A Comprehensive Review of the Safety and Efficacy of Bioidentical Hormones for the Management of Menopause and Related Health Risks

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Abstract

Numerous forms of estrogens and progestins are utilized for the treatment of menopausal complaints and associated conditions that occur temporally. Although known to be different with respect to molecular structure, receptor affinity, metabolism, and other physiological traits, most have been treated as if they were clinically identical. The majority of these hormone preparations, commonly referred to as hormone replacement therapy (HRT), should perhaps be more aptly referred to as hormone substitution therapy, as most of the therapies utilized do not exactly match those produced in the body. Research indicates these synthetic hormones vary clinically in safety and efficacy. As such, women and their physicians have, in increasing numbers, been opting for the use of bioidentical hormones; i.e., those that match the structure and function of hormones produced in the body. With greater utilization and research surrounding bioidentical hormones, the differences can now begin to be fully assessed and appreciated. This article reviews the disparities between synthetic and bioidentical estrogens and progestins/progesterone with respect to safety and efficacy; special attention is devoted to clinical outcomes in the breast, endometrium, bone, cardiovascular system, and brain. The studies reviewed suggest bioidentical progesterone does not have a negative effect on blood lipids or vasculature as do many synthetic progestins, and may carry less risk with respect to breast cancer incidence. Studies of both bioidentical estrogens and progesterone suggest a reduced risk of blood clots compared to non-bioidentical preparations. Bioidentical hormone preparations have demonstrated effectiveness in addressing menopausal symptoms. The author advocates for continued research on bioidentical hormones and concludes there is currently sufficient evidence to support their preferred use over that of their synthetic cousins. (*Altern Med Rev* 2006;11(3):208-223)

Introduction

Over the last decade, women and their physicians have in increasing numbers been opting for the use of natural, bioidentical hormones for treatment of symptoms of menopause and to support bone and heart health.[1] The trend away from the use of conventional synthetic hormones, toward those specifically matching the hormones produced in humans (bioidentical) has been driven by several factors, including a global trend toward everything "natural" as seen in the increased interest in organic foods and complementary and alternative medicine (CAM). Perhaps the most significant factor driving the increased interest in bioidentical hormones is the rising fear or suspicion of the "synthetic" hormones used in conventional hormone replacement therapy (HRT). Over the last decade, research-based media reports of risks associated with conventional HRT have prompted women's concerns and altered the approach to hormone use.[2,3] This has been most evident following the results of the U.S. government-sponsored Women's Health Initiative (WHI) study in 2002. The WHI study results

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led to the conclusion of experts in the field that the risk of using conventional HRT (non-bioidentical hormones), specifically Premarin® and Provera®, outweighed 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. The question, without the value of a similar long-term study looking at bioidentical hormones, is whether or not the evidence exists to support their preferred use over their synthetic cousins.

Hormone Changes Surrounding Natural (Non-induced) Menopause

Menopause is defined as the cessation of menstruation occurring as a result of the loss of ovarian follicular activity. At birth, a woman has a million eggs, by puberty a mere 300,000. This loss of eggs is referred to as atresia, a natural, albeit incompletely understood, process whereby the follicles enter an incomplete growth phase. This process continues throughout a woman's life. Thousands of follicles are lost to atresia compared to one or a few lost each month to ovulation. As a woman ages and as a result of the decreasing follicles, follicle-stimulating hormone (FSH) levels gradually increase and the cycle begins to shift, with a shortening of the follicular phase that can begin as early as a woman's 20s.[5,6] In the 10-15 years prior to menopause, this rate of follicular atresia begins to accelerate.[7,8] Perimenopause is the term used to describe the time of transition between a woman's reproductive years and cessation of menstruation. Typically perimenopause occurs between the ages of 40 and 51 and can last anywhere from six months to 10 years. During this time, hormone levels fluctuate and decline naturally, although not necessarily in an orderly manner.

Perimenopause often begins with an alteration in cycle and bleeding regularity due to fluctuating hormones, anovulatory cycles, and changes in timing of ovulation. Cycles may be long or short, ovulatory or anovulatory.[8] Even women who cycle regularly during perimenopause can have significant variability in hormone levels.[7] Progesterone levels drop with anovulatory cycles and a decline in luteal function. Estrogen levels fluctuate in response to rising FSH levels and provide feedback inhibition to FSH.[6] Significant variability may occur in estradiol and inhibin (a hormone that inhibits FSH), and gonadotropins may rise abruptly.[5,6,9] Testosterone levels decline with age and do not appear to change significantly with natural menopause. By menopause, few follicles remain, yet intermittent estradiol production from the ovaries may still occur.[8,9] Adrenal androstenedione is the primary source of estrogen after menopause; sex-hormone-binding globulin falls slightly.[10] FSH levels remain high for several years after menopause, after which levels decline considerably.[10,11]

Although FSH is commonly used, there are no consistently reliable endocrine markers to establish a woman's menopausal status.[9] Shifts in hormones contribute significantly to a sense of physical, mental, and emotional imbalance that may characterize a woman's experience of menopause. As a clinician, it is important to note the changes that occur, link them to the physiology of the various hormones, and address imbalances individually. Addressing other aspects of endocrine health is also necessary and may involve assessing adrenal and liver function, as well as diet, exercise, and other lifestyle factors.

