Close-Up on Complementary Care

Bioidentical Hormone Replacement Therapy

A Natural Option for Perimenopause and Beyond

By Carolyn R. Walker, NP

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"My previous physician was playing guessing games with my hormones."
"I was on synthetic hormones and could not tolerate a synthetic progestin."
"I had a severe reaction to medroxyprogesterone acetate—it felt like the cells in my brain were screaming."
"I am concerned about headaches if I take a higher dose of conjugated equine estrogens."
"Conjugated equine estrogens made me crazy after my hysterectomy."
"Conjugated equine estrogens only helped with hot flashes—
I still had mood swings, cognitive decline, severe fatigue and depression."
"My body felt out of whack on synthetic estrogens."
"I experienced severe headaches, a 40-pound weight gain, breast and abdominal pain during the year I was taking synthetic estrogen and progestin."

These are actual comments made by women who switched from traditional hormone replacement to bioidentical hormone replacement therapy (BHRT), a plant-based approach that uses substances identical in organic structure and function to human hormones. I have been using BHRT for 3 years and have experienced reversal of a perimenopause-induced syndrome of fibrocystic breasts, dysfunctional uterine bleeding, dysthymia and thyroid dysfunction.

My experience led me to further study BHRT during my graduate work at the University of Iowa. Last year, I conducted a retrospective, descriptive chart review of 100 peri- and postmenopausal women who requested bioidentical natural HRT. I recorded baseline symptoms of steroid hormonal imbalance, as well as follow-up of symptoms up to 12 months post-BHRT administration. The women ranked their symptoms in order of frequency and documented noticable improvement for 35 of 37 presenting symptoms; statistically significant improvement occurred for 24 of the 37 symptoms. After 12 months, the subjects had a 96% rate of compliance with BHRT—a finding that suggests more women will be approaching nurse practitioners about this more natural method of managing menopause.

History of HRT

Research and development of synthetic and equine hormones since the 1940s has provided the basis for most references on hormone replacement therapy (HRT). Current conventional practice, which is derived from this research, is to prescribe progestins and estrogens that are not bioidentical to those found in the human body. Even though bioidentical hormones were known to be effective and were available as early as the 1930s, the only way to avert their destruction by the digestive tract was to administer them intramuscularly in a painful oil-based injection. Since pharmaceutical companies could not patent natural substances and technology wasn't available to painlessly get bioidentical hormones into the body, researchers came up with an alternative.

Oral conjugated equine estrogens (CEEs) were the first non-bioidentical hormones to be developed. Mass marketing helped make estrogen-only replacement therapy (ERT) popular until the mid-1970s, when ERT was associated with endometrial cancer. The popularity of ERT then plummeted, until scientists observed that endometrial cancer was not a significant occurrence in women whose ovaries produced a proper balance of estrogen and progesterone. A synthetic form of progesterone, called progestin, was developed by the 1980s to balance the non-bioidentical estrogens in commercially available HRT preparations. To add to the confusion in HRT development, the term "progesterone" was used interchangeably with the term "progestin" in medical, nursing and pharmaceutical literature. Prescribers often assumed them to be one in the same, although their effects on the human body were very different.

In the late 1980s, the micronization of bioidentical steroids allowed absorption of progesterone, estradiol, estriol and testosterone in therapeutic amounts via oral, buccal and transdermal routes.

Micronized progesterone, for example, became available in Europe in the late 1980s, in Canada in 1995, and was approved by the U.S. FDA in 1998. It has been available from U.S. compounding pharmacists for years, and the active component is bioidentical to endogenous progesterone. Micronization of BHRT enables it to be released slowly and readily absorbed by several routes other than the painful IM injections of the 1930s. However, providers of HRT don't typically learn about this option in their medical, nursing or pharmaceutical educational programs and often don't consider it unless their patients ask them for BHRT.[1-6]

Despite clinical studies that document benefits of HRT, many women don't take any form of HRT and experience a diminishing quality of life related to perimenopausal symptoms.

On the other hand, female baby boomers are entering menopause at an ever increasing rate and many do not experience total remission of perimenopausal symptoms with the conventional, non-bioidentical, synthetic or equine HRT options they do use. By using non-bioidentical hormones, women may also trade off perimenopausal symptoms for unwanted medication side effects.

Several factors can influence how each women uniquely responds to non-bioidentical HRT. Women who take traditional HRT preparations metabolize stronger hormones that bind 2.1 to 3.2 times more firmly to receptor sites than our endogenous hormones.[7]

The chemical structure of these non-bioidentical substances is very different from hormones that humans produce. Non-bioidentical estrogens elicit an exaggerated twofold to eighteenfold potency in the hepatic system, which can produce metabolites that contribute to hypertension.[8]

Synthetic progestins tend to increase LDL and decrease HDL cholesterol concentrations, as well as decrease sex hormone-binding globulin (SHBG). This decrease in SHBG can result in an increase in free sex hormone levels and potentially increased androgenicity.[9] Compliance can be an issue due to the varied side effects of conventional non-bioidentical HRT. In fact, only an estimated 10% to 20% of postmenopausal women continue HRT on a long-term basis.[10] Non-bioidentical hormones cannot flow through the steroid pathway and produce moment-to-moment balance as do our endogenous precursor steroids.

