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Bioidentical Hormone Replacement: Guiding Principles for Practice

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Introduction

Before synthetic and nonhuman hormones were in common use, there was no need for a term like *bioidentical*. For the purpose of this review, bioidentical hormones are defined as hormones identical in structure to human hormones. However, when physicians began prescribing hormones to postmenopausal women, manufacturing limitations like the poor bioavailability of oral progesterone meant that bioidentical hormones were not an option. The fact that synthetic hormone analogs and nonhuman hormones were patentable, relatively inexpensive to produce, effective, and seemingly very safe led to their acceptance as the standard for hormone supplementation.

Conjugated equine estrogens (CEE) became a popular treatment for menopause symptoms after the 1968 book *Feminine Forever*. Over time though, continuous use of unopposed estrogen led to an increased incidence of endometrial cancer. This resulted in the addition of synthetic progesterone analogs like medroxyprogesterone acetate (MPA) to suppress endometrial growth and oppose the effects of estrogen. MPA was and still is very effective at suppressing endometrial growth, but its interactions with progesterone receptors in heart and bone tissue of postmenopausal women went largely unnoticed. Although small clinical trials and *in vitro* studies indicated MPA was not equivalent to progesterone, it wasn't until large clinical trials reported that the combination of CEE and MPA increased the risk of heart attack, stroke, and cancer in postmenopausal women that hormone replacement really went under the microscope.[1,2,3,4]

While combined CEE and MPA was the reigning champion of hormone replacement, a few innovative thinkers suggested that bioidentical hormones might be safer and more effective than nonhuman or synthetic molecules. Most influential was the late John R. Lee, MD, who, in addition to advocating for bioidentical progesterone as the ideal progestogen, also coined the term *estrogen dominance*.[5] Erratic estrogen production combined with higher average estrogen levels are recognized characteristics of perimenopause, producing a condition of functional estrogen excess now commonly called estrogen dominance in the complementary medicine community.[6] Lee devoted his career to educating women and healthcare providers on the benefits of using progesterone cream to correct this imbalance during perimenopause and beyond.

Meanwhile another innovator, Jonathan Wright, MD, evaluated women's options for estrogen replacement. After menses ceases and menopause begins, estrogen levels begin to decline. In a quest for safer estrogen options, Wright reviewed the breast cancer research done by Henry Lemon, MD, in the 1960s. Lemon studied estriol, the weakest of the three main endogenous estrogens, and discovered that women with breast cancer had significantly lower urinary estriol numbers than healthy controls.[7] Lemon's research got Wright thinking that combining estriol with estradiol might be protective against cancer. He put this idea into practice and created BiEst (bi-estrogen) and TriEst (tri-estrogen). BiEst and TriEst can be compounded into capsules, creams, gels, and troche (lozenge) forms—BiEst usually in an 80:20 estriol-to-estradiol ratio and TriEst in an 80:10:10 estriol-to-estradiol-to-estrone ratio. The use of BiEst and TriEst is common in complementary medicine, and in some circles it has become the *de facto* definition of bioidentical hormone replacement (BHRT).

Once BiEst and TriEst made inroads into hormone replacement regimens, the debate over the safest and most effective forms of hormone replacement began to heat up.

Bioidentical Hormone Replacement

The term *bioidentical hormone replacement* has been variously interpreted. Some suggest BHRT is the practice of individualizing hormone therapy (by compounding individualized hormone doses), but most correctly interpret it as the use of hormones that are structurally identical to endogenous hormones.[8,9] Therefore, the core principle of BHRT is the use of bioidentical hormones. However, there are 2 other principles that complementary medicine practitioners generally adhere to when prescribing bioidentical hormone replacement. This review will deal with each of these 3 principles in some detail. They are as follows:

- Use hormones identical in structure to endogenous hormones.
- Optimize hormone delivery: non-oral delivery methods may be preferable for estrogens.
- Use doses that mimic physiologically normal levels.

To understand the theory and importance of these principles, an awareness of the research comparing the various hormone products is essential.

1) Rationale for the Use of Bioidentical Hormones

By definition, the term bioidentical means *life-identical*—that is, hormones identical to those found in life (in this case, human). Literally then, bioidentical hormone replacement includes all human-identical hormones, not just compounded hormone products like BiEst, TriEst, and progesterone. For example: oral micronized progesterone and 17-beta estradiol patches are considered bioidentical because they are structurally identical to human hormones. A discussion of the clinically relevant differences between bioidentical and non-bioidentical /synthetic hormones illustrates why use of bioidentical hormones may be considered more beneficial.

