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RESEARCH ARTICLE

Utilizing Bioidentical Hormone as Efficacious and Safe Hormone

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Abstract

Background: The relative safety and efficacy of bioidentical hormone compared with synthetic version of hormone replacement therapy (HRT) is still the subject of debate. Some data suggest that bioidentical hormones have opposite physiological effects to synthetic hormones, which associated with lower risk of breast cancer and cardiovascular events. Nevertheless, there is still little evidence to support claims that bioidentical hormones are safer and more effective. Methods: Published papers were identified from PLOS, PubMed/MEDLINE, ProQuest, ScienceDirect, Google Scholar, and Elsevier (SCOPUS) databases, written in English, and fully accessible by reviewers, for studies enrolled postmenopausal women using bioidentical hormones vs. synthetic hormones as HRT. Results: A hundred and eighteen of 341 citations were reviewed. The results of this study found the disparities between bioidentical and synthetic hormones with respect to safety and efficacy. Bioidentical hormones have demonstrated effectiveness in addressing menopausal symptoms. Clinical data has indicated that bioidentical hormone, especially progesterone is associated with a diminished risk for breast cancer and cardiovascular disease, compared with commonly used synthetic versions. Conclusions: The use of bioidentical hormone therapy is well tolerated, provides symptom relief and can address the safer and more efficacious forms of HRT with respect to the lower risk for breast cancer and cardiovascular disease. Thus, bioidentical hormones remain the preferred method of HRT.

Keywords: *Progesterone, Estradiol, Synthetic progestins, Breast cancer, Cardiovascular disease,*

Introduction

Recently in nearly two decades, women and their physicians have in increasing numbers been opting for the use of natural, bioidentical hormones for treatment of menopause symptoms, and diseases of aging, as well as a source of health risk, especially breast cancer risk and heart diseases [1].

The trend away from the use of conventional synthetic hormones, toward those specifically matching the hormones produced in humans (bioidentical). The term bioidentical refers to the use of hormones that are exact copies of endogenous human hormones, including estriol, estradiol, and progesterone [2], as opposed to synthetic versions with different chemical structures or non-human versions, such as conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA).

The rising fear or suspicion of the synthetic hormones used in conventional hormone replacement therapy (HRT) probably has been the most significant factor driving the increased interest in bioidentical hormones. Moreover, risks associated with conventional HRT have provoked women's concerns and altered the approach to hormone use, as reported by numerous research-based media towards the U.S. government-sponsored Women's Health Initiative (WHI) study in 2002 [3]. The WHI study results led to the conclusion of using conventional HRT out-weighed the benefits provided [4].

This report was followed by a significant decline in the use of synthetic hormones at menopause, and a growing number of women and their physicians utilizing and advocating the use of bioidentical hormones. This makes the safety of HRT, used worldwide by millions of women, highly questionable with regard to breast cancer risk and heart diseases. Yet unfortunately, 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 [2].

Furthermore, there is still little evidence to support the claim that bioidentical hormones are safer or more effective than the commonly used synthetic versions of HRT [5], which can be confusing for patients and physicians. Therefore, we conducted a systematic review to synthesize the existing evidence about the efficacy and safety of bioidentical hormones i.e. progesterone compared with synthetic hormones, each in combination with estradiol, associated with the risk of breast cancer and cardiovascular disease.

Methodology

This systematic review was conducted from March to April 2019 following the standards set in PRISMA reporting guidelines. According to these guidelines, there are several steps in this study: 1) defining eligibility criteria; 2) defining information sources; 3) study selection; 4) data collection process; and 5) data item selection [6]. Figure 1 explains the steps of our work in conducting a systematic review.

Eligibility Criteria

The following inclusion criteria (IC) were defined for the review guidelines:

IC1: Original and peer-reviewed research written in English; and

IC2: Studies aimed at evaluating the evidence comparing bioidentical hormones, including progesterone, and estradiol, with the commonly used synthetic versions of HRT in postmenopausal women for clinical efficacy, physiological effects and risks for breast cancer and cardiovascular disease.

IC3: Comparative/controlled studies including human clinical studies, animal studies based on comparison, and in vitro that enrolled women aged more than 45 years old who were within 10 years of menopause, received hormone replacement therapy and reported outcomes of interest for a follow-up period ≥ 6 months. The outcomes of interest were the risk of breast cancer and cardiovascular disease.