Problems with Conventional HRT

In July 2002, after determining that estrogen in combination with progestin increased a woman's risk of breast cancer, coronary events, stroke, and blood clots, the National Institutes of Health (NIH) prematurely halted the first part of the WHI, a study designed to identify the risks and benefits associated with long-term hormone use. In this study, 16,608 healthy postmenopausal women with a uterus, ages 50-79, were randomized to either test or placebo group.[4] The test group received a combination of equine estrogen and synthetic progestin (PremPro®); no bioidentical hormones were used. At the time the study was halted, PremPro compared to placebo resulted in:

▼26-percent increased risk of invasive breast cancer (eight additional cases per 10,000 women per year);

▼29-percent increased risk of myocardial infarction (MI) or death from coronary heart disease (CHD) (seven additional cases per 10,000 women per year);

▼41-percent increased risk of stroke (eight additional cases per 10,000 women per year); and

▼200-percent increased risk of blood clots (18 additional cases per 10,000 women per year).

The WHI study also confirmed benefits seen in previous studies, most notably:

▼33-percent decreased risk of hip fracture (five fewer fractures per 10,000 women per year);

▼37-percent decreased risk of colorectal cancer (six fewer cases per 10,000 women per year); and

▼Relief of menopausal symptoms like hot flashes and vaginal atrophy.

An ancillary study the following year, the Women's Health Initiative Memory Study (WHIMS), demonstrated additional risks for women on combination equine estrogens and synthetic progestins. The study found combination therapy doubled the risk of developing dementia in women age 65 and older.[12]

Even prior to the WHI and WHIMS studies, relatively few women who might benefit from HRT chose to use it, despite the previous findings that HRT has established benefits for the treatment of menopausal complaints, reduction in bone loss, and some beneficial effects on the cardiovascular system.[13-15] In addition, women prescribed HRT often discontinue it before long-term benefits are realized. The most common reasons for discontinuation of HRT are unwanted side effects and weight gain, with one-third to two-thirds of women discontinuing it within the first two years.[13,14,16-18] Most side effects are attributed to the synthetic progestin portion of HRT, with the most common complaints being bloating, breast tenderness, and irregular bleeding.[13,14,19] Secondary reasons for discontinuation include fear of cancer and recommendation by a physician.

For women not initiating HRT, reasons cited include: HRT perceived as unnecessary, a preference to not take medications, a fear of the effects of long-term HRT, confusion over the scientific information as presented in the media, and the view that menopause is a natural event.[2,3,14,20] Use of HRT was correlated with older women's wishes to reduce osteoporosis risk, while younger women sought relief from menopausal symptoms, predominantly vasomotor flushing.[2,19]

Given this information, it should follow that utilizing hormones that have fewer side effects and risks, correlate with a woman's perception of "natural," and address long-term health benefits could increase hormone use and therefore improve a woman's health and well-being. Bioidentical hormones may provide these benefits.

What is Bioidentical Hormone Therapy?

Bioidentical hormones are identical to hormones produced endogenously. In the case of HRT, these include estrone (E1), estradiol (E2), estriol (E3), and progesterone (P4). Although bioidentical hormones have long been utilized in other countries, the United States has predominantly used non-bioidentical hormones for the past 40-45 years, beginning with the introduction of oral contraceptives in the early 1960s.

