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

1) 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 Brizendine 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 D1[21] 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 trials[16] 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] Preeclampsia, 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-alpha-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 al[150] 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.

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