

Bioidentical hormones: What's fact and what's fable?

Questions about “bioidentical” hormones reflect the concerns patients have about hormone therapy (HT) as well as the success of self-help books in convincing them that there is a risk-free alternative. Typically, women who ask about “bioidenticals” are interested in “individualized” treatment with “natural” hormones for their menopausal symptoms. When these concerns are recognized for what they are, such questions may open a productive dialogue. Clinicians can explain that HT with *pharmaceutical* products actually does accommodate these concerns and wishes while providing the investigational and standardized dosing benefits that come with using products approved by the US Food and Drug Administration (FDA).

Marketing not science

A primary source of confusion for patients is the terminology used to describe compounded hormone creams. These products are described by their proponents as “natural, nonsynthetic, and bioidentical.” This may be good marketing, but is it real science?

Whether compounded or pharmaceutically manufactured, all estradiol, even if it comes from “natural” sources, is still synthetic. The hormones in compounded creams and most pharmaceutical HT products are synthesized from yams or soy, which contain neither estrogen nor progesterone. A compound extracted from the yams or soy called diosgenin has a similar structure to that of human cholesterol, from which all human sex hormones are made. Diosgenin is then exposed to a series of enzymes in the laboratory and synthesized to—made into—bioidentical estradiol. In fact, the same process can produce bioidentical progesterone as well as cortisol. Labeling these hormones as



“nonsynthetic” is purely public relations to allow for greater sales.

Importantly, physicians actually use the term “synthetic” with regard to hormones, but in a different sense: they use the term to describe a hormone created from the natural hormone. As an example, the term “synthetic estrogen” is often used to describe estrogens that are not estradiol but are converted from estradiol for use in products such as birth control pills. Similarly, medroxyprogesterone acetate is a “synthetic progestin” made from progesterone, and norethindrone acetate is a “synthetic progestin” made from testosterone.

The term “bioidentical” refers to hormones that are the same as those naturally produced by the human body, such as estradiol, progesterone, and testosterone. All postmenopausal, nonoral estrogen products, whether delivered by the transdermal or transvaginal route, are also bioidentical estradiol. Hence, patients do not need to resort to compounded preparations, which are not FDA approved, in order to use bioidentical hormones.

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KEY POINT

FDA-approved products meet strict guidelines for dose consistency; this essential quality allows clinicians to adjust HT regimens incrementally to provide optimal symptom relief.

Federal regulation through the FDA guarantees that products have been tested according to specific protocols and that they meet strict guidelines for dose consistency. Stability and consistency of dosage are extremely important with respect to the use of postmenopausal estrogen because even small changes in levels of estrogen can cause withdrawal symptoms, such as vasomotor flushing, night sweats, headaches, etc. In contrast, compounded hormonal products are not governed with the same stringent oversight provided by the FDA, so levels can vary and patients can become symptomatic.

Individualized hormone therapy

The Women's Health Initiative (WHI) studied only one, orally administered, combination drug. Unfortunately, the media coverage of the WHI informed much of the public's understanding of HT, and made women believe this pharmaceutical HT is the only regimen offered to all patients. This leads women to see compounding pharmacies, which create a cream product "specifically for them," as a welcome alternative to "one-size-fits-all" prescribing.

In fact, there is a plethora of pharmaceutical products that can be used as HT. There are various dosing ranges as well as delivery systems, so that individualization of therapy can be achieved for each patient. Patients should understand that their clinician will work with them to adjust dosages to levels that work specifically for them.

The potency of compounded creams can vary widely, even within the same prescription. Estrogen withdrawal complications, including bleeding and migraine headaches, can result when the hormone in the cream is variable; breast tenderness can occur if the estradiol concentration in the dose is too high. It is impossible to guarantee standardized dosing in a non-regulated environment and, therefore, difficult to accurately adjust a regimen incrementally.