The differences in the actions, risks, and benefits of various hormones depend on numerous factors, including method of administration, absorption, bioavailability, metabolism, receptor affinity, receptor specificity, and molecular structure.[21,22]

Bioidentical versus Synthetic Estrogens

The body naturally produces three main forms of estrogen: estrone, estradiol, and estriol. Bioidentical estrogens are molecularly identical to these naturally produced estrogens. Synthesized in the ovaries and metabolized in the liver, estradiol is the most physiologically active form of estrogen. Increased serum estradiol levels are linked to an increased risk of breast and endometrial cancer.[23] Estrone is converted reversibly from estradiol in the liver and small intestine and increases after menopause when the adrenal glands play a more prominent role than the ovaries in hormone synthesis. Like estradiol, increased estrone levels are linked to an increased risk of estrogen-receptor positive (ER^+) breast cancer and an increase in breast density, an independent risk factor for breast

Table 1. Synthetic and Bioidentical Estrogen Preparations Available in the United States

ESTROGENS	BRANDS
Bioidentical	
17-beta estradiol (E2)	Alora®, Climara®, Estraderm®, Fempatch®, Oesclim®, Vivelle® (all E2 patches); Combi Patch® (E2 + norethindrone); Emcyt® (capsule); Estrace® (vaginal cream and tablet); Femring® and Estring® (vaginal rings); Estrasorb® and Estragel® (transdermal preparations); and available generically in troches, sublingual drops, suppositories, creams, gels, or capsules from compounding pharmacies.
Estrone sulfate (E1)	Available generically in troches, sublingual drops, suppositories, creams, gels, or capsules from compounding pharmacies.
Estropipate (E1)	Ogen® (tablet and vaginal cream); Ortho-Est® (tablet); generic tablet
Estriol (E3)	Available generically in troches, sublingual drops, suppositories, creams, gels, or capsules from compounding pharmacies.
Non-Bioidentical	
Ethinyl estradiol	Brevicon®, Demulen®, Levlen®, Lo-Ovral®, Loestrin®, Modicon®, Nordette®, Norinyl®, Ortho-Cept®, Ortho-Cyclen®, Ortho-Novum®, Ortho-Tri-Cyclen®, Ovcon®, Tri-Levlen®, Tri-Norinyl®, Triphasil®, Nelova® (all tablets in combination with synthetic progestins); Estinyl® and Feminone® (tablet)
Esterified estrogens	Estratab® (tablet, vaginal cream); PremPro® (tablet in combination with MPA); PremPhase® (tablet in combination with MPA); generic (tablet)
Conjugated equine estrogens (CEE)	Premarin® (tablet, vaginal cream); PremPro® (tablet in combination with MPA); generic (tablet)
Dienestrol	Ortho Dienestrol Cream® (vaginal cream)

Table 2. Synthetic Progestin and Bioidentical Progesterone Preparations Available in the United States

PROGESTOGEN/PROGESTERONE	BRAND NAME
Bioidentical (Progesterone)	
Progesterone (P4)	Crinone® and Utrogestan® (vaginal gels); Pro-Gest® and other brands (transdermal cream); Prometrium® (capsule); and available generically in troches, sublingual drops, suppositories, creams, gels, or capsules from compounding pharmacies.
Non-Bioidentical (Progestogen)	
Medroxyprogesterone acetate (MPA)	Provera®, Amen®, Curretab®, and Cycrin® (tablet); PremPro® and PremPhase® (tablet in combination with CEE)
Norethindrone acetate	Aygestin®, Micronor®, Norlutate®, Nor-QD® (tablet)
Norethindrone	Norlutin® (tablet)
Norgestrel	Ovrette® (tablet)
Norgestimate	Ortho-Tri-Cyclen® (tablet in combination with EE)
Levo-Norgestrel	Preven® (tablet in combination with EE)
Desogestrel	Desogen® (tablet)
Megestrol acetate	Megace® (tablet)

cancer.[24,25] Both estradiol and estrone can be metabolized to estriol, which is the primary urinary metabolite. Estriol is considered the "weakest" estrogen, as it has a shorter-acting effect than estradiol or estrone.[26] However, depending on sufficient dosing and route of application, estriol can attain a full estrogenic effect on target tissue, such as the vaginal mucosa.[26] Estriol remains intact when supplemented orally (i.e., unlike estradiol, estriol is not converted to estrone, nor is it converted to estradiol).[27] In Europe and China, estriol is commonly used for HRT. A comprehensive review of the safety and efficacy of estriol suggests it may be safer than estrone or estradiol, but can still have a stimulatory action on the endometrium and breast when given in high doses.[28]

In a comparison of bioidentical (estropipate, estradiol) versus non-bioidentical estrogens (ethinyl estradiol, conjugated equine estrogens, diethylstilbestrol), non-bioidentical estrogens had significantly exaggerated responses across multiple hepatic and non-hepatic measures of estrogenic effects.[29]

The predominant estrogen currently prescribed in the United States is Premarin, a brand name for conjugated equine estrogens (CEE). Premarin

contains approximately 100 distinctly different estrogens, mainly estrone sulfate, equilins, equilenins, and alpha-estradiol, all of which are estrogens occurring naturally in horses; with few natural to the human body. Over 30-percent drop in sales revenues from both Premarin and PremPro occurred following reports of the WHI study.[30]

Many estrogen formulations presently available in the United States contain bioidentical estrogens (Table 1). A growing number of conventional and CAM physicians are now prescribing "Tri-Est," or "Bi-Est," nicknames given to individually-compounded formulations of estriol, estrone and estradiol, or estriol and estradiol, respectively. Licensed pharmacists can fill a doctor's prescription for these combinations of natural estrogens in a variety of doses and delivery systems to specifically address patient needs.

