

The Bioidentical Hormone Debate: Are Bioidentical Hormones (Estradiol, Estriol, and Progesterone) Safer or More Efficacious than Commonly Used Synthetic Versions in Hormone Replacement Therapy?

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Abstract

Background: The use of bioidentical hormones, including progesterone, estradiol, and estriol, in hormone replacement therapy (HRT) has sparked intense debate. Of special concern is their relative safety compared with traditional synthetic and animal-derived versions, such as conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins. Proponents for bioidentical hormones claim that they are safer than comparable synthetic and nonhuman versions of HRT. Yet according to the US Food and Drug Administration and The Endocrine Society, there is little or no evidence to support claims that bioidentical hormones are safer or more effective. **Objective:** This paper aimed to evaluate the evidence comparing bioidentical hormones, including progesterone, estradiol, and estriol, with the commonly used nonbioidentical versions of HRT for clinical efficacy, physiologic actions on breast tissue, and risks for breast cancer and cardiovascular disease. **Methods:** Published papers were identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT. Papers that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and in vitro results, were selected. **Results:** Patients report greater satisfaction with HRTs that contain progesterone compared with those that contain a synthetic progestin. Bioidentical hormones have some distinctly different, potentially opposite, physiological effects compared with their synthetic counterparts, which have different chemical structures. Both physiological and clinical data have indicated that progesterone is associated with a diminished risk for breast cancer, compared with the increased risk associated with synthetic progestins. Estriol has some unique physiological effects, which differentiate it from estradiol, estrone, and CEE. Estriol would be expected to carry less risk for breast cancer, although no randomized controlled trials have been documented. Synthetic progestins have a variety of negative cardiovascular effects, which may be avoided with progesterone. **Conclusion:** Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT. Further randomized controlled trials are needed to delineate these differences more clearly.

Keywords: bioidentical hormones; synthetic hormones; hormone replacement therapy; estriol; progesterone; conjugated equine estrogens; medroxyprogesterone acetate; breast cancer; cardiovascular disease

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Introduction

The relative safety of bioidentical hormone replacement compared with traditional synthetic and animal-derived versions, such as conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins is the subject of intense debate. According to The Endocrine Society Position Statement, there is little or no evidence to support the claim that bioidentical hormones are safer or more effective than the commonly used synthetic versions of hormone replacement therapy (HRT).¹ Furthermore, the US Food and Drug Administration (FDA) has ordered pharmacies to stop providing estriol, stating that it is a new, unapproved drug with unknown safety and effectiveness.

Nevertheless, estriol has been used for decades without reported safety concerns and is a component of medications approved for use worldwide. The FDA has acknowledged that it is unaware of any adverse events associated with the use of compounded medications containing estriol, and US Congress is considering a resolution (HR342) to reverse the FDA's decision to restrict its use. Claims by The Endocrine Society and the FDA are in direct contrast to those of proponents of bioidentical hormones, who argue that these hormones are safer than comparable synthetic versions of HRT. Such claims are not fully supported, which can be confusing for patients and physicians.

One major reason for a lack of conclusive data is that, until recently, progestogens were lumped together because of a commonly held belief that different forms of progestogens would have identical physiological effects and risks, because they all mediate effects via the same (progesterone) receptor. This view also applies to the different forms of estrogen, which are commonly grouped together and referred to as estrogen replacement therapy.

The term "bioidentical HRT" refers to the use of hormones that are exact copies of endogenous human hormones, including estriol, estradiol, and progesterone, as opposed to synthetic versions with different chemical structures or nonhuman versions, such as CEE. Bioidentical hormones are also often referred to as "natural hormones," which can be confusing because bioidentical hormones are synthesized, while some estrogens from a natural source, such as equine urine, are not considered bioidentical because many of their components are foreign to the human body.

This review will examine the differences between the bioidentical hormones estriol, estradiol, and progesterone when used as components of HRT compared with synthetic or nonidentical hormones such as CEE and synthetic progestins, including MPA. The article attempts to determine whether

there is any supporting evidence that bioidentical hormones are a potentially safer or more effective form of HRT than the commonly used synthetic versions.

Methods

Definitions

Bioidentical hormones have a chemical structure identical to human hormones but are chemically synthesized, such as progesterone, estriol, and estradiol. Nonbioidentical hormones are not structurally identical to human hormones and may either be chemically synthesized, such as MPA, or derived from a nonhuman source, such as CEE.

Databases and Keywords

Literature searches were conducted for HRT formularies, focusing on those that either are or have been used in the United States. Published papers identified for review by PubMed/MEDLINE, Google Scholar, and Cochrane database searches included the keywords: "bioidentical hormones," "synthetic hormones," "progestin," "menopausal hormone replacement," "hormone replacement therapy," "HRT," "estriol," "progesterone," "natural hormones," "conjugated equine estrogens," "medroxyprogesterone acetate," "breast cancer," and "cardiovascular disease."

Comparisons

Published papers that focused on 3 key areas were identified: 1) clinical efficacy, 2) physiologic actions on breast tissue, and 3) risks for breast cancer and cardiovascular disease. Papers included human clinical studies that compared bioidentical and nonbioidentical hormones, animal studies based on similar comparisons, and in vitro experimental work that focused on physiological or biochemical aspects of the hormones.

Results

I) Symptomatic Efficacy of Synthetic Progestins versus Progesterone

Four studies of patients using HRT, including either progesterone or MPA, compared efficacy, patient satisfaction, and quality of life. Women in all 4 studies reported greater satisfaction, fewer side effects, and improved quality of life when they were switched from synthetic progestins to progesterone replacement.²⁻⁶ In a cross-sectional survey, Fitzpatrick et al compared patient satisfaction and quality of life, as well as other somatic and psychological symptoms (ie, anxiety, depression, sleep problems, menstrual bleeding,

vasomotor symptoms, cognitive difficulties, attraction, and sexual functioning) in 176 menopausal women on HRT with MPA versus HRT with progesterone.² Significant differences were seen for all somatic, vasomotor, and psychological symptoms, except for attraction, when bioidentical progesterone was used rather than MPA ($P < 0.001$).

The effect of progesterone compared with MPA included a 30% reduction in sleep problems, a 50% reduction in anxiety, a 60% reduction in depression, a 30% reduction in somatic symptoms, a 25% reduction in menstrual bleeding, a 40% reduction in cognitive difficulties, and a 30% improvement in sexual function. Overall, 65% of women felt that HRT combined with progesterone was better than the HRT combined with MPA.²

In a randomized study comparing HRT with MPA or progesterone in 23 postmenopausal women with no mood disorders such as depression or anxiety, Cummings and Buzdin found significantly more negative somatic effects but no differences in mood assessment with synthetic hormones. These negative effects included increased vaginal bleeding ($P = 0.003$) and increased breast tenderness ($P = 0.02$), with a trend for increased hot flashes with the use of MPA compared with progesterone.³ In the 3-year, double-blind, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, 875 menopausal women received either placebo, CEE with MPA (cyclic or continuous), or progesterone (cyclic). Those taking progesterone had fewer episodes of excessive bleeding than those on MPA (either continuous or cyclic),⁴ but no differences were noted in symptomatic relief.⁵

2) Differing Physiological Effects of Bioidentical Progesterone and Synthetic Progestins

Progesterone and synthetic progestins generally have indistinguishable effects on endometrial tissue, which are not the focus of this review. Studies that compared the physiological differences in breast tissue of those on progesterone, with those on other progestins, have the potential to predict differing risks of breast cancer. While variations in methodology and study design are considerable, most of the literature demonstrates physiological differences between progestins and progesterone and their effects on breast tissue.

Synthetic progestins have potential antiapoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation.⁷⁻²¹ In contrast, progesterone inhibits estrogen-stimulated breast epithelial cells.^{16,22-28} Progesterone also downregulates estrogen receptor-1 (ER-1)

in the breast,²⁷⁻²⁹ induces breast cancer cell apoptosis,^{30,31} diminishes breast cell mitotic activity,^{7,16,22-24,26-28,31,32} and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1.^{23,32}

Synthetic progestins, in contrast, upregulate cyclin D1²¹ and increase breast cell proliferation.⁷⁻²¹ Progesterone consistently demonstrates antiestrogenic activity in breast tissue.^{7,16,22,24-29,31-34} This result is generally in contrast to that for synthetic progestins, especially the 19-nortestosterone-derived progestins, which bind to estrogen receptors in breast tissue (but not in endometrial tissue) and display significant intrinsic estrogenic properties in breast but not endometrial tissue.^{11,23,35-39}

Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens,^{7,40-45} potentially contributing to their carcinogenic effects, which are not apparent with progesterone. Synthetic progestins may promote the formation of the genotoxic estrogen metabolite 16-hydroxyestrone.⁴¹ Synthetic progestins, especially MPA, stimulate the conversion of inactive estrone sulfate into active estrone by stimulating sulfatase,^{43,44} as well as increasing 17-beta-hydroxysteroid reductase activity,^{7,40,42,43,45} which in turn increases the intracellular formation of more potent estrogens and potentially increases breast cancer risk. Progesterone has an opposite effect, stimulating the oxidative isoform of 17-beta-hydroxysteroid dehydrogenase, which increases the intracellular conversion of potent estrogens to their less potent counterparts.^{34,46,47}

At least 3 subclasses of progesterone receptors (PR) have been identified: PRA, PRB, and PRC, each with different cellular activities.⁴⁸⁻⁵² In normal human breast tissue, the ratio of PRA:PRB is approximately 1:1.^{50,53} This ratio is altered in a large percentage of breast cancer cells and is a risk for breast cancer.^{50,53,54} In contrast to progesterone, synthetic progestins alter the normal PRA:PRB ratio,⁵⁵⁻⁵⁷ which may be a mechanism by which synthetic progestins increase the risk for breast cancer.