Only articles written in English (IC1) were selected since English is a common language used by researchers in the scientific community. IC2 was included to answer the research questions. IC3 was included to exclude non-comparative studies and case series papers.

Information Sources

Literature searches were conducted for HRT formularies, focusing on those that either are or have been used in the United States, reviewed by large repositories of academic studies, including Plos, Pubmed/Medline, ProQuest, ScienceDirect, Google Scholar, and Elsevier (Scopus). Articles that could not be fully accessed were eliminated by the reviewers. In addition, we scanned the reference lists included in the articles to find related studies.

Study Selection

The study selection was conducted in the following three phases:

- The keyword search, or search string, was chosen according to our research interest in comparing the effects of bioidentical and synthetic hormones; thus, it was including terms such as “bioidentical hormones,” “synthetic hormones,” “progestin,” “menopausal hormone replacement,” “hormone replacement therapy,” “HRT,” “estradiol,” “progesterone,” “natural hormones,” “conjugated equine estrogens,” “medroxyprogesterone acetate,” “breast cancer,” and “cardiovascular disease.” Those exact search strings were searched one by one in each online database mentioned in section 2.2.

- Exploration and selection of title, abstract, and keywords of identified articles were conducted based on eligibility criteria and independently evaluated by the two reviewers.

- A complete or partial reading of the articles not eliminated in the previous phases was conducted to determine whether they should be included in the review, in accordance with the eligibility criteria.

These phases were carried out collaboratively by the two reviewers in an iterative process of the reviewers’ assessments. The level of agreement between the two reviewers (k level) was 0.7 and 0.8 for abstract screening and full-text screening, respectively. Thus, any discrepancies were discussed by the two reviewers until a unanimous agreement was reached. Disagreements were harmonized by consensus and, if not possible, by consensus through arbitration by a third reviewer.