Natural Progesterone versus Synthetic Progestins

Inconsistency in use of the terms "progesterone," "progestin," and "progestogen" has led to confusion over these substances. Progesterone refers to a single (note the "one" at the end of the term) molecular structure that is identical to the progesterone molecule that the body makes, also referred to biochemically as "P4." Progestogen is the category of hormone molecules (natural and synthetic) that act like progesterone in the uterus. Progestin generally refers to synthetic progestogens. See Table 2 for a list of commonly prescribed progestogens.

Progesterone was originally procured by extraction methods from animal placenta. Natural progesterone products today are produced in a laboratory setting via a process designated as the "Marker Degradation" from saponins found in soy and *Dioscorea villosa* (wild yam). Hudson presents a detailed historic perspective of the series of events surrounding the discovery of this process.[31]

Progesterone was first used as HRT in 1934 for the treatment of ovariectomized women.[32] Due to significant first-pass effect of progesterone, synthetic progestins were developed in the 1940s, either from progesterone (e.g., medroxyprogesterone acetate) or from testosterone (e.g., 19-nortestosterone).[33] Progestins mimic the body's progesterone closely enough to bind to progesterone receptor sites, but do not deliver the full range of "messages" a natural progesterone molecule does. A synthetic progestin, for example, may have similar effects on the endometrium, yet can initiate widely different actions elsewhere in the body (e.g., brain, mineralocorticoid receptors, etc.) depending on the classification of the particular progestin (nortestosterone derivatives, ethyl-13 derivatives, progesterone derivatives, or norprogesterone derivatives.)[34,35] These different progestins have been mapped as to affinity to androgen, progesterone, glucocorticoid, and estrogen receptors.[36] In contrast to progesterone, 19-nortestosterone derivatives are known to have estrogenic properties, which could be attributed to their estrane structure (an 18-carbon tetracyclic hydrocarbon nucleus that is the parent structure to all estrogens) or to the production of estrogen as a metabolite.[37] Derivatives of 19-nortestosterone have been shown to increase the growth of ER^+ breast cancer cells *in vitro*.[38] A paper published in 2000 discussed the development of newer synthetic progestins that more closely fit the profile of bioidentical progesterone.[39]

Estrogen, Progesterone, or Both?

Current recommendations from the American College of Obstetricians and Gynecologists suggest that estrogens be prescribed in conjunction with progestins (to prevent endometrial hyperplasia) when a woman has an intact uterus;[40] conversely, unopposed estrogens are the norm post-hysterectomy. Although progesterone and estrogen receptors both exist in tissue outside the uterus, it has not been thought necessary to provide progestins after the uterus is removed.

In contrast, when using natural hormones, many physicians consider the concomitant use of progesterone with estrogen to be an important aspect of bioidentical hormone therapy and hormonal balancing. The growing research on the synergism of these two hormones, as well as an expanded understanding of progesterone's effect in the body, are prompting some to recommend these hormones be prescribed together, regardless of the presence or absence of a uterus.[41,42]

When considering estrogen replacement during perimenopause and early menopause, the level of endogenous estrogen production must also be considered, since elevated FSH levels can be associated with either increased or decreased levels of estrogen.[9,11] Since progesterone levels can fall first with the advent of anovulatory cycles, some women may do well with progesterone-only supplementation during perimenopause, which may help balance the effects of unopposed endogenous estrogen production. FSH, although commonly used as a diagnostic indicator of menopause, may not be the most reliable tool for determining estrogen needs perimenopausally.[9] One should also note that women with a greater amount of body fat can produce a significant amount of endogenous estrogen postmenopausally. This can occur exclusively through aromatization of estrogens from adrenal androstenedione by the fat cells.[10] In one study, 10-15 percent of postmenopausal women produced enough estrogen to build the endometrial lining, further emphasizing the need to determine individually the potential hormonal needs of each woman during the climacteric.