Bioidentical HRT

Bioidentical HRT is also referred to as "nat-

Table 1
Examples of Compounded BHRT Formulations

Triestrogen (po):	E3 (80%)/E2 (10%)/E1 (10%), 1.25 mg-2.5 mg daily
Biestrogen (po):	E3 (70%)/E2 (30%), 1.25 mg-2.5 mg daily
Progesterone (po):	Premenopause (days 14-28 of cycle): 150 mg to 200 mg b.i.d. (effectively provides about 30 mg/day to 40 mg/day due to first pass metabolization in the liver) Postmenopause: 100 mg to 200 mg daily
DHEA (po):	5 mg to 25 mg daily

ural" HRT and "human-identical" HRT in the literature.[1] A bioidentical steroid hormone is not human in origin but is identical in organic structure and function to human hormones. Bioidentical hormones are derived from a plant oil called diosgenin, which is very similar in chemical structure to our endogenous precursor steroid hormone, cholesterol. Diosgenin is extracted from soybeans and wild yams. These crops can abundantly and inexpensively produce the oil, which is also available in several thousand other plants worldwide. Diosgenin is then chemically altered in a lab to exactly match our human bioidentical steroids. Any allergenicity to these plants is also removed during the conversion process.

There are more than 15 endogenous steroid hormones, each with its own metabolites and an enzyme system that converts them from one steroid to another from moment to moment. This is known as the steroid hormone cascade (see figure). Any deficiency in this system will cause symptoms that are unique to certain steroids. Another important concept is that we need an appropriate amount of precursor hormones, such as cholesterol and pregnenolone, which are located at the top of the cascade. The enzymes then convert these on down the cascade into the steroids that are essential to our hormonal balance.

The steroid family is classified in five major categories including the estrogens (estradiol, estriol, estrone), progesterone, androgens (DHEA, testosterone, androstenedione), glucocorticoids (cortisol, cortisone) and mineralcorticoids (aldosterone).[5,6,11] The human female body produces three estrogens with very specific roles. Estrone (E1) is a proliferative estrogen that comprises about 10% of the total estrogens premenopausally. Estradiol (E2) is a proliferative estrogen and the most abundant potent estrogen, premenopausally comprising another 10% of the total. Estriol (E3) is the non-proliferative estrogen that comprises about 80% or more of the total estrogens. Unfortunately, E3 historically has been the most ignored of the estrogens, yet when replaced to physiologic values, it can help restore balance in women who are estrogen-dominant because of too much E2 replacement.[12]

BHRT can be compounded to replace any of several types of deficient steroids in amounts individualized to the unique needs of each woman. Commonly compounded BHRT formulations include various combinations of estrone, estradiol, estriol, progesterone, DHEA and testosterone (Table 1). These can be formulated into oral slow-release capsules, transdermal creams or gels, buccal troches, sublingual drops and vaginal suppositories or creams. Compounding pharmacists, who work closely with prescribers, have hundreds of individualized formulations in their databases that are representative of the unique needs of their clients. Compounding pharmacists who are specifically trained and assisted by the Professional Compounding Centers of America comply with specific, well-researched guidelines to produce pure, standardized formulations. These compounding pharmacists obtain pharmaceutical-grade hormones, researched formulas, guidelines and technical support to provide the highest quality product to consumers.

As compounded BHRT becomes more popular, prescribers need to familiarize themselves with pharmacists who are members of their professional compounding organization. The International Academy of Compounding Pharmacists (IACP) will refer patients and prescribers to IACP members in their areas (Table 2).

Over the past few years, a handful of bioidentical hormones have become available among commercially prepared HRT options. Pharmaceutical companies have avoided the restriction on patenting natural substances by patenting the delivery systems of the bioidentical hormones. Allergic skin reactions to the patented glue in the estradiol patches and allergies to the patented peanut oil release mechanism in oral progesterone capsules are examples of limitations with commercial bioidentical preparations. Other concerns are that the half-life of the commercially-available oral progesterone capsule is only about 3 hours and the estradiol patches only replace one of the three estrogens the female body produces. Commercially available bioidentical estrogens are sold as creams, tablets or patches as estradiol (E2) only. Our most abundant, non-proliferative estrogen, estriol (E3), is not available in any commercial form. The commercial form of bioidentical progesterone

Table 2
Resources for Compounded Bioidentical Hormones and Salivary Assessment

International Academy of Compounding Pharmacists (IACP)
P.O. Box 1365
Sugar Land, TX 77487
(281) 933-8400; (800) 927-4227
http://www.iacprx.org
Professional organization for compounding pharmacists; offers referral service for patients and prescribers

