderson Road, Suite 12B*

*Davis, CA 95616*

*E-mail: michaelgoodman250@gmail.com*