Hormone Synergy

Hormone function can be affected by the presence of other hormones, as is seen in the synergistic effects of E2 and P4.[41,43] Even the receptors can exhibit synergism, although the exact mechanisms have not been fully elucidated.[44,45] An example of this phenomenon in clinical practice is the synergistic antiovulatory effects of estrogen and progestogens resulting in efficacy of lower-dose oral contraceptives equal to that of higher-dose regimens. More recently, a study found estradiol in combination with progesterone inhibited bone resorption to a greater degree than either hormone alone.[46]

Differences in Hormone Delivery

Continuous versus Pulsed Delivery

There is sufficient evidence to suggest the pulsatile delivery of estrogen and progesterone that occurs naturally serves to enhance the functioning of these hormones in the body.[47-49] In theory, continuous application of hormones may serve to down-regulate receptors, contributing to a general decrease in the activity of those particular hormones. Research has demonstrated that sequential pulsed estrogen and progestin therapy allows for smaller amounts of hormones to be used.[47] Reduced dosage would translate to reduced likelihood of unwanted side effects as well as a reduced impact on the liver via metabolism of supplemented hormones. This also supports the most recent U.S. Food and Drug Administration recommendation surrounding hormone therapy for women that advocates using the lowest effective dose for the least amount of time necessary.[50]

Routes of Administration

Many different routes of delivery are available for natural hormones, including oral, transdermal (patch), percutaneous (cream, gel), intramuscular (IM), subcutaneous, sublingual, vaginal (gels, cream, tablet, ring, and pessary), and nasal. The route of administration can confer differences in absorption, metabolic pathway, and bioavailability. In general, the oral route leads to more rapid metabolism and a greater impact on hepatic processes, requiring larger doses than those bypassing the entero-hepatic circulation. The same sized doses of progesterone and estradiol resulted in greater circulating blood levels when delivered vaginally compared to oral administration, due to entero-hepatic metabolism.[51] In comparing different E2 delivery systems, percutaneous, transdermal, and vaginal delivery resulted in a reduction in metabolism to E1 via the entero-hepatic circulation.[51-53] Side effects common with oral E2 were not seen when administration was via the percutaneous or transdermal routes.[54,55]

Approximately 90 percent of oral progesterone is metabolized by the "first pass effect" (caused by shunting through the entero-hepatic circulation), leading to difficulties in dosing as well as an abrupt increase in 5-alpha-progesterone metabolites.[56] Oral progesterone administration resulted in higher levels of progesterone metabolites (deoxycorticosterone, deoxycorticosterone sulfate, and 5-alpha and beta pregnenolone) when compared to vaginal administration.[51-57] A study by Hermann et al compared 80 mg progesterone daily via a topical cream (Pro-Gest®) to 200 mg oral micronized progesterone (OMP) as Prometrium® daily and found no difference between the two products with respect to steady-state blood levels of progesterone as measured by area under the

curve (AUC).[58] In another comparison study, similar endpoints were achieved with 300 mg oral micronized progesterone and 90 mg vaginal progesterone, with fewer side effects of drowsiness noted with the vaginal application (an effect attributed to 5-alpha and beta metabolites of progesterone).[59]

It is important to note that progesterone and its metabolites have differing effects in the brain, uterus, smooth muscle, and oocyte.[60] For example, depressive effects of progesterone are predominantly attributed to pregnane metabolites, such as allopregnanolone, as opposed to progesterone itself. Given the increase in metabolites seen with OMP, vaginal or topical delivery systems may reduce expression of side effects attributed to these metabolites.

Because numerous factors can influence intestinal absorption and metabolism, some preparations may have more variable effects. In a study of the pharmacokinetics of oral versus IM administration of E2, 4 mg IM demonstrated a rate of release into the bloodstream that achieved therapeutic levels over 2-4 weeks (depot effect). To achieve the same therapeutic equivalency with an oral dose, some individuals required as much as 2 mg daily for three weeks.[61]

Oral micronized progesterone also exhibits substantial variability in absorption among individuals. In one study, maximum serum concentration ranged from 15.72-625.98 ng/mL, following a single 300 mg dose; the authors also noted that absorption increased with age.[62] In a separate study of percutaneous absorption of a progesterone cream, the authors reported moderate variability among individuals.[63]

Forms of Administration

The base of a cream, gel, or suppository can also affect absorption. In a study of topical applications comparing progesterone in a hydrophilic gel, lipophilic base, and emulsion-type base,[64] the emulsion-type base led to a two-fold greater AUC and peak plasma concentration than either the hydrophilic gel or lipophilic base.[64] Another study by the same authors comparing two suppository bases found an emulsion-type base resulted in improved pharmaceutical availability when compared to a lipophilic base of cocoa butter.[65] A comparison between the percutaneous and vaginal delivery systems found the elimination half-life for the three transdermal forms of progesterone was in the range of 30-40 hours,[64] compared to the cocoa butter vaginal suppository with an elimination half-life of 9-10 hours and the emulsion-based suppository with an average elimination half-life of 14 hours.[65]

Physiological levels of serum progesterone were reached via a novel nasal spray application.[66] Also unique is an effervescent progesterone vaginal tablet that results in adequate serum progesterone levels. In this study there was significant age-related difference in time of maximum concentration (Tmax), with women over 40 years attaining a lower Tmax than younger women.[67]

Given the differences that abound in both the type and route for administration of hormones, physicians should assess an individual woman's need for hormone therapy and tailor the regimen to her needs.