Synthetic progestins and progesterone have a number of differences in their molecular and pharmacological effects on breast tissue, as some of the procarcinogenic effects of synthetic progestins contrast with the anticarcinogenic properties of progesterone.^{8,16,22,24-26,31,33,40,58-70}

3) Breast Cancer and Cardiovascular Disease Risks

Risk for Breast Cancer with Synthetic Progestins

Many studies have assessed the risk for breast cancer with the use of a synthetic progestin for HRT. Despite significant variability in study design, synthetic progestins have been clearly associated with an increased risk for breast cancer.^{7,8,58,71-98}

The Women's Health Initiative (WHI), a large randomized clinical trial, demonstrated that a synthetic progestin, MPA, as a component of HRT significantly increased the risk for breast cancer (relative risk [RR] = 1.26, 95% confidence interval [CI]: 1.00-1.59).⁷¹⁻⁷⁴ This trial confirmed results from numerous other groups demonstrating that a synthetic progestin significantly increases breast cancer risk.^{7,75-98} In addition, higher doses of progestins, testosterone-derived synthetic progestins, and progestin-only regimens further increase the risk for breast cancer.^{8,75-77,80,91} The Nurses' Health Study, which followed 58 000 postmenopausal women for 16 years (725 000 person-years), found that, compared with women who never used hormones, use of unopposed postmenopausal estrogen from ages 50 to 60 years increased the risk for breast cancer to age 70 years by 23% (95% CI: 6-42). The addition of a synthetic progestin to the estrogen replacement resulted in a tripling of the risk for breast cancer (67% increased risk) (95% CI: 18-136).⁹⁸

Ross et al compared the risk for breast cancer in 1897 women on combined estrogen and synthetic progestin with 1637 control patients who had never used HRT. Synthetic progestin use increased the risk for breast cancer by approximately 25% for each 5 years of use compared with estrogen alone (RR = 1.25, 95% CI: 1.02-1.18).⁸² In a meta-analysis of 61 studies, Lee et al found a consistently increased risk for breast cancer with synthetic HRT, with an average increase of 7.6% per year of use (95% CI: 1.070-1.082), and also found that higher doses of synthetic progestins conferred a significantly increased risk for breast cancer.⁷⁵ Ewertz et al examined the risk for breast cancer for approximately 80 000 women aged 40 to 67 years from 1989 to 2002. For women older than 50 years, current use of synthetic HRT increased the risk for breast cancer by 61% (95% CI: 1.38-1.88). Longer duration of use and the use of synthetic progestins derived from testosterone were associated with increased risk.⁷⁶ Newcomb et al studied the risk for breast cancer with synthetic HRT (80% used CEE and 86% used MPA) in more than 5000 postmenopausal women aged 50 to 79 years. They found a significant increase in breast cancer of 2% per year for the estrogen-only group (RR = 1.02/yr, 95% CI: 1.01-1.03/

yr), and a 4% increase per year if a synthetic progestin was used in addition to the estrogen (RR = 1.04/yr, 95% CI: 1.01-1.08/yr). Higher doses of progestin increased the risk for breast cancer, and use of a progestin-only preparation doubled the risk for breast cancer (RR = 2.09, 95% CI: 1.07-4.07).⁷⁷

Risk for Breast Cancer with Bioidentical Progesterone

Progesterone and synthetic progestins have generally indistinguishable effects on endometrial tissue. However, as discussed above, there is significant evidence that progesterone and synthetic progestins have differing effects on breast tissue proliferation. Thus, progesterone and synthetic progestins would be expected to carry different risks for breast cancer. Although no randomized, controlled trials were identified that directly compared the risks for breast cancer between progesterone and synthetic progestins, large-scale observational trials^{58,59} and randomized placebo control primate trials¹⁶ do show significant differences. Furthermore, in contrast to the demonstrated increased risk for breast cancer with synthetic progestins,^{7,8,58,71-98} studies have consistently shown a decreased risk for breast cancer with progesterone.^{22,23,25,60,61,66-70,99-101}

In 2007, Fournier et al reported an association between various forms of HRT and the incidence of breast cancer in more than 80 000 postmenopausal women who were followed for more than 8 postmenopausal years.⁵⁹ Compared with women who had never used any HRT, women who used estrogen only (various preparations) had a nonsignificant increase of 1.29 times the risk for breast cancer ($P = 0.73$). If a synthetic progestin was used in combination with estrogen, the risk for breast cancer increased significantly to 1.69 times that for control subjects ($P = 0.01$). However, for women who used progesterone in combination with estrogen, the increased risk for breast cancer was eliminated with a significant reduction in breast cancer risk compared with synthetic progestin use ($P = 0.001$).⁵⁹

In a previous analysis of more than 50 000 postmenopausal women in the E3N-EPIC cohort, Fournier et al found that the risk for breast cancer was significantly increased if synthetic progestins were used (RR = 1.4), but was reduced if progesterone was used (RR = 0.9). There was a significant difference in the risk for breast cancer between the use of estrogens combined with synthetic progestins versus estrogens combined with progesterone ($P < 0.001$).⁵⁸

Wood et al investigated whether the increased breast cancer risk with synthetic progestins was also seen when

progesterone was used.¹⁶ Postmenopausal primates were given placebo, estradiol, estradiol and MPA, and estradiol and bioidentical progesterone, with each treatment for 2 months with a 1-month washout period. Ki67 expression is a biomarker for lobular and ductal epithelial proliferation in the postmenopausal breast and is an important prognostic indicator in human breast cancer.¹⁰² Compared with placebo, significantly increased proliferation was found with the combination of estrogen and MPA in both lobular ($P = 0.009$) and ductal ($P = 0.006$) tissue, but was not seen with the combination of estrogen and progesterone. Intramammary gene expressions of the proliferation markers Ki67 and cyclin B1 were also higher after treatment with estrogen and MPA (4.9-fold increase, $P = 0.007$ and 4.3-fold increase, $P = 0.002$, respectively) but not with estrogen and progesterone. Inoh et al investigated the protective effect of progesterone and tamoxifen on estrogen- and diethylstilbestrol-induced breast cancer in rats. The induction rate, multiplicity, and size of estrogen-induced mammary tumors were significantly reduced by simultaneous administration of either tamoxifen or progesterone.²⁵

Chang et al examined the effects of estrogen and progesterone on women prior to breast surgery in a double-blind, placebo-controlled study in which patients were given placebo, estrogen, transdermal progesterone, or estrogen and transdermal progesterone for 10 to 13 days before breast surgery. Estrogen increased cell proliferation rates by 230% ($P < 0.05$), but progesterone decreased cell proliferation rates by 400% ($P < 0.05$). Progesterone, when given with estradiol, inhibited the estrogen-induced breast cell proliferation.²² Similarly, in a randomized, double-blind study, Foidart et al also showed that progesterone eliminated estrogen-induced breast cell proliferation ($P = 0.001$).²³

A prospective epidemiological study demonstrated a protective role for progesterone against breast cancer.⁹⁹ In this study, 1083 women who had been treated for infertility were followed for 13 to 33 years. The premenopausal risk for breast cancer was 5.4 times higher in women who had low progesterone levels compared with those with normal levels (95% CI: 1.1–49). The result was significant, despite the fact that the high progesterone group had significantly more risk factors for breast cancer than the low progesterone group, highlighting the importance of this parameter. Moreover, there were 10 times as many deaths from cancer in the low progesterone group compared with those with normal progesterone levels (95% CI: 1.3–422).⁹⁹ Women with low progesterone have significantly worse breast cancer

survival rates than those with more optimal progesterone levels.^{100,101}

In a prospective study, luteal phase progesterone levels in 5963 women were measured and compared with subsequent risk for breast cancer. Progesterone was inversely associated with breast cancer risk for the highest versus lowest tertile (RR = 0.40, 95% CI: 0.15–1.08, P for trend = 0.077). This trend became significant in women with regular menses, which allowed for more accurate timing of collection (RR = 0.12, 95% CI: 0.03–0.52, $P = 0.005$).⁶¹ Other case-control studies also found such a relationship.^{66–70}