Currently, FDA-approved products include a range of nonoral delivery systems as patches, creams, gels, and rings. There are important differences between oral and nonoral delivery of estrogen. A large body of data has clearly demonstrated that oral estrogens, because of their first pass through the liver, increase the production of thrombogenic proteins,¹⁻³ C-reactive protein,^{4,5} sex hormone-binding globulin,⁶ and triglycerides. Oral estrogens also increase the estrone/estradiol ratio, which has been implicated in increased breast cancer risk.⁷

In contrast, nonoral estrogens are delivered directly into the bloodstream, avoiding the first pass through the liver and the consequent negative health effects of oral administration.

What do blood and saliva levels indicate?

Compounded hormone regimens are said to be guided by blood and saliva testing that measures hormone levels and purportedly leads to individualization of therapy. The results of these tests are used to alter the customized creams in order to "normalize" the patient's hormone levels.

Proponents of compounded creams believe that monthly blood tests for levels of estradiol, estrone, estriol, follicle-stimulating hormone, luteinizing hormone, thyroid hormones, dehydroepiandrosterone, dehydroepiandrosterone sulfate, testosterone, and free testosterone, among others, indicate where a woman's hormone levels are in relation to "optimal" levels. However, nothing in the medical literature indicates what these optimal postmenopausal levels should be.

Salivary testing is used in the belief that it indicates what hormone levels are in the tissues, as opposed to the bloodstream. As an example, salivary progesterone levels are used to "confirm" the protective effect against the development of uterine cancer. In fact, not one study has shown a correlation between salivary progesterone levels and uterine progesterone levels, so such tests provide no relevant information and, worse, may give misleading information about uterine protection. Once again, more PR.

All women are different, and they all have different estrogen needs postmenopausally. A woman's need for estrogen is reflected best by symptoms and symptom relief. Recognizing this, clinicians can treat patients based on their symptoms, adjusting dosages until the level needed for symptom resolution is reached without causing constant breast tenderness, an important clinical sign of too much estrogen. Women who seek individualized treatment should recognize that this is the most individualized approach, while manipulating the potency of compounded creams to "normalize" hormonal levels (ie, make all women's levels the same) is its antithesis.

Misinformation about breast cancer

The WHI was suspended when the data showed the risk of invasive breast cancer outweighed any potential benefits of reduced coronary heart disease.⁸ HT continues to be linked in the minds of

Expanding the HT Issue: Living Longer, Feeling Better?

The promises of compounded hormone creams—good health, vitality, and longevity after menopause—brought many women back to hormone therapy (HT) after the first media reports of the Women's Health Initiative (WHI) drove them away 5 years ago. Within the medical community, a similar shift has taken place: At first reluctant to continue prescribing hormones, clinicians now generally accept that the WHI provided good data only about a very specific, older population on a particular oral combination drug. Careful analyses of the data from a variety of studies support the use of hormones beginning within a few years of the final menstrual period for women who experience vasomotor symptoms.

Numerous studies, including the WHI, have now helped establish that estrogen is a preserver of good function when it is begun during a window of opportunity within 5 to 6 years after the final menstrual period. It is not a repairer of bad function 15 to 20 years beyond the final menstrual period when damage has already been done. With that in mind, what about the pronouncement by the FDA and many professional societies that estrogen should be used only in women who are "symptomatic"?

First, the "asymptomatic" postmenopausal woman who is in excellent health may be an example of the very function we would like to preserve. Second, we do have to ask ourselves, is there really such an entity as the asymptomatic postmenopausal woman? Does the lack of vasomotor symptoms, joint pains, palpitations, and headaches, mean that she is truly asymptomatic? What about the ongoing changes in her bones, joints, coronary arteries, brain, skin, and genitalia that will not become symptomatic until a number of years have passed?

There are data that clearly demonstrate that coronary artery disease risk drops by 50% with the use of HT beginning within 5 years after the cessation of menses. This has been shown in early observational data, the Nurses' Health Study,¹ the subgroup analysis from the WHI of early postmenopausal women in both the combined and the estrogen-only arms,² and the observational arm of the WHI.