Progesterone

Progesterone versus synthetic progesterone analogs

When it became clear that unopposed estrogens increased the risk of endometrial cancer in postmenopausal women, MPA and other synthetic progesterone analogs were added to suppress estrogen-induced endometrial growth.[10] At the time, oral progesterone was poorly absorbed and was not an option. It wasn't until the latter part of the 20th century that micronization of progesterone into particles less than 10 microns in size led to increased surface area, enhanced dissolution, and improved intestinal absorption, making oral progesterone a viable hormone therapy.[11]

Over the years, numerous scientific papers have used the word "progesterone" as a catchall term that included synthetic progesterone analogs as well as progesterone. This misrepresentation of progesterone created confusion for both researchers and clinicians, as it suggested synthetic progesterone analogs had the same effect on progesterone receptors as progesterone. There are clinical scenarios that strongly suggest otherwise. For example, MPA is considered a teratogen and is contraindicated in the first 4 months of pregnancy.[12] In contrast, progesterone vaginal suppositories are often used in the first trimester to sustain pregnancy.[13] Clearly, the 2 molecules have very different effects in childbearing women and could reasonably be expected to have other differences. Unfortunately, they were considered sufficiently equivalent for MPA to be widely recommended as hormone replacement in perimenopausal and postmenopausal women. Eventually, problems with MPA were exposed in these populations, particularly in the areas of cardiovascular health and hormone-related cancers.

Cardiovascular disease

To examine the cardiovascular effects of MPA, women on estrogen therapy combined with MPA were compared with those on combined estrogen and oral micronized progesterone (OMP). The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial found oral CEE significantly elevated levels of the inflammatory marker C-reactive protein regardless of whether CEE was unopposed, combined with MPA, or combined with OMP. However, CEE combined with MPA elevated CRP significantly more than CEE alone or in combination with OMP.[14]

The PEPI Trial also found that increases in high-density lipoprotein (HDL) levels from oral estrogen supplementation were preserved when OMP was used, but not when MPA was the progesterone analog of choice.[15]

MPA also interferes with the benefits of estrogens on coronary vasospasm and exercise-induced myocardial ischemia. In young women, acute MPA administration negates the beneficial endothelium-dependent vasodilatation effects of estradiol.[16] In contrast, use of OMP maintains the cardioprotective effects of estrogens.[17,18,19]

A review of the scientific literature to date shows that OMP, but not MPA, preserves the beneficial cardiovascular effects of estrogens without observable negative effects.

Cancer

Although breast cell proliferation, and therefore potential for DNA damage, is increased in the luteal phase when progesterone levels are at their peak, evidence to date does not indicate that progesterone increases the risk of breast cancer.[20] A French study of 1,150 women with fibrocystic breasts saw no increased breast cancer risk in women using topical progesterone. In fact, the study showed that breast cancer risk decreased significantly when topical progesterone was combined with oral progesterone (RR = 0.5 compared to nonusers).[21] In addition, a French prospective study of more than 50,000 women found that the relative risk (RR) for breast cancer when estrogens were combined with MPA was 1.4, but the RR dropped to 0.9 when OMP was used instead of MPA.[22] Another study found breast cancer patients with the highest endogenous progesterone levels at the time of surgery had significantly better survival at 18 years followup.[23]

A *Maturitas* review of progesterone reported "progesterone is able to counteract the estrogen-induced proliferation of human mammary epithelial cells." In contrast, postmenopausal women using MPA reported significantly greater cell proliferation and density than women treated with estrogen only or those receiving no treatment.[24] In other words, progesterone appears to reduce breast cancer cell proliferation while MPA fuels it.

Bone density

Neither synthetic progesterone analogs nor progesterone have demonstrable benefits on bone density. A 3-year study of progesterone cream 20 mg daily failed to show any benefit for progesterone versus placebo on markers of bone density.[25] A 1999 study by Leonetti similarly found no benefit for progesterone cream on bone density after 1 year.[26] However, the use of a long-acting injectable MPA contraceptive in young women decreased lumbar bone significantly after 2 years.[27] This preliminary data suggests that while progesterone has no benefit on bone density, MPA may in fact have a negative effect.