Peck et al conducted a nested case-control study to examine third-trimester progesterone levels and maternal risk of breast cancer in women who were pregnant between 1959 and 1966. Cases ($n = 194$) were diagnosed with in situ or invasive breast cancer between 1969 and 1991. Controls ($n = 374$) were matched to cases by age at the time of index pregnancy using randomized recruitment. Increasing progesterone levels were associated with a decreased risk of breast cancer. Relative to those with progesterone levels in the lowest quartile (< 124.25 ng/mL), those in the highest quartile (> 269.97 ng/mL) had a 50% reduction in the incidence of breast cancer (RR = 0.49, CI 0.22–1.1, P for trend = 0.08). The association was stronger for cancers diagnosed at or before age 50 years (RR = 0.3, CI: 0.1–0.9, P for trend = 0.04).⁶⁰ Pre-eclampsia, with its associated increased progesterone levels, is also associated with a reduced risk for breast cancer.^{103–105}

Estriol and the Risk for Breast Cancer

Estrogen effects are mediated through 2 different estrogen receptors: estrogen receptor-alpha (ER- α) and estrogen receptor-beta (ER- β).^{106–111} Estrogen receptor- α promotes breast cell proliferation, while ER- β inhibits proliferation and prevents breast cancer development via G2 cell cycle arrest.^{106,112–117}

Estradiol equally activates ER- α and ER- β , while estrone selectively activates ER- α at a ratio of 5:1.^{118,119} In contrast, estriol selectively binds ER- β at a ratio of 3:1.^{118,119} This unique property of estriol, in contrast to the selective ER- α binding by other estrogens,^{107,118–121} imparts to estriol a potential for breast cancer prevention,^{59,122–125} while other estrogens would be expected to promote breast cancer.^{106,112–115,126} As well as selectively binding ER- α , CEE components are potent downregulators of ER- β receptors.¹¹⁴ Whether this activity is unique to CEE is unclear, but it could potentially increase carcinogenic properties.

Furthermore, synthetic progestins synergistically downregulate ER- β receptors,¹¹⁴ a possible mechanism underlying

the breast-cancer-promoting effect of CEE in conjunction with synthetic progestins. Conjugated equine estrogens also contains at least one particularly potent carcinogenic estrogen, 4-hydroxy-equilenin, which promotes cancer by inducing DNA damage.^{127–131}

Because of its differing effects on ER- α and ER- β , we would expect that estriol would be less likely to induce proliferative changes in breast tissue and to be associated with a reduced risk of breast cancer.^{40,59,80,103–105,122–125,132–144} Only one *in vitro* study on an estrogen receptor-positive breast cancer tissue cell line demonstrated a stimulatory effect of estriol as well as for estrone and estradiol.¹⁴⁵ Melamed et al demonstrated that, when administered with estradiol, estriol may have a unique ability to protect breast tissue from excessive estrogen-mediated stimulation. Acting alone, estriol is a weak estrogen, but when given with estradiol, it functions as an antiestrogen. Interestingly, estriol competitively inhibits estradiol binding and also inhibits activated receptor binding to estrogen response elements, which limits transcription.¹³⁵ Patentable estriol-like selective estrogen receptors modulators (SERMs) are being developed to prevent and treat breast cancer.^{106,112,113,115}

Estriol and progesterone levels dramatically increase during pregnancy (an approximate 15-fold increase in progesterone and a 1000-fold increase in estriol), and postpartum women continue to produce higher levels of estriol than nulliparous women.¹³⁶ This increased exposure to progesterone and estriol during and after pregnancy confers a significant long-term reduction in the risk for breast cancer.^{40,103–105,136–141} If these substances were carcinogenic, it would be expected that pregnancy would increase the risk for breast cancer rather than protect against it. Urinary estriol levels in postmenopausal women show an inverse correlation with the risk for breast cancer in many,^{125,132–134,142,143,146} but not all, studies.¹⁴⁷

Lemon et al demonstrated that estriol and/or tamoxifen, as opposed to other estrogens, prevented the development of breast cancer in rats after the administration of carcinogens.^{123,124} Mueck et al compared the proliferative effects of different estrogens on human breast cancer cells when combined with progesterone or synthetic progestins.²⁴ They found that progesterone inhibited breast cancer cell proliferation at higher estrogen levels, but that synthetic progestins had the potential to stimulate breast cancer cell proliferation when combined with the synthetic estrogens equilin or 17- α -dihydroequilin, which are major components of CEE. This demonstrates a mechanism for the particularly marked increased risk for breast cancer when CEE is combined with a synthetic progestin.

In a large study of more than 30 000 women by Bakken et al, the use of estrogen-only HRT increased the risk of breast cancer compared with that in nonusers (RR = 1.8, 95% CI: 1.1–2.9). The addition of a synthetic progestin further increased breast cancer risk (RR = 2.5, 95% CI: 1.9–3.2) while the use of an estriol-containing preparation was not associated with the risk of breast cancer that was seen with other preparations (RR = 1.0, 95% CI: 0.4–2.5).¹⁴⁴

In a large case-control study of 3345 women aged 50 to 74 years, the use of estrogen only, estrogen and synthetic progestin, or progestin only was associated with a significantly increased risk of breast cancer (RR = 1.94, 95% CI: 1.47–2.55; RR = 1.63, CI: 1.37–1.94; and RR = 1.59, CI: 1.05–2.41, respectively). The risk of breast cancer among estriol users was, however, not appreciably different than among nonusers (RR = 1.10, CI: 0.95–1.29).⁸⁰ Large-scale randomized control trials are needed to quantify the effects of estriol in the risk of breast cancer.

Cardiovascular Risk with Synthetic Progestins versus Progesterone

The WHI study demonstrated that the addition of MPA to Premarin[®] (a CEE) resulted in a substantial increase in the risk of heart attack and stroke.^{71–73} This outcome with MPA is not surprising because synthetic progestins produce negative cardiovascular effects and negate the cardioprotective effects of estrogen.^{71,73,148–172} Progesterone, in contrast, has the opposite effect because it maintains and augments the cardioprotective effects of estrogen, thus decreasing the risk for heart attack and stroke.^{148–151,153,155,157,162,165,167,173–178}

One mechanism contributing to these opposing effects for cardiovascular risk is the differing effects on lipids. Medroxyprogesterone acetate and other synthetic progestins generally negate the positive lipid effects of estrogen and show a consistent reduction in HDL,^{148,153–159,163} the most important readily measured determinant of cardioprotection, while progesterone either maintains or augments estrogen's positive lipid and HDL effects.^{148,154,155,157,173,176} For instance, the PEPI trial, a long-term randomized trial of HRT, compared a variety of cardiovascular effects including lipid effects of both MPA and progesterone in combination with CEE. While all regimens were associated with clinically significant improvements in lipoprotein levels, many of estrogen's beneficial effects on HDL-C were negated with the addition of MPA. The addition of progesterone to CEE, however, was associated with significantly higher HDL-C levels than with MPA and CEE (a notable sparing of estrogen's beneficial effects) ($P < 0.004$).¹⁵⁴

Fahraeus et al compared the lipid effects of synthetic progestins with progesterone in 26 postmenopausal women who had been receiving cutaneous estradiol for 3 to 6 months. Women received either 120 µg of l-norgestrel or 300 mg of progesterone sequentially for another 6 months. Compared with the use of progesterone, l-norgestrel resulted in significant reductions in HDL and HDL-2 ($P < 0.05$).¹⁵⁵

Ottosson et al compared the lipid effects of estrogen when combined with either of 2 synthetic progestins, or bioidentical progesterone.¹⁴⁸ Menopausal women were initially treated with 2 mg estradiol valerate (cyclical) for 3 cycles, and then were randomized to receive MPA, levonorgestrel, or progesterone. Serum lipids and lipoproteins were analyzed during the last days of the third, fourth, and sixth cycles. Those receiving estrogen combined with levonorgestrel had a significant reduction in HDL and HDL subfraction 2 (18% and 28%, respectively; $P < 0.01$), as did those receiving MPA (8% and 17%, respectively; $P < 0.01$). Conversely, there were no significant changes seen in the HDL and HDL subfraction levels with the use of progesterone.¹⁴⁸ Furthermore, a randomized trial by Saarikoski et al which compared the lipid effects in women using the synthetic progestin norethisterone and progesterone, those on synthetic progestin had a significant decrease in HDL, whereas those using progesterone had no decrease in HDL ($P < 0.001$).¹⁵³

A number of studies have shown that coronary artery spasm, which increases the risk for heart attack and stroke, is reduced with the use of estrogen and/or progesterone.^{149–151, 174, 179, 180} However, the addition of MPA to estrogen has the opposite effect, resulting in vasoconstriction,^{149–151, 174} thus increasing the risk for ischemic heart disease. Minshall et al compared coronary hyperreactivity by infusing a thromboxane A2 mimetic in primates, which were administered estradiol along with MPA or progesterone. When estradiol was given with progesterone, the coronary arteries were protected against induced spasm. However, the protective effect was lost when MPA was used instead of progesterone.¹⁴⁹

Miyagawa et al also compared the reactivity of coronary arteries in primates pretreated with estradiol combined with either progesterone or MPA. None of the animals treated with bioidentical progesterone experienced vasospasm, while all of those treated with MPA showed significant vasospasm.¹⁵¹ Mishra et al¹⁵⁰ also found that progesterone protected against coronary hyperreactivity, while MPA had the opposite effect and induced coronary constriction.