Effect of Hormones on the Cardiovascular and Endocrine Systems

Hormones have multiple effects on the cardiovascular and endocrine systems, including eliciting actions on blood pressure, vascular tone, hemostasis, lipid metabolism, cardiac vasospasm, and glucose metabolism.

Blood Pressure Effects

Progesterone antagonizes mineralocorticoids such as aldosterone. Since aldosterone enhances sodium retention and potassium loss via the urine, antagonism of this effect results in increased sodium excretion in the urine. This effect on sodium loss has been shown to reduce blood pressure in hypertensive patients in some studies, as well as ease symptoms of water retention.[68,69] This anti-mineralocorticoid effect is not seen with the majority of available synthetic progestins. Moreover, some progestins enhance estrogen activity, contributing to the potential for increased blood pressure.[70,71]

In normotensive patients, progesterone can decrease sympathetic vascular tone, without concomitant drop in blood pressure.[72] Progesterone acts via the nitric oxide pathway to enhance vasodilation and improve microcirculation.[73,74] In animal studies, endogenous and low-dose parenteral E2 have also been shown to increase vasodilation.[70]

Blood Clots

Estrogen replacement therapy is known to increase the risk of blood clots. High-dose estrogens, especially synthetic and oral estrogens, increase liver protein synthesis, including coagulation factors. Oral estrogens also increase angiotensin, and may raise blood pressure and stroke risk in susceptible women.[70] In a randomized crossover study, estriol did not affect hemostatic function, whereas ethinyl estradiol decreased prothrombin time while increasing plasminogen and factor VII.[75] In the WHI study, CEE with medroxyprogesterone acetate (MPA) was shown to increase blood-clotting events.[76]

In contrast to synthetic hormone use, a recent study evaluating progesterone cream for safety and efficacy found no markers for inflammation or clotting.[77] The study also found that in women with higher than normal cortisol levels, there was a marked decline in the level of cortisol to the normal range while using progesterone cream compared to placebo.[77]

Hormone Effects on Lipids, Atherosclerosis, Vasospasm, and Insulin Resistance

Activated by stress, increased cortisol has been associated with an increased risk of atherosclerosis, obesity, and other manifestations of heart disease. Cortisol can contribute to atherosclerosis by increasing cholesterol ester formation. While estrogen was seen to have no effect on cholesterol esters, progesterone blocked cholesterol ester formation, signifying an anti-atherogenic effect of progesterone.[78]

Whereas some synthetic progestins are known to exert a negative effect on blood lipids, bioidentical progesterone does not appear to do so.[79,80] In the Postmenopausal Estrogen and Progestin Interventions (PEPI) Trial, oral micronized progesterone fared significantly better than MPA, as OMP did not blunt the beneficial effects of estrogen on HDL elevation.[81] This was also found in an earlier study comparing progesterone with both nortestosterone and MPA.[82]

Third generation progestins, such as norgestimate and desogestrel, have not demonstrated this same adverse effect on serum lipids.[83]

MPA increases the extent of atherosclerosis in coronary arteries, suppresses the protective effect of estrogen on arterial injury, increases insulin resistance, and attenuates the beneficial effects of estrogen on vasodilation.[84-86] This is consistent with findings that synthetic estrogen as well as 19-nortestosterone can result in a decrease in glucose tolerance, whereas glucose metabolism is unaffected by P4.[87] Progesterone has furthermore been shown to have an antiproliferative effect on vascular smooth muscle in normal human and animal tissues as well as in models simulating hyperinsulinemia and hyperglycemia.[88,89]

In two studies comparing E2 and P4 with E2 and MPA, E2 and P4 protected against coronary hyper-reactivity and subsequent coronary vasospasm, whereas coronary vasospasm was increased in monkeys receiving MPA.[90,91] In a separate study, the same authors demonstrated an inhibition of coronary vasospasm with topical progesterone cream in pre-atherosclerotic primates.[92]

One study comparing MPA to progesterone demonstrated progesterone reduced the risk for arteriosclerosis by inhibiting vascular cell adhesion molecule-1 (VCAM-1), whereas MPA did not.[93] 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 P4, suggesting the combination may help protect postmenopausal women against cardiovascular disease.[94]