Other

Since the purpose of adding MPA to estrogen therapy was to prevent endometrial hyperplasia, it is important to consider the effects of progesterone on the endometrium.[28] Fitzpatrick's review of OMP found it as effective as another synthetic progesterone analog, norethisterone (norethindrone) for treating endometrial hyperplasia.[29] The results of the PEPI Trial confirmed that use of cyclic OMP with CEE was as effective as cyclic MPA in protecting the endometrium from hyperplasia.[30] In 2005, a small 1-year crossover trial by Leonetti et al found that progesterone cream 20 mg given twice daily for 6 months protected the endometrium as effectively as MPA 2.5 mg given daily for 6 months when combined with 0.625 mg CEE daily.[31] The Leonetti study found no statistically significant difference between MPA and progesterone cream with respect to producing an atrophic endometrial biopsy, a proliferative endometrial biopsy, or vaginal bleeding over the 6 months of each combination. Despite these positive results, the safety and efficacy of progesterone cream for prevention of endometrial hyperplasia remains unclear. Further discussion of the potential benefits of progesterone cream can be found in the "Optimize Hormone Delivery" section.

Progesterone exerts a neuroprotective effect by defending brain cells from glutamate toxicity. In contrast, MPA not only fails to protect against glutamate toxicity, it actually decreases the neuroprotective effects of estrogen.[32]

Finally, Holtorf reported in his review of bioidentical hormone replacement that 65% of women felt that a hormone replacement combination containing progesterone was better than hormone replacement containing MPA.[28]

In summary, OMP appears to protect the endometrium as effectively as synthetic progesterone analogs, when given in 100 mg daily continuous or 200 mg daily cyclical (12 days per month) doses with commonly prescribed estrogen doses (eg, CEE 0.625 mg). Synthetic progesterone analogs like MPA, when given in combination with estrogen, are associated with an increased risk of cardiovascular disease and breast cancer, and have also been shown to decrease the protective benefits of estrogens on the brain. Bioidentical progesterone is better tolerated with less potential for harm than synthetic progesterone analogs and should therefore be considered the progestogen of choice in long-term hormone replacement therapy.

Estrogens

CEE versus estradiol

Conjugated equine estrogens contain a myriad of estrogens including estrone, estrone sulfate, estradiol and a variety of human-identical and non–human-identical estrogen and androgen metabolites. Animal research has shown that the CEE metabolite 4-hydroxyequilenin is more mutagenic than its human equivalent, 4-hydroxyestrone.[33] Similarly, cell research found that equine metabolite 4-hydroxyequilenin induced considerably more DNA damage and apoptosis in breast cancer cells than 4-hydroxyestrone (4-OHE).[34]

The Women's Health Initiative Study in 2003 found a 40% increase in strokes among users of conjugated equine estrogens.[35] Although data on the long-term cardiovascular effects of estradiol is lacking, comparisons of transdermal estradiol to oral CEE have shown that transdermal estradiol has neutral or favorable cardiovascular effects compared to oral CEE. And, given their increased potential for mutagenicity, avoidance of nonhuman estrogen compounds like CEE seems prudent.

Estriol

Estriol is the principal estrogen in compounded BiEst and TriEst and is arguably the most controversial of the bioidentical hormones. Estriol, unlike estrone, does not convert to estradiol, binds very weakly to estrogen

receptors, and is rapidly excreted. Theoretically, this makes estriol safer than estradiol or estrone.[36] Research has also shown that estriol selectively activates estrogen receptor-beta, which has an antiproliferative effect.[37] Even large oral doses of estriol have not resulted in increased serum levels of estradiol, estrone, or their sulfated forms. Researchers have proposed that estriol, when combined with estradiol, acts as an anti-estrogen and effectively down-regulates the effects of stronger estrogens. However, clinical studies to support this finding are lacking.[38] Nevertheless, there are numerous studies attesting to the value of estriol in a variety of conditions, including multiple sclerosis.[39]

Intravaginal estriol has been used successfully to treat urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women. In a randomized, placebo-controlled trial of 88 postmenopausal women, 68% of the estriol vaginal suppository group experienced subjective improvement in symptoms of urogenital atrophy compared to only 16% of the placebo group.[40]

A Swedish case-control study found that estriol failed to reduce risk for hip fracture compared to 'never use' of hormones.[41] However a small Japanese study of 12 elderly women receiving 2 mg estriol daily for 30 weeks found estriol helped inhibit bone resorption compared to no hormone therapy. Bone density improvement occurred in the estriol group, and the study showed that estriol had no negative effects on lipids. In fact, the estriol-users had a nonsignificant increase in HDL.[42]

Examination of the endometrium in oral estriol users compared to untreated controls in postmenopause found no differences in endometrial histology but saw a statistically significant increase in incidence of polyps in the estriol users. The mean endometrial thickness in the estriol group was 3.0 mm versus 2.4 mm in the untreated control group.[43]