In a blinded, randomized, crossover study, the effects of estrogen and progesterone were compared with estrogen and MPA on exercise-induced myocardial ischemia

in postmenopausal women with coronary artery disease. Women were treated with estradiol for 4 weeks and then randomized to receive either progesterone or MPA along with estradiol. After 10 days on the combined treatment, the patients underwent a treadmill test. Patients were then crossed over to the opposite treatment, and the treadmill exercise was repeated. Exercise time to myocardial ischemia was significantly increased in the progesterone group compared with the MPA group ($P < 0.001$).¹⁶²

Adams et al^{152, 175} examined the cardioprotective effects of CEE and progesterone versus CEE and MPA in primates fed atherogenic diets for 30 months. The CEE and progesterone combination resulted in a 50% reduction in atherosclerotic plaques in the coronary arteries ($P < 0.05$).¹⁷⁵ This result was independent of changes in lipid concentrations. However, when MPA was combined with the CEE, almost all the cardioprotective effect (atherosclerotic plaque reduction) was reversed ($P < 0.05$).¹⁵² Other studies have shown that progesterone by itself,^{167, 177, 181} or in combination with estrogen,^{152, 175, 177} inhibits atherosclerotic plaque formation. Synthetic progestins, in contrast, have a completely opposite effect: they promote atherosclerotic plaque formation and prevent the plaque-inhibiting and lipid-lowering actions of estrogen.^{152, 164, 166}

Transdermal estradiol, when given with or without oral progesterone, has no detrimental effects on coagulation and no observed increased risk for venous thromboembolism (VTE).^{161, 182–184} This result is in contrast to an increased risk for VTE with CEE, with or without synthetic progestin, which significantly increases the risk for VTE, whether both are given orally (eg, oral estrogen and oral synthetic progestin),^{71, 73, 160, 171} as transdermal estrogen and oral synthetic progestin,¹⁶¹ or both estrogen and synthetic progestin given transdermally.^{185, 186} Canonico et al compared the risk for VTE with different forms of HRT in 271 cases and 610 controls. They found that transdermal estradiol and oral progesterone or pregnane derivatives (progestins derived from progesterone) were not associated with VTE risk (RR = 0.7; 95% CI: 0.3–1.9 and RR = 0.9; 95% CI: 0.4–2.3, respectively). In contrast, the use of nonpregnane derivatives increased VTE risk 4-fold (RR = 3.9; 95% CI: 1.5–10).¹⁶¹

Medroxyprogesterone acetate also has undesirable intrinsic glucocorticoid activity,^{187, 188} whereas progesterone does not have such negative effects and is a competitive inhibitor of aldosterone, which is generally a desirable effect.¹⁸⁹ No changes in blood pressure are observed with progesterone in normotensive postmenopausal women, but a slight reduction in blood pressure is shown in hypertensive women.^{190, 191}

Synthetic progestins can significantly increase insulin resistance,^{167–170,191} when compared with estrogen and progesterone.^{169,170,191}

The expression of vascular cell adhesion molecule-1 (VCAM-1) is one of the earliest events in the atherogenic process. Otsuki et al compared the effects of progesterone and MPA on VCAM-1 expression and found that progesterone inhibited VCAM-1. No such effect was observed with MPA ($P < 0.001$).¹⁶⁵

Discussion

Physicians must translate both basic science results and clinical outcomes to decide on the safest, most efficacious treatment for patients. Evidence-based medicine involves the synthesis of all available data when comparing therapeutic options for patients. Evidence-based medicine does not mean that data should be ignored until a randomized control trial of a particular size and duration is completed. Rather, it demands an assessment of the current available data to decide which therapies are likely to carry the greatest benefits and the lowest risks for patients.

Progesterone, compared with MPA, is associated with greater efficacy, patient satisfaction, and quality of life. More importantly, molecular differences between synthetic progestins and progesterone result in differences in their pharmacological effects on breast tissue. Some of the procarcinogenic effects of synthetic progestins contrast with the anticarcinogenic properties of progesterone, which result in disparate clinical effects on the risk of breast cancer. Progesterone has an antiproliferative, antiestrogenic effect on both the endometrium and breast tissue, while synthetic progestins have antiproliferative, antiestrogenic effects on endometrial tissue, but often have a proliferative estrogenic effect on breast tissue. Synthetic progestins show increased estrogen-induced breast tissue proliferation and a risk for breast cancer, whereas progesterone inhibits breast tissue proliferation and reduces the risk for breast cancer.

Until recently, estriol was available in the United States as a compounded prescription, but was banned in January 2008 by the FDA, which stated that it was a new, unapproved drug with unknown safety and effectiveness, although its symptomatic efficacy is generally not in question.^{192–196} The FDA has not received a single report of an adverse event in more than 30 years of estriol use. Estriol is also the subject of a US Pharmacopeia monograph. The FDA Modernization Act of 1997 clearly indicated that drugs with a US Pharmacopeia monograph could be compounded. It appears that the

FDA took action, not because estriol is at least as safe and effective as current estrogens on the market, but in response to what was considered unsupported claims that estriol was safer than current forms of estrogen replacement and because there is no standardized dose. Estriol has unique physiologic properties associated with a reduction in the risk of breast cancer, and combining estriol with estradiol in hormone replacement preparations would be expected to decrease the risk for breast cancer.

In cardiovascular disease, synthetic progestins, as opposed to progesterone, negate the beneficial lipid and vascular effects of estrogen. Transdermal bioidentical estrogen and progesterone are associated with beneficial cardiovascular and metabolic effects compared with the use of CEE and synthetic progestins.

Based on both physiological results and clinical outcomes, current evidence demonstrates that bioidentical hormones are associated with lower risks than their nonbioidentical counterparts. Until there is evidence to the contrary, current evidence dictates that bioidentical hormones are the preferred method of HRT.

Conclusion

A thorough review of the medical literature supports the claim that bioidentical hormones have some distinctly different, often opposite, physiological effects to those of their synthetic counterparts. With respect to the risk for breast cancer, heart disease, heart attack, and stroke, substantial scientific and medical evidence demonstrates that bioidentical hormones are safer and more efficacious forms of HRT than commonly used synthetic versions. More randomized control trials of substantial size and length will be needed to further delineate these differences.

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Conflict of Interest Statement

Kent Holtorf, MD discloses no conflicts of interest.

References

1. The Endocrine Society. Bioidentical Hormones Position Statement, October 2006. <http://www.endo-society.org/publicpolicy/policy/upload/>