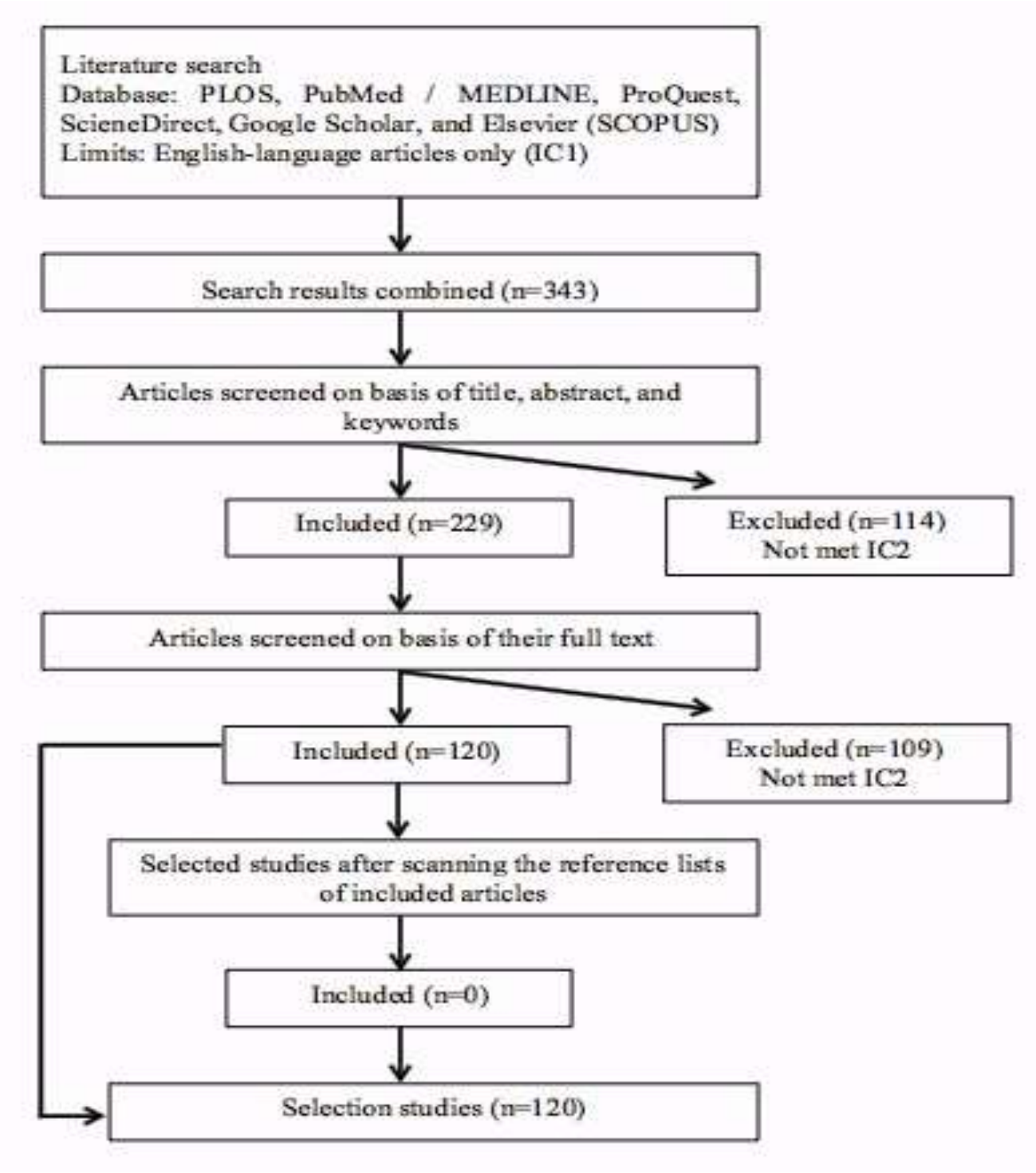

Figure 1: Study selection process as seen on PRISMA flow diagram

The selected articles were thoroughly screened, first by looking at the inclusion criteria.

Data Collection Process

Data collection was carried out manually using a data extraction form consisting of the following contents: article type, name of journal or conference, year, topic, title, participant, keyword, country, research methodology, and utilization of bioidentical hormones. Potentially relevant articles were assessed by each reviewer. The assessment consisted of reading the full text and the extracted data. Any discrepancies were resolved through a discussion between the two reviewers.

Data Items

Information extracted from each article was comprised of:

- Symptomatic efficacy of synthetic hormone compared with bioidentical hormone
- Differing physiological effects of synthetic hormone compared with bioidentical hormone

- Breast cancer and cardiovascular disease risks

The purpose of explaining data items was to provide an explanation about related studies mentioned in the results of data item in order to understand the safer and more efficacious bioidentical hormones compared with synthetic hormones as hormone replacement therapy.

Data Synthesis and Statistical Analysis

The relative risk (RR) of the outcomes of interest with 95 % confidence interval (CI) were extracted or calculated. The I2 statistic was used to assess heterogeneity of the treatment effect among studies for each outcome. I2 value >50 % and p <0.10 of the Cochrane Q test suggested substantial heterogeneity that is due to real differences in study populations, protocols, interventions, and/or outcomes. Publication bias was not assessed due to the small number of the studies included.

Results

Study Selection

The search results in the selected databases provided a total of 343 studies written in English from 1980 to 2013, matched with the keywords that needed to be analyzed. Next, those articles were screened on the basis of title, abstract, and keywords; the remaining 229 potentially articles were then reviewed on the basis of their full text. A total of 109 articles were discarded due to IC2 for the reasons shown in Fig 1. In addition, we eliminated 3 articles that could not be fully accessed by the reviewers. Finally, a total of 120 articles were selected in the review without additional articles resulting from the scanning of the reference lists.

Symptomatic Efficacy of Synthetic Hormone Compared with Bioidentical Hormone

An HRT containing progesterone may be preferable to one containing medroxyprogesterone acetate (MPA), especially regarding the quality of life issues, efficacy and patient satisfaction in postmenopausal women [9,10,11]. A cross-sectional study of Fitzpatrick et al suggested a better somatic, vasomotor and psychological symptoms (ie, anxiety, depression, sleep problems, menstrual bleeding, cognitive difficulties, and sexual functioning) was found in bioidentical progesterone use rather than MPA among 176 postmenopausal women (p <0.001)[9]. In a randomized study by Cummings and Brizendine, 23 postmenopausal women without significant psychiatric history reported that significantly increased vaginal bleeding (p 0.003) and increased breast tenderness (p 0.02) found in the use of synthetic hormone rather than bioidentical progesterone, but none of both hormone treatments had a detectable effect on mood [10].