Normal liver function is essential for lipid metabolism. Synthetic progestins retain undesirable effects on liver metabolism, even when administered through the skin.[83] In regard to estrogen, a comparison between orally administered ethinyl estradiol (EE) and E2 demonstrated beneficial effects on serum lipids (EE>E2); however, EE demonstrated a marked increase in liver protein synthesis, including sex-hormone binding globulin (SHBG) and pregnancy zone protein (PZP), markers of increased estrogenic effect.[95] SHBG elevation can result in lower testosterone activity due to its greater affinity to testosterone and dihydrotestosterone than estrogen.

Natural progesterone, in either oral, vaginal, or topical administrations, has demonstrated safety in its effects on lipid metabolism and blood clotting.[77,80,96] 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.

The Effect of Hormones on the Breast

In the past, the effect of synthetic progestins on the breast was unclear. Whereas progestins have been used historically to treat some forms of advanced breast cancer, a re-evaluation of results of a cohort study suggest an increased risk in the occurrence of breast cancer in women using combined HRT (predominantly CEE plus MPA) beyond that seen with unopposed estrogen; the risk increase, however, was not statistically significant.[97] Recently, the effect of HRT on breast tissue was demonstrated in the WHI study. A 26-percent increased risk of invasive breast cancer was seen in women using a combination of CEE and MPA compared to placebo.[4]

Several reviews suggest a protective effect of progesterone and some progestins on normal and pathological breast tissue, including a strong anti-proliferative effect both in the presence and absence of estrogens.[98-102] Low endogenous progesterone levels were also correlated with a five-fold increase in premenopausal breast cancer risk in women experiencing infertility when compared with infertile women with normal hormone levels.[103] In women undergoing breast surgery for benign breast conditions, pretreatment with topical estrogen resulted in increased epithelial proliferation compared to a reduction in proliferation seen with percutaneous progesterone treatment; furthermore, progesterone reduced estrogen-induced proliferation when both treatments were used.[104] An *in vitro* study evaluating the effect of progesterone on the growth of T47-D breast cancer cells demonstrated increased apoptosis as mediated by the regulation of genes controlling apoptosis.[105] In a review by Desreux et al, the authors emphasized progesterone's role in supporting healthy breast homeostasis.[106] Progesterone opposes the proliferative effects of estradiol in the breast,[106,107] a role not seen with synthetic progestins.[106]

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), a common European treatment for breast mastalgia. Furthermore, the researchers noted a decrease in breast cancer risk among women using progesterone cream plus an oral progestogen (RR=0.5), compared with women using oral progestogens alone.[108]

Two recent studies point to a difference in breast cancer risk when comparing synthetic progestins to bioidentical progesterone as a part of the HRT regimen. A French cohort study involving 3,175 postmenopausal women predominantly using natural HRT (83 percent using transdermal estradiol and a non-MPA progestogen – progesterone and others) found no increased risk in users of these forms of HRT.[109] The French E3N-EPIC cohort study is probably the most significant examination of the differences between progestogens and breast cancer risk. It assessed the risk of breast cancer associated with HRT use in 54,548 postmenopausal women and found the risk was significantly greater ($p<0.001$) with HRT containing synthetic progestins (RR=1.4 [1.2-1.7]) than with HRT containing micronized progesterone (RR=0.9 [0.7-1.2]).[110] Although there are no prospective trials looking at the safety of bioidentical progesterone with respect to the breast, these large cohort studies, in combination with studies examining the effects of progesterone on normal and cancerous breast cells, do provide enticing evidence for the safety of bioidentical progesterone.

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 and estradiol levels are associated with an increased risk of breast cancer. The supplementation of either of these forms of estrogen increases serum estradiol and estrone due to the pathways by which they are metabolized. In contrast, several studies have demonstrated an inverse relationship between estriol levels and breast cancer as well as antitumor effects of estriol.[27,111-113] However, while there is reason to believe that estriol in low doses could be protective for the breast in some individuals, when supplementing estrogens, one must also consider the differences among individuals with respect to metabolism. A recent study looking at the effects of 14 different endogenous estrogen metabolites demonstrated proliferative, antiproliferative, and bi-phasic effects on a specific human breast cancer line (MCF-7), further emphasizing the importance of individualized consideration.[114]

The Effect of Hormones on the Endometrium

Both OMP and vaginal delivery of progesterone result in sufficient end-organ effect on the uterus with doses beginning at 100 mg daily x 25 days/month or 45 mg every other day for six doses/month, respectively.[83,115,116] Similar end-organ results have been seen using percutaneous progesterone cream.[117]