- BH_Position_Statement_final_10_25_06_w_Header.pdf. Accessed January 21, 2008.
- Fitzpatrick LA, Pace C, Witt B. Comparison of regimens containing oral micronized progesterone of medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. *J Womens Health Gen Based Med*. 2000;9(4):381–387.
 - Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. *Menopause*. 2002;9:253–263.
 - Lindenfeld EA, Langer RD. Bleeding patterns of the hormone replacement therapies in the postmenopausal estrogen and progestin interventions trial. *Obstet Gynecol*. 2002;100(5 pt 1):853–863.
 - Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol*. 1998;92(6):982–988.
 - Hargrove JT, Maxon WS, Wentz AC, Burnett LS. Menopausal hormone replacement therapy with continuous daily oral micronized progesterone. *Obstet Gynecol*. 1989;73(4):606–612.
 - de Lignières B. Effects of progestogens on the postmenopausal breast. *Climacteric*. 2002;5(3):229–235.
 - Campagnoli C, Clavel-Chapelon F, Kaaks R, Peris C, Berrino F. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *J Steroid Biochem Mol Biol*. 2005;96(2):95–108.
 - Ory K, Lebeau J, Levalois C, et al. Apoptosis inhibition mediated by medroxyprogesterone acetate treatment of breast cancer cell lines. *Breast Cancer Res Treat*. 2001;68(3):187–198.
 - Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA, Haslam SZ. Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. *J Clin Endocrinol Metab*. 1999;84(12):4559–4565.
 - Jeng MH, Parker CJ, Jordan VC. Estrogenic potential of progestins in oral contraceptives to stimulate human breast cancer cell proliferation. *Cancer Res*. 1992;52(23):6539–6546.
 - Kalkhoven E, Kwakkenbos-Isbrücker L, de Laat SW, van der Saag PT, van der Burg B. Synthetic progestins induce proliferation of breast tumor cell lines via the progesterone or estrogen receptor. *Mol Cell Endocrinol*. 1994;102(1–2):45–52.
 - Papa V, Reese CC, Brunetti A, Vigneri R, Siiteri PK, Goldfine ID. Progestins increase insulin receptor content and insulin stimulation of growth in human breast carcinoma cells. *Cancer Res*. 1990;50(24):7858–7862.
 - Hissom JR, Moore MR. Progestin effects on growth in the human breast cancer cell line T-47D—possible therapeutic implications. *Biochem Biophys Res Commun*. 1987;145(2):706–711.
 - Catherino WH, Jeng MH, Jordan VC. Norgestrel and gestodene stimulate breast cancer cell growth through an oestrogen receptor mediated mechanism. *Br J Cancer*. 1993;67(5):945–952.
 - Wood CE, Register TC, Lees CJ, Chen H, Kimrey S, Cline JM. Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys. *Breast Cancer Res Treat*. 2007;101(2):125–134.
 - Cline JM, Soderqvist G, von Schoultz E, Skoog L, von Schoultz B. Effects of conjugated estrogens, medroxyprogesterone acetate, and tamoxifen on the mammary glands of macaques. *Breast Cancer Res Treat*. 1998;48(3):221–229.
 - Cline JM, Soderqvist G, von Schoultz E, Skoog L, von Schoultz B. Effects of hormone replacement therapy on the mammary gland of surgically postmenopausal cynomolgus macaques. *Am J Obstet Gynecol*. 1996;174(1 pt 1):93–100.
 - Braunsberg H, Coldham NG, Wong W. Hormonal therapies for breast cancer: can progestogens stimulate growth? *Cancer Lett*. 1986;30(2):213–218.
 - van der Burg B, Kalkhoven E, Isbrücker L, de Laat SW. Effects of progestins on the proliferation of estrogen-dependent human breast cancer cells under growth factor-defined conditions. *J Steroid Biochem Mol Biol*. 1992;42(5):457–465.
 - Saitoh M, Ohmichi M, Takahashi K, et al. Medroxyprogesterone acetate induces cell proliferation through up-regulation of cyclin D1 expression via phosphatidylinositol 3-kinase/Akt/nuclear factor-kappaB cascade in human breast cancer cells. *Endocrinology*. 2005;146(11):4917–4925.
 - Chang KJ, Lee TY, Linares-Cruz G, Fournier S, de Lignières B. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertil Steril*. 1995;63(4):785–791.
 - Foidart JM, Colin C, Denoo X, et al. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. *Fertil Steril*. 1998;69(5):963–969.
 - Mueck AO, Seeger H, Wallwiener D. Comparison of proliferative effects of estradiol and conjugated equine estrogens on human breast cancer cells and impact of continuous combined progestogen addition. *Climacteric*. 2003;6(3):221–227.
 - Inoh A, Kamiya K, Fujii Y, Yokoro K. Protective effects of progesterone and tamoxifen in estrogen induced mammary carcinogenesis in ovariectomized W/Fu rats. *Jpn J Cancer Res*. 1985;76(8):699–704.
 - Barrat J, de Lignières B, Marpeau L, et al. Effect in vivo de l'administration locale de progesterone sur l'activite mitotique des glaucophores humains. [The in vivo effect of the local administration of progesterone on the mitotic activity of human ductal breast tissue. Results of a pilot study.] *J Gynecol Obstet Biol Reprod (Paris)*. 1990;19(3):269–274.
 - Malet C, Spritzer P, Guillaumin D, Kuttann F. Progesterone effect on cell growth, ultrastructural aspect and estradiol receptors of normal breast epithelial (HBE) cells in culture. *J Steroid Biochem Mol Biol*. 2000;73(3–4):171–181.
 - Mauvais-Jarvis P, Kuttann F, Gompel A. Antiestrogen action of progesterone in breast tissue. *Breast Cancer Res Treat*. 1986;8(3):179–188.
 - Soderqvist G, von Schoultz B, Tani E, Skoog L. Estrogen and progesterone receptor content in breast epithelial cells from healthy women during the menstrual cycle. *Am J Obstet Gynecol*. 1993;168(3 pt 1):874–879.
 - Formby B, Wiley TS. Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53. *Ann Clin Lab Sci*. 1998;28(6):360–369.
 - Formby B, Wiley TS. Bcl-2, survivin and variant CD44 v7–v10 are downregulated and p53 is upregulated in breast cancer cells by progesterone: inhibition of cell growth and induction of apoptosis. *Mol Cell Biochem*. 1999;202(1–2):53–61.
 - Groshong SD, Owen GI, Grimison B, et al. Biphasic regulation of breast cancer cell growth by progesterone: role of the cyclin-dependent kinase inhibitors, p21 and p27(Kip1). *Mol Endocrinol*. 1997;11(11):1593–1607.
 - Segaloff A. Inhibition by progesterone of radiation-estrogen-induced mammary cancer in the rat. *Cancer Res*. 1973;33(5):1136–1137.
 - Schmidt M, Renner C, Löffler G. Progesterone inhibits glucocorticoid-dependent aromatase induction in human adipose fibroblasts. *J Endocrinol*. 1998;158(3):401–407.
 - Jordan VC, Jeng MH, Catherino WH, Parker CJ. The estrogenic activity of synthetic progestins used in oral contraceptives. *Cancer*. 1993;71(4 suppl):1501–1505.
 - Botella J, Duranti E, Viader V, Duc I, Delansorne R, Paris J. Lack of estrogenic potential of progesterone- or 19-nor-progesterone-derived progestins as opposed to testosterone or 19-nor-testosterone derivatives on endometrial Ishikawa cells. *J Steroid Biochem Mol Biol*. 1995;55(1):77–84.
 - Botella J, Duc I, Delansorne R, Paris J, Lahlou B. Regulation of rat uterine steroid receptors by nomegestrol acetate, a new 19-nor-progesterone derivative. *J Pharmacol Exp Ther*. 1989;248(2):758–761.
 - Markiewicz L, Hochberg RB, Gurdip E. Intrinsic estrogenicity of some progestogenic drugs. *J Steroid Biochem Mol Biol*. 1992;41(1):53–58.
 - Rabe T, Bohlmann MK, Rehberger-Schneider S, Prifti S. Induction of estrogen receptor-alpha and -beta activities by synthetic progestins. *Gynecol Endocrinol*. 2000;14(2):118–126.