In a 12-month study of oral estriol 2 mg per day, all 68 women had normal endometrial histology and breast ultrasounds on completion of the study.[44] However, a Swedish case-control study found that women taking 1 to 2 mg oral estriol daily for at least 5 years were 3 times more likely to develop endometrial cancer than women who had never used estrogens. The excess relative risk disappeared quickly after cessation of therapy. There was no increased risk associated with use of vaginal estriol.[45]

A large Finnish study compared breast cancer incidence for women on oral estriol, vaginal estrogens, and oral or transdermal estradiol. Neither oral estriol nor vaginal estrogens were associated with any increase in breast cancer risk.[46]

Commonly used in Europe and Japan, the decreased affinity estriol has toward estrogen receptors, combined with the fact that it is an end-metabolite, theoretically makes estriol safer than either estradiol or estrone. That said, estriol cannot be considered completely without risk, given its demonstrated ability to stimulate endometrial growth.

In summary, bioidentical estrogens may have some benefits over non-bioidentical hormones, although the advantages are less significant than for progesterone over MPA. For additional research highlighting the differences between bioidentical and non-human/synthetic hormones, review Kent Holtorf's paper in *Post Graduate Medicine*.[47] The full-text version is available at http://www.holtorfmed.com/wp-content/pdfs/BHRT-PGM-2009.pdf

2) Optimize Hormone Delivery

Another commonly applied principle of BHRT is the preference for delivery of hormones to mimic endogenous hormone production. In practical terms, this means administering hormones via non-oral methods. When hormones are released endogenously, they enter the bloodstream directly for distribution to tissues. In contrast, orally administered hormones undergo significant first-pass metabolism by the liver, resulting in the formation of many undesirable metabolites. This is of particular concern with oral estrogens as some estrogen metabolites have been linked to increased incidence of hormone-related cancers.

Oral versus transdermal estrogens

The majority of research compares transdermal estradiol to oral CEE, the most commonly used oral estrogen. However, because CEE contains numerous human bioidentical and non-human bioidentical estrogen metabolites, it cannot be directly compared to transdermal estradiol. Nevertheless, some studies provide perspective on the advantages of transdermal delivery over orally administered estrogens.

In their 2008 review, "Could transdermal estradiol + progesterone be a safer postmenopausal HRT?" L'Hermite et al make a convincing argument in favor of transdermal estradiol. They describe one study that found oral estradiol led to a 10-fold increase in potentially toxic metabolites, along with another that found oral estrogens resulted in an increased incidence of breast cancer compared to transdermal estradiol.[48][18]

Oral estradiol significantly suppresses levels of insulin-growth factor (IGF-1), whereas neither transdermal nor intranasal estradiol have any effect on IGF-1.[49] Animal models suggest that replenishment of depleted IGF-1 reverses age-related changes.

Analysis of data from the Million Women Study found that gallbladder disease risk is significantly lower for women on transdermal estradiol compared to oral estradiol.[50]

Women on oral estrogens show enhanced platelet reactivity compared to women on transdermal estrogens.[51] Oral estradiol increases coagulability and inflammation as measured by serum CRP levels, whereas transdermal estradiol has no effect.[52] Oral CEE significantly increases matrix metalloproteinase (MMP-9), which plays a significant role in the mechanics of atherosclerotic plaque rupture. Transdermal estradiol does not affect MMP.[53] Results from a French prospective cohort study of more than 80,000 women found that use of transdermal estrogens, alone or in combination with progesterone, did not cause an increased risk of thrombosis. The same study found that oral estrogens were associated with an increased risk of thrombosis.[54]

In summary, transdermal delivery of estrogens appears beneficial for reducing risk of inflammation and hypercoagulability and may also decrease cancer risk, but long-term studies are lacking. To date, there is no research indicating whether or not the risks associated with oral CEE are also linked to compounded oral BiEst (estriol + estradiol) and TriEst (estriol + estrone + estradiol) products.

Oral versus transdermal progesterone

Although transdermal estradiol is clearly preferable to oral CEE, the advantages of transdermal progesterone are less clear. A 2003 paper by Leonetti found that progesterone cream had an antiproliferative effect on an estrogen-stimulated endometrium, but these results have not been confirmed by other researchers.[55] In fact, an earlier study by Wren found that transdermal progesterone given in 16 mg, 32 mg or 64 mg doses provided no protection from endometrial proliferation caused by transdermal estradiol.[56] A 2005 clinical update by Wren concluded that transdermal progesterone was no better than placebo with respect to symptom relief or biochemical markers.[57] In contrast to Wren's finding that transdermal progesterone provides inadequate hormone to tissue, Hermann et al compared progesterone exposure from an over-the-counter (OTC) progesterone cream to OMP. They found no differences in the 24-hour progesterone exposure between progesterone cream and oral progesterone (as measured by the area-under-the curve from whole blood samples), indicating that whole blood progesterone levels from an OTC progesterone cream are equivalent to those achieved from OMP.[58] However, the Hermann study did not compare clinical effects for transdermal versus oral progesterone. From a patient preference perspective, progesterone cream is favored over oral MPA by 77% of patients.[59]