The finding is consistent with a randomized, placebo-controlled study of Girdler et al, 54 postmenopausal women were showed no significant change in daily mood, prior to bioidentical progesterone and estradiol, although they did experience mild increases in cramping (p <0.05) and breast tenderness (p <0.05) in progesterone use, but do not appear to be clinically meaningful in normal functioning [12].

Differing Physiological Effects of Synthetic Hormone Compared with Bioidentical Hormone

Synthetic progestin and progesterone and generally have distinguishable physiological effects on breast tissue. Several studies suggest at least there are 3 subclasses of progesterone receptors (PR) have been identified: PRA, PRB, and PRC, which have different cellular activities [13, 17]. The ratio of PRA: PRB is approximately 1:1 in normal human breast tissue [15, 18].

Whereas synthetic progestins alter the normal PRA: PRB ratio, [19, 21] which may be a mechanism by which synthetic progestins increase the risk for breast cancer. Synthetic progestins have potential anti-apoptotic effects as demonstrated in an in vitro study which is meditating the regulation of genes controlling apoptosis on T47-D breast cancer cells [22] and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation [23,30], especially the 19-nortestosterone derived progestins, which bind to estrogen receptors in breast tissue and display significant intrinsic estrogenic properties in breast in in vitro study [25, 31, 36].

Synthetic progestins also upregulate cyclin D1, [37] increase the conversion of weaker endogenous estrogens into more potent

estrogens potentially contributing to their carcinogenic effects [38, 43]. However, Plu-bureau et al assessed the result in contrast. The study showed when only 19-nortestosterone derivatives, compared with other non-bioidentical progesterone, were significantly associated with a decreased risk in breast cancer [69]. Synthetic progestins, especially MPA, stimulate the conversion of inactive estrone sulfate into active estrone by stimulating sulfatase [41, 42] as well as increasing 17-beta-hydroxysteroid reductase activity, [38, 40, 41, 43] which in turn increases the intracellular formation of more potent estrogens and potentially increases breast cancer risk, a role not seen with progesterone.

In contrast, progesterone opposes estrogen-stimulated breast epithelial cells [23]. Progesterone also downregulates estrogen receptor-1 (ER-1) in the breast [29, 30, 44] induces breast cancer cell apoptosis [45, 46] diminishes breast cell mitotic activity [23,26,28-30,45,46] and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1 [25, 46].

It stimulates the oxidative isoform of 17-beta-hydroxysteroid dehydrogenase, which increases the intracellular conversion of potent estrogens to their less potent counterparts [47, 49]. Comparing both hormones**,** 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 [23,24,26,28,38,45,9-62]. It is well understood that, due to proliferative effect on normal breast cells as well as on numerous breast cancer cell lines, estrogens are contraindicated for women at risk for breast cancer, because, as referenced above, increased estrone levels are associated with an increased risk of breast cancer.

In contrast, several studies have demonstrated an inverse relationship between estriol levels and breast cancer as well as antitumor effects of estriol, when administered with estradiol [4,63, 65].However, while there is reason to believe that estriol in low doses could be protective for the breast in some individuals. Nonetheless, research has shown that estriol's weakness may very well be its strength. The benefits of estriol may, in part, be explained by its mixed pro-estrogenic and anti-estrogenic effects, when administered with estradiol. Scientists investigated the mixture of stimulating and non-stimulating effects posed by estriol upon estrogen receptors [66]. Experimental studies suggest that estriol, when given with estradiol, has a protective effect against radiation-induced cancer of the breast [67].

Breast Cancer and Cardiovascular Disease Risks

Risk for Breast Cancer with Synthetic Progestins Versus Bioidentical Progesterone

There is a significant evidence that synthetic progestins and progesterone have unsimilar effects on breast tissue proliferation. Number of studies shown consistently increased risk for breast cancer with synthetic progestin. The potential role of progestins in increasing breast cancer risk associated with HRT becomes a big concern after the Women's Health Initiative (WHI), a large randomized clinical trial, suggested a significant increased risk of breast cancer [relative risk (RR) = 1.26, 95% confidence interval (CI): 1.00–1.59] [63] with continuous use of CEE and MPA for greater than 5 years compared with CEE alone, which showed no increased risk [68].