Hormones and Menopausal Symptoms

Although most physicians attribute vasomotor flushing to a lack of estrogen, progestogens can have a beneficial effect.[118] A study using a progesterone cream applied to the skin resulted in a significant reduction in the number and intensity of hot flashes in 83 percent of the study participants, as well as benefits in other quality-of-life measurements.[119] In a separate study, subjects receiving 20 mg of topical progesterone cream daily for four weeks demonstrated significant improvement of menopausal symptoms, measured by Greene Climacteric Scale scores.[77]

In a study comparing the effects of CEE plus MPA to CEE plus OMP in postmenopausal women, the latter group had significantly improved sleep efficiency over the synthetic progestin group.[120] Another study comparing MPA to OMP found micronized progesterone to be better tolerated than MPA, as well as conferring additional benefits in cognition and improvement of menstrual problems.[121]

Oral and transdermal estradiol preparations have been found to confer benefit for menopausal symptoms and vaginal cytology, as well as reduce bone loss in postmenopausal women.[53,55] Estriol has also been demonstrated to reverse vaginal atrophy.[122,123] Estriol doses must be increased up to three times the dose of estradiol to achieve similar effects (e.g., reducing hot flashes and vaginal dryness in menopausal women) and is typically dosed twice daily to achieve steady blood levels.[27]

Hormones and Bone Health

Bone turnover increases at menopause and may remain high for 25 or more years following the last menstrual cycle.[124] Hormonal control of bone turnover is not limited to a single hormone, but rather the complex interrelationship of a number of steroid and other hormones, including estrogen, progesterone, testosterone, corticosteroids, vitamin D, thyroid hormones, and retinoids.[125] When given alone, estrogens have a known beneficial effect on limiting bone loss as well as reducing the number of fractures. Studies with progesterone alone are mixed. Progesterone supports bone health through its effects on the proliferation and differentiation of human osteoblasts.[126] Several animal and human studies have demonstrated progesterone's positive effect on bone formation as well as inhibition of bone resorption.[127-130] However, double-blind placebo-controlled studies in humans have yet to demonstrate a significant increase in bone mineral density (BMD) or a reduction in fracture rate with progesterone alone. One short-term human study of OMP showed no difference in markers of bone resorption compared to placebo.[131] Longer-term studies evaluating BMD and fracture rate are needed to determine the value of progesterone supplementation alone for preventing or treating osteoporosis. Several studies looking at estrogen and progesterone supplementation suggest estrogen and progesterone have distinct and complementary roles in the maintenance of bone.[46,130,132] Testosterone can also decrease urinary calcium loss and bone resorption.[76,133]

Hormones and the Brain

Progesterone has numerous beneficial effects on the brain and nervous system, including supporting myelin formation and activating GABA receptors.[134] Progesterone also plays a role in the reduction of ischemia in the brain and decreasing the inflammatory response after traumatic brain injury.[135,136] A review of progesterone's effect on the brain suggests viable therapeutic possibilities for the prevention and treatment of neurodegenerative diseases, as well as for repair processes and preservation of cognitive function with age.[137] Synthetic progestins do not share these physiological effects. In fact, the WHIMS found equine estrogen plus synthetic progestins (PremPro) doubled the risk of developing dementia in women age 65 and older.[12]

Estrogens have known physiological effects on the brain, including improved blood flow via vasodilation and stimulation of serotonin and norepinephrine, which can impact nerve cell function and mood. It was postulated that estrogen could help delay age-

related cognitive decline or help prevent Alzheimer's disease, and small studies on animals appeared to confirm this.[138] However, two large-scale human studies failed to demonstrate any significant benefit of estrogen supplementation on cognitive function.

The Atherosclerosis Risk in Communities (ARIC) study evaluated the effects of estrogen on memory and cognitive function in 2,000 women participants ages 48-67 over a 10-year period and found no correlation (either positive or negative) between estrogen and cognitive function.[138]

The WHIMS also failed to demonstrate a cognitive benefit for estrogen alone. In fact, results demonstrated an increased risk for dementia in women using estrogen alone, although not as great a risk as combined synthetic HRT.[12] It should be noted that the WHIMS utilized equine estrogens with or without MPA, while the prospective ARIC study did not denote estrogens utilized.

Conclusion

The use of bioidentical hormone therapy is well tolerated, provides symptom relief, and can address many of the health needs as well as the individual preferences of menopausal and perimenopausal women. Physicians are encouraged to take the time and effort to help women determine the regimen that best suits their needs, including testing hormone levels directly prior to supplementation and using the least amount necessary 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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