Data also show a neurologic benefit when HT is started in recently menopausal women. The Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study demonstrated a 65% decrease in Alzheimer's disease risk in women aged 50 to 63 years when using HT versus those who did not.³ The Women's Health Initiative Memory Study (WHIMS) showed that the oral hormone combination used increased the risk of dementia and cognitive decline only in the women who were in the 75- to 80-year age group.⁴

As our understanding of menopause and HT becomes more sophisticated, our questions will become more age-specific, as we try to determine who the asymptomatic woman really is, and how to best protect her, now that her life expectancy can extend 3 to 4 decades beyond her final menstrual period, her menopause.

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many women with the risk for breast cancer. Unfortunately, many proponents of compounded hormone creams respond to this concern with the claim that cycling hormones to mimic a menstrual cycle maintains youthfulness and thereby prevents many diseases of aging, including breast cancer. Nothing could be further from the truth. In fact, such regimens may enhance the risk of breast cancer.

The medical literature has established that one of the biggest risk factors for breast cancer is incessant ovulation, that is, ovulating 12 to 13 times per year for 25 to 30 years without any breaks for pregnancy or lactation.^{9,10} Mammary epithelial proliferation occurs with each cycle, causing breast hypertrophy prior to menstruation and a resolution once bleeding occurs. Proliferating breast cells differ from cancer cells only in that they are programmed to stop proliferating at the end of each cycle. In contrast, cancer cells have mutated and lost this control. Therefore, the more menstrual cycles a woman experiences over her lifetime, the greater the risk that a normal proliferating cell will mutate and go on to become a cancer that is not found until 10 to 15 years later.

For postmenopausal women, and especially women who are at higher risk of breast cancer, mimicking "normal" cycles postmenopausally presents the same hormonal environment as incessant ovulation. This is more likely to increase rather than decrease breast cancer risk.

Treating the woman who desires compounded creams

The most important first step in engaging the patient who desires compounded creams is educating her about pharmaceutical versus compounded hormone preparations. Once she has received this information, it is then possible to begin a typical conversation about HT, including its risks and benefits and the treatment options.

Transdermal or transvaginal estradiol may be ideal for such patients. These delivery systems are consistent with their desire to use bioidentical hormones and at the same time address the concerns that clinicians have about the first pass of oral estrogen through the liver. Dosages can be adjusted according to each individual patient's needs, and consistent dosing is ensured.

The use of compounded transdermal progesterone cream has repeatedly been shown not to offer adequate endometrial protection due to absorption problems through the skin. One nationally known

KEY POINT

Cycling hormones postmenopausally to mimic a menstrual cycle may actually enhance breast cancer risk.



KEY POINT

A patient's question about bioidentical hormones is an opening to discuss her concerns and educate her about HT.

celebrity author's hysterectomy for postmenopausal endometrial hyperplasia occurred while she was using a compounded cream that included what was thought to have been adequate progesterone. For more appropriate endometrial protection, oral micronized "natural" pharmaceutical progesterone can be added on a daily basis to safely prevent endometrial buildup without bleeding. Alternatively, a synthetic progestin can be given every 3 to 6 months in a long-cycle fashion to shed any endometrial buildup, which will result in bleeding after each progestogen challenge.

Conclusion

The HT many clinicians would prefer to prescribe, namely, nonoral estradiol, can, in fact, provide what women are looking for in compounded hormonal creams: that is, relief of symptoms and potential long-term benefit in an individualized regimen with bioidentical hormones. Compounded hormonal creams are certainly no more effective or safe than FDA-approved products at doing this and, in fact, may have many downsides, such as nonstandardized dosing and inadequate uterine protection.

Patients must understand that there are inaccurate—and, in the case of monthly cycling to prevent breast cancer, dangerous—aspects of the hormone regimens touted by high-profile personalities without a medical background. Now, as much as at anytime since the publica-

tion of the WHI data, it is critical that health care providers counteract misinformation about hormones through patient education. ■

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