Fournier et al reported the number of breast cancer events in postmenopausal women receiving MPA was 29 in 7035 person-years [RR = 0.67 (95 % CI 0.76–0.81) with p of <0.0001] [50].Many cohort studies demonstrated progesterone was found to be associated with lower breast cancer risk compared with synthetic progestins in combination with estradiol (RR = 0.67, (95 % CI 0.55–0.81) with p of <0.0001) [50]. Plu-bureau et al conducted a large cohort study involving 1,150 French women with benign breast disease showed no increase in breast cancer risk with women using topical progesterone cream [RR=0.8 (95 % CI 0.4-1.6)]. Furthermore, the researchers noted a decrease in breast cancer risk among women using progesterone cream plus an oral progestogen [RR=0.8 (95 % CI 0.15-1.65], compared with women using oral progestogens alone [69].

The French E3N-EPIC cohort study, which followed the use of HRT in 54,548 postmenopausal women found the risk of breast cancer was significantly greater in HRT containing synthetic progestins [RR = 1.4 (95 % CI 1.20-1.70) with p <0.001] compared with progesterone [RR = 0.9 (95 % CI 0.70–1.20) with p <0.0001] [70]. Similar results reported in a population-based case control study that showed no significant increased risk of breast cancer among women treated with progesterone in combination with estradiol [odds ratio (OR) = 0.80 (CI 95 % 0.44–1.43)] [71].

A harmful effect associated with duration of progestin and estradiol use for greater than 4 years with a BMI index less than 24.4kg/m^2 was reported in US cohort study [72]. Eighteen of 101 cases was diagnosed invasive breast cancer in recent users [RR = 1.08 (95 % CI 1.02-1.16)] [72]. All other progestins were associated with an increased risk for breast cancer, with no difference between various progestins [50].

Risk for Breast Cancer with Estrogen

A greater understanding of estradiol's anti-estrogenic activity becomes apparent when examining the differing effects of the three primary estrogens upon estrogen receptor binding activity. Estrogen effects are mediated through two different estrogen receptors: estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-ß). Estradiol bind to ER-α and ER-ß, while estrone selectively activates ER-α [73,74]. Estriol, on the other hand, binds to and activates ER-ß, thereby explaining the potential breast cancer-prevention effect via G2 cell cycle arrest [73, 75].

Estriol may be as a weak estrogen when acting alone but it has a unique ability to protect breast tissue from excessive estrogen-mediated stimulation when administered with estradiol. It competitively inhibits estradiol binding and activated receptor binding to estrogen response elements which limits transcription [75, 80]. In contrast to estriol combined with estradiol, Conjugated equine estrogens (CEE), most used synthetical estrogen in HRT, has components that downregulate ER-ß which synergistically as synthetic progestins. It also contains 4-hydroxy-equilenin, a particularly potent carcinogenic estrogen which induces DNA damage, thus promotes cancer.

It is a possible mechanism underlying the breast cancer-promoting effect of CEE in conjunction with synthetic progestins [81, 85]. This is supported by the findings in WHI study. A 26-percent increased risk of invasive breast cancer was seen in women using a combination of CEE and MPA86,87] but CEE alone was associated with a lower risk of breast cancer than placebo after 11 years of observation [62]. A similar study by Mueck et al found that higher estrogen level inhibited breast cancer cell proliferation combined with progesterone, but had contrast effects when synthetic estrogens equilin or 17-alpha-dihydroequilin, a major components of CEE, combined with synthetic progestins [26].

These are consistent with findings that women who used estrogen (almost exlusively estradiol compounds) only had no significant increased risk for breast cancer [RR = 1.29 (95 % CI 1.24-1.30) with p 0.73] as reported by Fournier et al. The effect of combined estradiol and progesterone on breast cancer showed a RR 0.42 (95% CI 0.13-1.31) in Espie [87] whereas Fournier showed a RR 0.68 (95 % CI 0.56-0.82). In contrast, the risk increased significantly when the use of estradiol combined with synthetic progestins [RR = 1.69 (95 % CI 0.80-1.32) with p < 0.01] [50].