40. Campagnoli C, Abba C, Ambroggio S, Peris C. Pregnancy, progesterone and progestins in relation to breast cancer risk. *J Steroid Biochem Mol Biol.* 2005;97(5):441–450.
41. Seeger H, Mueck AO, Lippert TH. Effect of norethisterone acetate on estrogen metabolism in postmenopausal women. *Horm Metab Res.* 2000;32(10):436–439.
42. Coldham NG, James VH. A possible mechanism for increased breast cell proliferation by progestins through increased reductive 17 beta-hydroxysteroid dehydrogenase activity. *Int J Cancer.* 1990;45(1):174–178.
43. Xu B, Kitawaki J, Koshiba H, et al. Differential effects of progestogens, by type and regimen, on estrogen-metabolizing enzymes in human breast cancer cells. *Maturitas.* 2007;56(2):142–152.
44. Prost-Avallet O, Oursin J, Adessi GL. In vitro effect of synthetic progestogens on estrone sulfatase activity in human breast carcinoma. *J Steroid Biochem Mol Biol.* 1991;39(6):967–973.
45. Pasqualini JR. Differential effects of progestins on breast tissue enzymes. *Maturitas.* 2003;46:45–54.
46. Pollow K, Boquoi E, Baumann J, Schmidt-Gollwitzer M, Pollow B. Comparison of the in vitro conversion of estradiol-17 beta to estrone of normal and neoplastic human breast. *Mol Cell Endocrinol.* 1977;6(4–5):333–348.
47. Fournier S, Kuttent F, de Cicco F, Baudot N, Malet C, Mauvais-Jarvis P. Estradiol 17 beta-hydroxysteroid dehydrogenase activity in human breast fibroadenomas. *J Clin Endo Metab.* 1982;55(3):428–433.
48. Giangrande PH, Kimbrel EA, Edwards DP, McDonnell DP. The opposing transcriptional activities of the two isoforms of the human progesterone receptor are due to differential cofactor binding. *Mol Cell Biol.* 2000;20(9):3102–3115.
49. Wei LL, Gonzalez-Aller C, Wood WM, Miller LA, Horwitz KB. 5'-Heterogeneity in human progesterone receptor transcripts predicts a new amino-terminal truncated "C"-receptor and unique A-receptor messages. *Mol Endocrinol.* 1990;4(12):1833–1840.
50. Mote PA, Bartow S, Tran N, Clarke CL. Loss of co-ordinate expression of progesterone receptors A and B is an early event in breast carcinogenesis. *Breast Cancer Res Treat.* 2002;72(2):163–172.
51. Graham JD, Clarke C. Expression and transcriptional activity of progesterone receptor A and progesterone receptor B in mammalian cells. *Breast Cancer Res.* 2002;4(5):187–190.
52. Kastner P, Krust A, Turcotte B, et al. Two distinct estrogen-regulated promoters generate transcripts encoding the two functionally different human progesterone receptor forms A and B. *EMBO J.* 1990;9(5):1603–1614.
53. Mote P, Clarke C. Relative expression of progesterone receptors A and B in premalignant and invasive breast lesions. *Breast Cancer Res.* 2000;2(suppl 1):P2.01.
54. Hopp TA, Weiss HL, Hilsenbeck SG, et al. Breast cancer patients with progesterone receptor PR-A-rich tumors have poorer disease-free survival rates. *Clin Cancer Res.* 2004;10(8):2751–2760.
55. Isaksson E, Wang H, Sahlin L, von Schoultz B, Cline JM, von Schoultz E. Effects of long-term HRT and tamoxifen on the expression of progesterone receptors A and B in breast tissue from surgically postmenopausal cynomolgus macaques. *Breast Cancer Res Treat.* 2003;79(2):233–239.
56. Vereide AB, Kaino T, Sager G, Arnes M, Ørbo A. Effect of levonorgestrel IUD and oral medroxyprogesterone acetate on glandular and stromal progesterone receptors (PRA and PRB), and estrogen receptors (ER-alpha and ER-beta) in human endometrial hyperplasia. *Gynecol Oncol.* 2006;101(2):214–223.
57. Custodia-Lora N, Novillo A, Callard IP. Regulation of hepatic progesterone and estrogen receptors in the female turtle, *Chrysemys picta*: relationship to vitellogenesis. *Gen Comp Endocrinol.* 2004;136(2):232–240.
58. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer.* 2005;114:448–454.
59. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2008;107(1):103–111.
60. Peck JD, Hulka BS, Poole C, Savitz DA, Baird D, Richardson BE. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2002;11(4):361–368.
61. Micheli A, Muti P, Secreto G, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. *Int J Cancer.* 2004;112(2):312–318.
62. Gottardis M, Ertürk E, Rose DP. Effects of progesterone administration on N-nitrosomethylurea-induced rat mammary carcinogenesis. *Eur J Cancer Clin Oncol.* 1983;19(10):1479–1484.
63. Grubbs CJ, Farnell DR, Hill DL, McDonough KC. Chemoprevention of N-nitroso-N-methylurea induced mammary cancers by pretreatment with 17 beta-estradiol and progesterone. *J Natl Cancer Inst.* 1985;74(4):927–931.
64. Kledzik GS, Bradley CJ, Meites J. Reduction of carcinogen-induced mammary cancer incidence in rats by early treatment with hormones or drugs. *Cancer Res.* 1974;34(11):2953–2956.
65. Welsch CH, Clemens JA, Meites J. Effects of multiple pituitary homografts or progesterone on 7,12-dimethylbenz[a]anthracene-induced mammary tumors in rats. *J Natl Cancer Inst.* 1968;41(2):465–478.
66. Bernstein L, Yuan JM, Ross RK, et al. Serum hormone levels in pre-menopausal Chinese women in Shanghai and white women in Los Angeles: results from two breast cancer case-control studies. *Cancer Causes Control.* 1990;1(1):51–58.
67. Drafta D, Schindler AE, Milcu SM, et al. Plasma hormones in pre- and postmenopausal breast cancer. *J Steroid Biochem.* 1980;13(7):793–802.
68. Malarkey WB, Schroeder LL, Stevens VC, James AG, Lanese RR. Twenty-four-hour preoperative endocrine profiles in women with benign and malignant breast disease. *Cancer Res.* 1977;37(12):4655–4659.
69. Meyer F, Brown JB, Morrison AS, MacMahon B. Endogenous sex hormones, prolactin, and breast cancer in premenopausal women. *J Natl Cancer Inst.* 1986;77(3):613–616.
70. Secreto G, Toniolo P, Berrino F, et al. Increased androgenic activity and breast cancer risk in premenopausal women. *Cancer Res.* 1984(12 pt 1); 44:5902–5905.
71. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321–333.
72. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701–1712.
73. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA.* 2003;289(24):3243–3253.
74. Porch JV, Lee IM, Cook NR, Rexrode KM, Burin JE. Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control.* 2002;13(9):847–854.
75. Lee SA, Ross RK, Pike MC. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. *Br J Cancer.* 2005;92(11):2049–2058.
76. Ewertz M, Møllerkjær L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. *Br J Cancer.* 2005;92(7):1293–1297.
77. Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. *Cancer Epid Bio Prev.* 2002;11(7):593–600.

78. Stahlberg C, Pedersen AT, Lynge E, et al. Increased risk of breast cancer following different regimens of hormone replacement therapy frequently used in Europe. *Int J Cancer*. 2004;109(5):721–727.
79. Li CI. Postmenopausal hormone therapy and the risk of breast cancer: the view of an epidemiologist. *Maturitas*. 2004;49(1):44–50.
80. Magnusson C, Baron JA, Correia N, Bergström R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer*. 1999;81(3):339–344.
81. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Estrogen-progestin replacement and risk of breast cancer. *JAMA*. 2000;284(6):691–694.
82. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst*. 2000;92(4):328–332.
83. Warren MP. A comparative review of the risks and benefits of hormone replacement therapy regimens. *Am J Obstet Gynecol*. 2004;190(4):1141–1167.
84. Weiss LK, Burkman RT, Cushing-Haugen KL, et al. Hormone replacement therapy regimens and breast cancer risk(1). *Obstet Gynecol*. 2002;100(6):1148–1158.
85. Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA*. 2003;289(24):3254–3263.
86. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419–427.
87. Kirsh V, Kreiger N. Estrogen and estrogen-progestin replacement therapy and risk of postmenopausal breast cancer in Canada. *Cancer Causes Control*. 2002;13(6):583–590.
88. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350(9084):1047–1059.
89. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283(4):485–491.
90. Colditz G, Rosner B. Use of estrogen plus progestin is associated with greater increase in breast cancer risk than estrogen alone. *Am J Epidemiol*. 1998;147:S45.
91. Persson I, Weiderpass E, Bergkvist L, Bergström R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. *Cancer Causes Control*. 1999;10(4):253–260.
92. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. *JAMA*. 2002;287(6):734–741.
93. Pike MC, Ross RK. Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer. *Steroids*. 2000;65(10–11):659–664.
94. Santen RJ, Pinkerton J, McCartney C, Petroni GR. Risk of breast cancer with progestins in combination with estrogen as hormone replacement therapy. *J Clin Endocrinol Metab*. 2001;86(1):16–23.
95. Stahlberg C, Pedersen AT, Lynge E, Ottesen B. Hormone replacement therapy and risk of breast cancer: the role of progestins. *Acta Obstet Gynecol Scand*. 2003;82(7):335–344.
96. Olsson HL, Ingvar C, Bladström A. Hormone replacement therapy containing progestins and given continuously increases breast carcinoma risk in Sweden. *Cancer*. 2003;97(6):1387–1392.
97. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med*. 1995;332(24):1589–1593.
98. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol*. 2000;152(10):950–964.
99. Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol*. 1981;114(2):209–217.
100. Badwe RA, Wang DY, Gregory WM, et al. Serum progesterone at the time of surgery and survival in women with premenopausal operable breast cancer. *Eur J Cancer*. 1994;30A(4):445–448.
101. Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS. Serum progesterone and prognosis in operable breast cancer. *Br J Cancer*. 1996;73(12):1552–1555.
102. Veronese SM, Gambacorta M. Detection of Ki-67 proliferation rate in breast cancer. Correlation with clinical and pathologic features. *Am J Clin Pathol*. 1991;95(1):30–34.
103. Innes KE, Byers TE. First pregnancy characteristics and subsequent breast cancer risk among young women. *Int J Cancer*. 2004;112(2):306–311.
104. Troisi R, Weiss HA, Hoover RN, et al. Pregnancy characteristics and maternal risk of breast cancer. *Epidemiology*. 1998;9(6):641–647.
105. Vatten LJ, Romundstad PR, Trichopoulos D, Skjærven R. Pre-eclampsia in pregnancy and subsequent risk for breast cancer. *Br J Cancer*. 2002;87(9):971–973.
106. Paruthiyil S, Parma H, Kerekatte V, Cunha GR, Firestone GL, Leitman DC. Estrogen receptor beta inhibits human breast cancer cell proliferation and tumor formation by causing a G2 cycle arrest. *Cancer Res*. 2004;64(1):423–428.
107. Paech K, Webb P, Kuiper GG, et al. Differential ligand activation of estrogen receptors ERalpha and ERbeta at AP1 sites. *Science*. 1997;277(5331):1508–1510.
108. Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci U S A*. 1996;93(12):5925–5930.
109. Green S, Walter P, Greene G, et al. Cloning of the human oestrogen receptor cDNA. *J Steroid Biochem*. 1986;24(1):77–83.
110. Katzenellenbogen BS, Montano MM, Ediger TR, et al. Estrogen receptors: selective ligands, partners, and distinctive pharmacology. *Recent Prog Horm Res*. 2000;55:163–193.
111. Nilsson S, Mäkelä S, Treuter E, et al. Mechanisms of estrogen action. *Physiol Rev*. 2001;81(4):1535–1565.
112. Helguero LA, Faulds MH, Gustafsson JA, Haldosén LA. Estrogen receptors alpha (ERalpha) and beta (ERbeta) differentially regulate proliferation and apoptosis of the normal murine mammary epithelial cell line HC11. *Oncogene*. 2005;24(44):6605–6616.
113. Bardin A, Boulle N, Lazennec G, Vignon F, Pujol P. Loss of ERbeta expression as a common step in estrogen-dependent tumor progression. *Endocr Relat Cancer*. 2004;11(3):537–551.
114. Isaksson E, Wang H, Sahlin L, et al. Expression of estrogen receptors (alpha, beta) and insulin-like growth factor-1 in breast tissue from surgically postmenopausal cynomolgus macaques after long-term treatment with HRT and tamoxifen. *Breast*. 2002;11(4):295–300.
115. Weatherman RV, Clegg NJ, Scanlan TS. Differential SERM activation of the estrogen receptors (ERalpha and ERbeta) at AP-1 sites. *Chem Biol*. 2001;8(5):427–436.
116. Pettersson K, Delaunay F, Gustafsson JA. Estrogen receptor beta acts a dominant regulator of estrogen signaling. *Oncogene*. 2000;19(43):4970–4978.
117. Saji S, Jensen EV, Nilsson S, Rylander T, Warner, Gustafsson JA. Estrogen receptors alpha and beta in the rodent mammary gland. *Proc Natl Acad Sci U S A*. 2000;97(1):337–342.
118. Zhu BT, Han GZ, Shim JY, Wen Y, Jiang XR. Quantitative structure-activity relationship of various endogenous estrogen metabolites for human estrogen receptor alpha and beta subtypes: Insights into the structural determinants favoring a differential subtype binding. *Endocrinology*. 2006;147(9):4132–4150.
119. Rich RL, Hoth LR, Geoghegan KF, et al. Kinetic analysis of estrogen receptor/ligand interactions. *Proc Natl Acad Sci U S A*. 2002;99(13):8562–8567.
120. Ekena K, Katzenellenbogen JA, Katzenellenbogen BS. Determinants of ligand specificity of estrogen receptor-alpha: estrogen versus androgen discrimination. *J Biol Chem*. 1998;273(2):693–699.