Professional Compounding Centers of America, Inc. (PCCA)
9901 South Wilcrest Dr.
Houston, TX 77099
(281) 933-6948; (800) 331-2498
http://www.pccarx.com
Provides accredited training for compounding pharmacists, pharmaceutical-grade hormones, researched formulations and technical support

ZRT Laboratory
1815 NW 169th Pl., Ste. 3090
Beaverton, OR 97006
(503) 466-2445
http://www.salivatest.com/
Provides saliva testing of steroid hormones with interpretation of symptoms correlated with deficiency or excess

Table 3

Commercially Available Bioidentical Hormone Replacement Therapy

GENERIC NAME	BRAND NAME
17 ß-estradiol (E2)	
Vaginal cream or tablet	Estrace
Transdermal estrogen	Climara
	Estraderm
	Vivelle
Progesterone	Prometrium
	Crinone Gel

comes in the form of a capsule or a gel (Table 3).

Evaluating the Need for BHRT

Candidates for BHRT include women who have had hysterectomies, who have personal or family histories of cardiovascular disease, osteoporosis or Alzheimer's, and women with perimenopausal symptoms that affect their quality of life.

The most commonly reported steroid hormone-related symptoms are hot flashes, night sweats, fatigue, vaginal dryness, mood swings, tender breasts, fluid retention, memory lapses, sleep disturbances and decreased libido.

Contrary to conventional thinking, evaluating the serum or saliva steroid hormone levels for imbalances often *does* correlate with perimenopausal symptoms. Saliva testing is the most accurate of the two methods since it measures the free, unbound, biologically-active hormone as it travels by passive diffusion from the capillaries into the saliva. This modality was approved by the World Health Organization in the early 1990s, when it was found to be an accurate, convenient, less expensive way to measure free hormone levels.[4] David Zava, PhD, has developed a patient- and prescriber-friendly system of salivary steroid hormone analysis that does an excellent job of correlating symptoms to particular hormone imbalances.[11,13,14]

To better understand clinical symptomology at mid-life and the importance of BHRT, an essential concept to master is that steroid hormone receptors are abundant throughout the body.

Therefore, it is incorrect to tell women that they do not need progesterone after a hysterectomy, since we have progesterone receptors throughout our body. Many systems beyond the gynecologic system suffer when progesterone is deficient.[4] This mistaken concept has been fueled by the original need to develop synthetic progestins to balance estrogens when women on ERT developed endometrial cancer in the 1970s. It was then believed that once a woman's uterus was removed, there was no need to worry about endometrial cancer so the progestin could be eliminated from the hormone replacement regimen. A deficiency in endogenous progesterone begins as early as age 35, as the female ovary ages. This level will plummet to 0% to 5% of premenopause levels after menopause, when its only source becomes adrenal production.

Replenishing bioidentical progesterone to physiologic levels often improves emotions, headaches, chronic sinusitis, asthma, breast cysts and dysfunctional uterine bleeding because it "feeds" the progesterone receptors in these important areas. After the cessation of menstruation, estrogen levels only drop to 40% to 60% of premenopausal levels. Progesterone-estrogen balance is essential to eliminating menopausal symptoms.

Prescribing BHRT

An in-depth gynecologic and obstetric history is necessary to evaluate the reason for each woman's menopause-related symptoms. Experts say that the first visit with a peri- or postmenopausal patient should take at least an hour, since it should also include preventive health care issues such as smoking cessation, exercise, proper diet and appropriate intake of nutritional supplements.[10]

Learning the facts about the production, purpose and deficiency or excess symptoms of each of the bioidentical steroids—progesterone, estrone, estradiol, estriol, DHEA and testosterone—is essential to evaluate, prescribe and monitor bioidentical HRT competently.[13] Examples of common steroid hormone imbalances are progesterone deficiency with estrogen dominance, progesterone and estrogen insufficiency, testosterone deficiency, and cortisol and DHEA imbalance. Compounded BHRT formulations often contain combinations of biestrogen (E3 and E2) or triestrogen (E3, E2, E1), progesterone, DHEA and testosterone. Several hormones can be conveniently compounded together for ease of dosing.

Patients experience very few side effects while taking BHRT that is prescribed in physiologic doses. Oral progesterone can cause drowsiness in about 2% to 5% of women who use it, an outcome of how it is metabolized by their hepatic systems. Bioidentical hormones prescribed in nonphysiologic doses can cause symptoms related to excessive supply, such as increased breast tenderness and headaches with too much estrogen.

The advantages of BHRT are that it is individualized, well-tolerated and produces exceptional symptom reversal in most cases. The only possible disadvantage of compounded BHRT is that prescribers must commit themselves to a new level of learning and creative problem-solving as they step beyond the basics taught in medical or nursing education to monitor steroid serum or saliva levels and prescribe BHRT.

With their emphasis on holistic, patient-centered care, nurse practitioners are poised to do just that. ❖

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The Steroid Hormone Cascade