Recent studies have suggested that preparations containing estrogen alone do not increase the breast cancer risk substantially while preparations containing both estrogens and progestins do increase the risk, but some studies suggest that long term use increases risk [88,90]. Study in Sweden reported long term use of replacement estrogens with or without progestins may substantially increase the incidence of postmenopausal breast cancer [OR for women treated at least 10 years, 2.43 (95% CI, 1.79-3.30), as compared to never-users], particularly among non-obese women (BMI 27 kg/m^2, p 0.02) [74].

The finding was supported by another study in Sweden which conducted by Rosenberg et al. The use of medium potency estrogen (mainly estradiol or conjugated estrogen) alone was similarly associated with increased risk of breast cancer (ductal [OR = 2.0, 95% CI 1.5-2.9] and lobular [OR = 2.4, 95% CI 1.3-4.6]) [99]. Furthermore, the use of low potency oral estrogen (oral estriol without

progestin) was associated with an increased risk for lobular-typed breast cancer (OR 2.0, 95% CI 1.3-3.2), but not either ductal or tubular breast cancer. The increased risk was confined to <5 years of use and past users (OR 1.40, 95% CI 1.1-1.8, and OR 1.0, 95% CI 0.7-1.5 respectively) [99]. The use of local estrogens (cream or pessary, without progestin) was not found to be associated with any of the subtypes of breast cancer in our study (OR 0.5, 95% CI 0.1-1.9).

However, further confirmation by Magnusson et at about estriol's safety was provided that compared the use of HRT in 3,345 women over age 50 with breast cancer to 3,454 women without breast cancer. Women who used estriol did not have an increased risk of breast cancer, compared to women who never used HRT [74]. A similar study also suggested that the risk of breast cancer among estriol users was, however, not appreciably different than among nonusers (RR = 1.10, CI: 0.95-1.29) [74]. Thus, large-scale randomized control trials are needed to quantify the effects of estriol, and other estrogens on the risk of breast cancer.

Risk for Cardiovascular Disease with Synthetic Progestins Versus Bioidentical Hormones

Progesterone is a competitive inhibitor of mineralocorticoids which leads to enhance sodium loss that has been shown to reduce blood pressure in hypertensive patients in some studies [100,101]. This anti mineralocorticoid effect is not seen with the majority of available synthetic progestins. Moreover, some progestins contribute in increasing blood pressure by enhancing estrogen activity [102,103]. Progesterone is able to decrease sympathetic vascular tone in normotensive patients [104]. The mechanism is known via nitric oxide pathway to enhance vasodilatation and improve microcirculation [103,104]. However, endogenous and low dose parenteral estriol have also been shown to increase vasodilatation [102]. Study of WHI reveals synthetic estrogen such as conjugated equine estrogens (CEE) with synthetic progestins such as MPA was shown to increase blood clotting events [103]. Ethinyl estradiol decreased prothrombin time while increasing plasminogen and factor VII. On the other hand, estriol did not affect hemostatic function as shown in a randomized crossover study [106]. A study by Zegura et al shown oral use of estradiol was associated with an improvement in fibrinolytic activity, as assessed by a decrease in plasminogen activator inhibitor-1 (PAI-1) activity and tissue-typed plasminogen activator (t-PA) antigen and with a shortage of euglobulin clot lysis time (ECLT) [119]. Another recent study evaluating progesterone cream for safety and efficacy found no markers for inflammation or clotting [105]. In two studies comparing estradiol combined with either progesterone or MPA in primates by infusing a thromboxane A2 mimetics [106].

Estradiol and progesterone protected against coronary hyperreactivity and subsequent coronary vasospasm, whereas coronary vasospasm was significantly increased in primates receiving MPA [92,106].Thus increasing the risk for ischemic cardiovascular disease. One study comparing MPA to progesterone demonstrated progesterone reduced the risk for arteriosclerosis by inhibiting vascular cell adhesion molecule-1 (VCAM-1), whereas no such effect was observed with MPA (P<0.001) [94].

MPA increases the extent of atherosclerosis in coronary arteries, suppresses the protective effect of estrogen on arterial injury, and attenuates the beneficial effects of estrogen on vasodilation [107, 109]. MPA and other synthetic progestins generally negate the positive lipid effects of estrogen and show a consistent reduction in HDL [96,97,110], while progesterone maintains estrogen's positive lipid and HDL effects [96,97,111].