121. Hanstein B, Liu H, Yancisin MC, Brown M. Functional analysis of a novel estrogen receptor-beta isoform. *Mol Endocrinol*. 1999;13(1):129–137.
122. Lemon HM. Pathophysiologic considerations in the treatment of menopausal patients with oestrogens; the role of oestriol in the prevention of mammary carcinoma. *Acta Endocrinol Suppl (Copenh)*. 1980;233:17–27.
123. Lemon HM, Kumar PF, Peterson C, Rodriguez-Sierra JF, Abbo KM. Inhibition of radiogenic mammary carcinoma in rats by estriol or tamoxifen. *Cancer*. 1989;63(9):1685–1692.
124. Lemon HM. Estriol prevention of mammary carcinoma induced by 7,12-dimethylbenzanthracene and procarbazine. *Cancer Res*. 1975;35(5):1341–1353.
125. MacMahon B, Cole P, Brown JB, et al. Oestrogen profiles of Asian and North American women. *Lancet*. 1971;2(7730):900–902.
126. Barkhem T, Carlsson B, Nilsson Y, Enmark E, Gustafsson J, Nilsson S. Differential response of estrogen receptor alpha and receptor beta to partial estrogen agonists/antagonists. *Mol Pharmacol*. 1998;54(1):105–112.
127. Pisha E, Lui X, Constantinou AI, Bolton JL. Evidence that a metabolite of equine estrogens, 4-hydroxyequilenin, induces cellular transformation in vitro. *Chem Res Toxicol*. 2001;14(1):82–90.
128. Zhang F, Chen Y, Pisha E, et al. The major metabolite of equilin, 4-hydroxyequilin, autoxidizes to an o-quinone with isomerizes to the potent cytotoxin 4-hydroxyequilenin-o-quinone. *Chem Res Toxicol*. 1999;12(2):204–213.
129. Chen Y, Liu X, Pisha E, et al. A metabolite of equine estrogens, 4-hydroxyequilenin, induces DNA damage and apoptosis in breast cancer cell lines. *Chem Res Toxicol*. 2000;13(5):342–350.
130. Zhang F, Swanson SM, van Breemen RB, et al. Equine estrogen metabolite 4-hydroxyequilenin induces DNA damage in the rat mammary tissues: formation of single-strand breaks, apurinic sites, stable adducts, and oxidized bases. *Chem Res Toxicol*. 2001;14(12):1654–1659.
131. Shen L, Qiu S, Chen Y, et al. Alkylation of 2'-deoxynucleosides and DNA by the Premarin metabolite 4-hydroxyequilenin semiquinone radical. *Chem Res Toxicol*. 1998;11(2):94–101.
132. Gross J, Modan B, Bertini B, et al. Relationship between steroid excretion patterns and breast cancer incidence in Israeli women of various origins. *J Natl Cancer Inst*. 1997;59(1):7–11.
133. Cole P, MacMahon B. Oestrogen fractions during early reproductive life in the aetiology of breast cancer. *Lancet*. 1969;1(7595):604–606.
134. Dickinson LE, MacMahon B, Cole P, Brown JB. Estrogen profiles of Oriental and Caucasian women in Hawaii. *N Engl J Med*. 1974;291(23):1211–1213.
135. Melamed M, Castaño E, Notides AC, Sasson S. Molecular and kinetic basis for the mixed agonist/antagonist activity of estriol. *Mol Endocrinol*. 1997;11(12):1868–1878.
136. Speroff L. The breast as an endocrine target organ. *Contemp Obstet Gynec*. 1977;9:69–72.
137. Rosner B, Colditz, GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. *Am J Epidemiol*. 1994;139(8):819–835.
138. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. *Breast Cancer Res Treat*. 1982;2(1):5–73.
139. Pasqualini JR. The fetus, pregnancy, and breast cancer. In: Pasqualini JR, ed. *Breast Cancer: Prognosis, Treatment, and Prevention*. New York, NY: Marcel Dekker Inc; 2002:19–71.
140. Vatten LJ, Romundstad PR, Trichopoulos D, Skjærven R. Pregnancy related protection against breast cancer depends on length of gestation. *Br J Cancer*. 2002;87(3):289–290.
141. Ekbohm A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intra-uterine environment and breast cancer risk in women: a population-based study. *J Natl Cancer Inst*. 1997;89(1):71–76.
142. Ursin G, Wilson M, Henderson BE, et al. Do urinary estrogen metabolites reflect the differences in breast cancer risk between Singapore Chinese and United States African-American and white women? *Cancer Res*. 2001;61(8):3326–3329.
143. Lemon HM. Genetic predisposition to carcinoma of the breast: multiple human genotypes for estrogen 16 alpha hydroxylase activity in Caucasians. *J Surg Oncol*. 1972;4(3):255–273.
144. Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. *Int J Cancer*. 2004;112(1):130–134.
145. Lippman M, Monaco ME, Bolan G. Effects of estrone, estradiol, and estriol on hormone-responsive human breast cancer in long-term tissue culture. *Cancer Res*. 1977;37(6):1901–1907.
146. Lemon HM, Wotiz HH, Parsons L, Mozden PJ. Reduced estriol excretion in patients with breast cancer prior to endocrine therapy. *JAMA*. 1966;196(13):1128–1136.
147. Marmorston J, Fowley LG, Myers SM, Stern E, Hopkins CE. II. Urinary excretion of estrone, estradiol and estriol by patients with breast cancer and benign breast disease. *Am J Obstet Gynecol*. 1965;92:460–467.
148. Ottosson UB, Johansson BG, von Schoultz B. Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: a comparison between progestogens and natural progesterone. *Am J Obstet Gynecol*. 1985;151(6):746–750.
149. Minshall RD, Stanczyk FZ, Miyagawa K, et al. Ovarian steroid protection against coronary artery hyperreactivity in rhesus monkeys. *J Clin Endocrinol Metab*. 1998;83(2):649–659.
150. Mishra RG, Hermsmeyer RK, Miyagawa K, et al. Medroxyprogesterone acetate and dihydrotestosterone induce coronary hyperreactivity in intact male rhesus monkeys. *J Clin Endocrinol Metab*. 2005;90(6):3706–3714.
151. Miyagawa K, Roöch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nat Med*. 1997;3(3):324–327.
152. Adams MR, Register TC, Golden DL, Wagner JD, Williams J. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol*. 1997;17(1):217–221.
153. Saarikoski S, Yliskoski M, Penttälä I. Sequential use of norethisterone and natural progesterone in pre-menopausal bleeding disorders. *Maturitas*. 1990;12(2):89–97.
154. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA*. 1995;273(3):199–208.
155. Fähræus L, Larsson-Cohn U, Wallentin L. L-norgestrel and progesterone have different influences on plasma lipoproteins. *Eur J Clin Invest*. 1983;13(6):447–453.
156. Larsson-Cohn U, Fähræus L, Wallentin L, Zador G. Lipoprotein changes may be minimized by proper composition of a combined oral contraceptive. *Fertil Steril*. 1981;35(2):172–179.
157. Ottosson UB. Oral progesterone and estrogen/progestogen therapy. Effects of natural and synthetic hormones on subfractions of HDL cholesterol and liver proteins. *Acta Obstet Gynecol Scand Suppl*. 1984;127:1–37.
158. Mäliköinen M, Manninen V, Hirvonen E. Effects of danazol and lynestrenol on serum lipoproteins in endometriosis. *Clin Pharmacol Ther*. 1980;28(5):602–604.
159. Hirvonen E, Malkonen M, Manninen V. Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. *N Engl J Med*. 1981;304(10):560–563.
160. Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004;292(13):1573–1580.
161. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*. 2007;115(7):840–845.
162. Rosano GM, Webb CM, Chierchia S, et al. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J Am Coll Cardiol*. 2000;36(7):2154–2159.
163. Miller VT, Muesing RA, LaRosa JC, Stoy DB, Phillips EA, Stillman RJ. Effects of conjugated equine estrogen with and without three different