Oral micronized progesterone may have benefits not found with transdermal progesterone. High levels of biologically active metabolites are formed from orally administered progesterone.[60] These metabolites (pregnanolone, allopregnanolone hydroxypregnanone) have useful sedative and anxiolytic properties and exert a barbiturate-like effect on GABA

receptors.[61] A small 6-month trial of OMP at bedtime objectively and subjectively improved sleep while MPA did not.[62] It is unclear whether similarly high levels of active metabolites are formed when progesterone is used topically.[63]

In summary, current research indicates that oral administration of CEE is associated with increased potential for harm compared to transdermal estradiol. Oral estrogens undergo first-pass metabolism by the liver, producing estrogen metabolites that may accumulate and increase the risk of coagulation and cancers. To date, there are no studies comparing the transdermal and oral forms of BiEst and TriEst.

OMP can be used to advantage as the metabolites produced from first-pass metabolism have sedative and anxiolytic properties. It remains to be seen whether topical progesterone shares the same safety and efficacy profile as OMP.

3) Use Physiologic Doses

Most BHRT prescribers agree that physiological doses of hormones are preferable. Unfortunately, there is little agreement as to what constitutes a physiologic dose. Many believe that use of the lowest dose required to relieve or prevent symptoms is the most prudent course given the increased risk of hormone-related cancers during the postmenopause years. L'Hermite et al conclude their review: "Low doses of physiologic [bioidentical] hormones, as well as their systemic administration, exert probably the least risk, and as a precaution, might be preferred."[64] However, many antiaging practitioners routinely recommend higher doses of bioidentical hormones, believing that overall health is improved by restoring the hormone levels of youth. Another subset of antiaging practice recommends cyclical use of high doses of hormones to produce a monthly bleed.[65] Thus, there are many possible interpretations as to what constitutes a physiologic dose.

The limitless dosing options available with compounded bioidentical hormones are a contributing factor to the ambiguity around optimal doses. With commercially available hormone preparations, the dose options are defined and limited. However, with custom compounded bioidentical hormones, some doses are common but none is considered standard. Thus, it is difficult to conduct or locate research in support of specific dosing protocols for compounded bioidentical hormones. And, although some contend that the broad therapeutic range for sex steroid hormones obviates the need for highly individualized dosing, the majority of women express satisfaction with custom compounded hormone products.[66]

Hormone Testing

A comprehensive review of laboratory testing for hormones is beyond the scope of this review, but testing can be a useful tool in hormone prescribing decisions. Saliva and serum tests are both effective for measuring baseline hormone levels and determining hormone deficiencies.[67,68,69,70] However, to monitor the therapeutic benefit of prescribed hormones, patient symptoms and well-being are generally the best guide. The role of laboratory testing is limited primarily to determining baseline hormone levels prior to initiation of therapy. There is no evidence that testing can be used *a priori* to determine a specific hormone dose for a patient. For women supplementing with hormones, tests may provide qualitative data to help determine whether unresolved symptoms are a result of excess or insufficient supplemented hormone.

Summary

Research supports the 3 common principles of BHRT: use of bioidentical hormones, optimization of hormone delivery, and use of physiologic doses. It appears that some bioidentical hormone options are safer than their non-bioidentical and synthetic analog counterparts. For example, it may be more breast-friendly to use estriol with estradiol, and there is evidence that progesterone is more breast-, heart-, and brain-friendly than synthetic progesterone analogs. In terms of the clinical efficacy of bioidentical hormones, Mahmud in his 2010 paper reported on the results of a bioidentical hormone protocol (including BiEst and progesterone) given to 189 women over a 12-month period. He found that 60% of women who had experienced menopausal weight gain lost weight on the bioidentical hormone protocol (average of 14.8 pounds) and 90% experienced improvement in mental symptoms. Mahmud reported that "complications described with traditional HRT did not develop in this population.[71]

Despite these positive research findings, bioidentical hormones cannot be considered completely risk-free. All forms of hormone replacement must be considered to have the potential to increase the risk of hormone-related cancers. Therefore, patient follow-up to monitor benefits or adverse effects is essential regardless of the type of hormone used. In addition, anyone prescribing hormones to postmenopausal women is well-advised to keep abreast of current hormone research.

About the Author

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