Meanwhile compared with placebo, postmenopausal women randomized to estradiol showed a higher mean on-trial HDL cholesterol level and a lower mean on-trial LDL cholesterol level.[120] showed Bolaji *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 DL and HDL-2 (P < 0.05) [111].

Adam *et al* compared the cardioprotective effects of CEE administration along with progesterone or MPA in primates fed

atherogenic diets for 30 months. The CEE and progesterone combination resulted in a 50% reduction in atherosclerotic plaques in coronary arteries (P<0.05) [112]. However, the CEE and MPA combination showed almost all the effect od atherosclerotic plaques reduction was reversed (P<0.05) [113]. Other studies examined that progesterone by itself [108,114,115], or combined with estradiol [112, 114] inhibits atherosclerotic plaque formation and lipid-lowering actions of estradiol, in contrast to synthetic progestins [113,116,117].

The differing effects of progesterone and MPA support progesterone as a better option. Progesterone and 17beta-estradiol both inhibited cardiac fibroblast growth, with the effects of 17beta-estradiol enhanced by progesterone, suggesting the combination may help protect postmenopausal women against cardiovascular disease [94]. Natural progesterone, in either oral, vaginal, or topical administrations, has demonstrated safety in its effects [96,104,118]. The research to date looking at cardiovascular risk points to bioidentical hormones, particularly progesterone, as the hormone therapy of choice to support healthy vascular function.

Discussion

Result shows that bioidentical hormone compared with synthetic hormone therapy giving more optimal result in postmenopausal women. In the term of efficacy, progesterone is more efficacious compared with synthetic progestin [9, 11]. Progesterone increase patient satisfaction because of better somatic, vasomotor and physiological symptom [9**].** Because of its physiological effects and clinical outcomes, current evidence demonstrates that bioidentical hormones are safer in terms of reduction of cancer and cardiovascular risk compared with synthetic hormones.

Progesterone, widely been used as bioidentical hormone, have distinguishable molecular differences that result in differences in their pharmacological effects on breast tissue. Synthetic progestin has procarcinogenic effects in which increase estrogen-induced breast tissue proliferation that increase risk of breast cancer. In contrast, progesterone has an antiestrogenic effect on both the endometrium and breast tissue that result in inhibition of breast tissue proliferation and reduces the risk for breast cancer. Researches also show that combination of progesterone with estradiol has more protective effect towards breast cancer, in contrast of combination of synthetic progestin with estradiol. This effect may be correlated with procarcinogenic effects of synthetic progestin-only because recent studies have suggested that preparations containing estradiol alone do not increase the breast cancer risk substantially [74,88, 90].

Other issues that appear regarding safety of bioidentical hormone compared with synthetic hormones is the risk of cardiovascular disease. Synthetic progesteron, progestin, consistently shows increase risk of cardiovascular disease when used alone or in combination with estradiol [66,91,95].

Many researches show that progesterone usage has no effect to increase risk of cardiovascular disease. This effect may be explained by anti mineralocorticoid and vasodilatation effects of progesterone that results in decrease of blood pressure [59,60,62]. Progesterone effect in reducing coronary vasospasm, arteriosclerosis formation, and maintain estradiol's positive lipid and HDL effect also lead to progesterone as hormone therapy of choice to support healthy vascular function [91,93,96, 98].

Therefore, all these findings suggest that for most postmenopausal women, the use of bioidentical hormones will not be associated with clinically significant changes in mood or physical symptoms, which weighs favorably into the cost-benefit ratio for women considering bioidentical hormone replacement therapy.

Conclusion

Researches support the claim that bioidentical hormones have some distinctly different, often opposite, physiological effects to those of synthetic hormones. With respect to decrease of breast cancer risk and cardiovascular risk, substantial scientific and medical evidence demonstrates that bioidentical hormones are safe and efficacious forms of hormonal replacement therapy. Until there is evidence to the contrary, current evidence states that bioidentical hormones are the preferred

method of hormone replacement therapy compared with synthetic hormones. Thus, physicians are able to take the time and effort to help women determining the regimen that best suits their needs to achieve the desired results. This effort will undoubtedly pay off in fewer unwanted side effects and greater quality of life.

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