- progesterone on lipoproteins, high-density lipoprotein subfractions, and apolipoprotein A-1. *Obstet Gynecol.* 1991;77(2):235–240.
164. Levine RL, Chen SJ, Durand J, Chen YF, Oparil S. Medroxyprogesterone attenuates estrogen-mediated inhibition of neointima formation after balloon injury of the rat carotid artery. *Circulation.* 1996;94(9):2221–2227.
 165. Otsuki M, Saito H, Xu X, et al. Progesterone, but not medroxyprogesterone, inhibits vascular cell adhesion molecule-1 expression in human vascular endothelial cells. *Arterioscler Thromb Vasc Biol.* 2001;21(2):243–248.
 166. Register TC, Adams MR, Golden DL, Clarkson TB. Conjugated equine estrogens alone, but not in combination with medroxyprogesterone acetate, inhibit aortic connective tissue remodeling after plasma lipid lowering in female monkeys. *Arterioscler Thromb Vasc Biol.* 1998;18(7):1164–1171.
 167. Wagner JD, Martino MA, Jayo MJ, Anthony MS, Clarkson TB, Cefalu WT. The effects of hormone replacement therapy on carbohydrate metabolism and cardiovascular risk factors in surgically postmenopausal cynomolgus monkeys. *Metabolism.* 1996;45(10):1254–1262.
 168. Lindheim SR, Presser SC, Ditkoff EC, Vijod MA, Stanczyk FZ, Lobo RA. A possible bimodal effect of estrogen on insulin sensitivity in postmenopausal women and the attenuating effect of added progestin. *Fertil Steril.* 1993;60(4):664–667.
 169. Spencer CP, Godsland IF, Cooper AJ, Ross D, Whitehead MI, Stevenson JC. Effects of oral and transdermal 17 β -estradiol with cyclical oral norethindrone acetate on insulin sensitivity, secretion, and elimination in postmenopausal women. *Metabolism.* 2000;49(6):742–747.
 170. Godsland IF, Gangar K, Walton C, et al. Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone replacement therapy. *Metabolism.* 1993;42(7):846–853.
 171. Feeman WE Jr. Thrombotic stroke in an otherwise healthy middle-aged female related to the use of continuous-combined conjugated equine estrogens and medroxyprogesterone acetate. *J Genet Specif Med.* 2000;3(8):62–64.
 172. Jeanes HL, Wanikiat P, Sharif I, Gray GA. Medroxyprogesterone acetate inhibits the cardioprotective effect of estrogen in experimental ischemia-reperfusion injury. *Menopause.* 2006;13(1):80–86.
 173. Jensen J, Riis BJ, Strøm V, Nilas L, Christiansen C. Long-term effects of percutaneous estrogens and oral progesterone on serum lipoproteins in postmenopausal women. *Am J Obstet Gynecol.* 1987;156(1):66–71.
 174. Williams JK, Honoré EK, Washburn SA, Clarkson TB. Effects of hormone replacement on therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. *J Am Coll Cardiol.* 1994;24(7):1757–1761.
 175. Adams MR, Kaplan JR, Manuck SB, et al. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. *Arteriosclerosis.* 1990;10(6):1051–1057.
 176. Bolaji II, Grimes H, Mortimer G, Tallon DF, Fottrell PF, O'Dwyer EM. Low-dose progesterone therapy in oestrogenised postmenopausal women: effects on plasma lipids, lipoproteins and liver function parameters. *Eur J Obstet Gynecol Reprod Biol.* 1993;48(1):61–68.
 177. Morey AK, Pedram A, Razandi M, et al. Estrogen and progesterone inhibit vascular smooth muscle proliferation. *Endocrinology.* 1997;138(8):3330–3339.
 178. Lee WS, Harder JA, Yoshizumi M, Lee ME, Haber E. Progesterone inhibits arterial smooth muscle cell proliferation. *Nat Med.* 1997;3(9):1005–1008.
 179. Minshall RD, Miyagawa K, Chadwick CC, Novy MJ, Hermsmeyer K. In vitro modulation of primate coronary vascular muscle cell reactivity by ovarian steroid hormones. *FASEB J.* 1998;12(13):1419–1429.
 180. Minshall RD, Pavcnik D, Halushka PV, Hermsmeyer RK. Progesterone regulation of vascular thromboxane A2 receptors in rhesus monkeys. *Am J Physiol Heart Circ Physiol.* 2001;281(4):H1498–H1507.
 181. Houser SL, Aretz HT, Quist WC, Chang Y, Schreiber AD. Serum lipids and arterial plaque load are altered independently with high-dose progesterone in hypercholesterolemic male rabbits. *Cardiovasc Pathol.* 2000;9(6):317–322.
 182. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol.* 1997;17(11):3071–3078.
 183. Martinez C, Basurto L, Zarate A, Saucedo R, Gaminio E, Collazo J. Transdermal estradiol does not impair hemostatic biomarkers in postmenopausal women. *Maturitas.* 2005;50(1):39–43.
 184. Oger E, Alhenc-Gelas M, Lacut K, et al. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. *Arterioscler Thromb Vasc Biol.* 2003;23(9):1671–1676.
 185. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol.* 2007;109(2 pt 1):339–346.
 186. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives contain norgestimate and 35 μ g of ethinyl estradiol. *Contraception.* 2006;73(3):223–228.
 187. Hellman I, Yoshida K, Zumoff B, Levin J, Kream J, Fukushima DK. The effect of medroxyprogesterone acetate on the pituitary-adrenal axis. *J Clin Endocrinol Metab.* 1976;42(5):912–917.
 188. Davila E, Vogel CL, East D, Cairns V, Hilsenbeck S. Clinical trial of high-dose oral medroxyprogesterone acetate in the treatment of metastatic breast cancer and review of the literature. *Cancer.* 1988;61(11):2161–2167.
 189. Corvol P, Elkik F, Feneant M, et al. Effect of progesterone and progestins on water and salt metabolism. In: Bardin CW, Milgrom E, Mauvais-Jarvis P, eds. *Progesterone and Progestins.* New York, NY: Raven Press; 1983;1979–1986.
 190. Rylance PB, Brincat M, Lafferty K, et al. Natural progesterone and antihypertensive action. *Bri Med J.* 1985(6461);290:13–14.
 191. Elkind-Hirsch KE, Sherman LD, Malinak R. Hormone replacement therapy alters insulin sensitivity in young women with premature ovarian failure. *J Clin Endocrinol Metab.* 1993;76(2):472–475.
 192. Tzingounis VA, Aksu MF, Greenblatt RB. Estriol in the management of the menopause. *JAMA.* 1978;239(16):1638–1641.
 193. Yang TS, Tsan SH, Chang SP, Ng HT. Efficacy and safety of estriol replacement therapy for climacteric women. *Chin Med J (Taipei).* 1995;55:386–391.
 194. Perović D, Kopajtic B, Stanković T. Treatment of climacteric complaints with oestriol. *Arzneimittel-Forschung.* 1975;25(6):962–964.
 195. van der Linden MC, Gerretsen G, Brandhorst MS, Ooms EC, Kremer CM, Doesburg WH. The effect of estriol on the cytology of urethra and vagina in postmenopausal women with genito-urinary symptoms. *Eur J Obstet Gynecol Reprod Biol.* 1993;51(1):29–33.
 196. Cardoza L, Rekers H, Tapp A, et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. *Maturitas.* 1993;18(1):47–53.