

Clinicians' FORUM

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

The viewpoints expressed in "Clinicians' Forum" are those of the contributors, and not necessarily those of *Menopause Management* or The North American Menopause Society (NAMS).

Question: In your clinical practice, how do you respond to women who request "bioidentical hormones" and salivary tests of hormone levels? In particular, what explanation do you give, do you utilize any printed explanatory materials (if so, what?) and, if hormones are indicated how do you prescribe them?

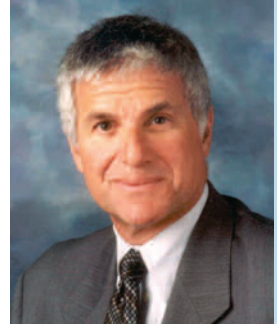
Answers:

There has recently been much publicity about "bioidentical hormones." Some books and articles also espouse that the best way to follow patients' "levels" is with salivary tests of various sex hormones.

We all realize that many patients who make such requests have concerns that stem from their basic fear and, often, distrust of the medical establishment. The media has been filled with stories of pharmaceutical agents that have ultimately turned out to have undesired side effects, some of which can be quite serious. Many patients, therefore, turn to "natural" remedies in the hope that things that come from nature will be safe. I have long ex-

plained to patients that all medicines had their origins in nature. For instance, digitalis originally came from a plant and is a potent medication. Several other natural remedies and botanicals can have powerful side effects even though they are often unregulated by the Food and Drug Administration (FDA). When explained this way, most patients understand that although they are looking for safety, "natural" is no guarantee of that.

With specific reference to salivary testing of hormone levels, I explain to patients that this has never been validated. It is obvious why this type of test appeals to patients, since they are often accustomed to hav-



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ing their lipids checked via blood tests, and their blood pressure and blood sugar levels checked in the office. Patients frequently come in requesting that their “hormone levels” be checked. I try to make them understand that it is the disruptive transitional symptoms that we are treating—not hormone “levels.” We utilize the lowest effective dose of hormone therapy (HT) for the shortest period of time possible consistent with the patient’s treatment goals. Furthermore, we use just enough progesterone to ensure endometrial protection, and I often employ transvaginal ultrasound to that end.

I first explain to patients that the term “bioidentical hormones” refers to hormones that are the same as those produced by a woman’s own ovary. I explain that, in the past, bioidentical hormones were available only as compounded products, and the art of compounding was developed for customized preparation of medicines not commercially available. I then go on to express my concern about quality control, noting that compounding pharmacies do not have the same level of quality control that manufacturers

If patients truly want “bioidentical” hormones, I suggest that they take those that are made pharmaceutically, with the superb quality control that this process offers.

—Steven R. Goldstein, MD

must comply with. I tell patients about studies of compounded substances (not just hormones) conducted by the FDA, in which slightly less than half of the samples did not have what they were supposed to and/or the amount of the active ingredient that they were claiming to contain.

The FDA regulates pharmaceutical manufacturers. If patients truly want “bioidentical” hormones, I suggest that they take those that are made pharmaceutically, with the superb quality control that this process offers.

I tell them that we are fortunate to now have ovarian estrogen and progesterone available in pharmaceutical-grade medications. Such estrogens are available both orally and transdermally in a number of appropriate preparations, and natural progesterone exists pharmaceutically in a vaginal gel as well as an oral micronized preparation.

—Steven R. Goldstein, MD

In Cleveland, like in other big cities, rumors about physicians’ practice habits spread quickly among patients. In my practice, I find that most women have a rather clear picture of my medical philosophy about the management of menopause in midlife women. Being a proponent of evidence-based medicine, I spend a relatively lengthy amount of time with new patients, answering directed questions and trying to provide clear information about hormone treatment. Since there is no clear-cut evidence for the efficacy of bioidentical hormones compared with traditional hormone treatments, and given that the practice of prescribing bioidentical hormones requires an additional layer of expenditure (that is, determinations of hormone levels), I do not usually recommend that mode of action to patients. Similarly, I do not recommend “natural products” as a substitute for pharmaceutically produced, FDA-approved medications.

I find that most of my patients know my opinion about bioidentical hormones prior to scheduling their visit. Occasionally, I receive telephone calls from potentially new patients who inquire about whether, in principle, I deal with this issue. From time to time, current patients raise the question as well. The latter is usually the result of patients being exposed to a new burst of patient-directed advertising. Interestingly, despite the increased amount of advertisement, there seems to be a decrease in women’s overall interest in bioidentical hormones. Whether it is a biased effect for reasons outlined above remains to be determined.

When faced with a request to consider bioidentical hormones, I try to get to the root

of the situation; namely, to determine with the patient the clinical problem/situation, and the line(s) of treatment that should be pursued to effectively help her with her vasomotor symptoms. If, and when, it comes down to making a choice about the HT that will be used, women most often inquire about testing blood levels of hormones, and are provided with information about the problem of lack of correlation between the severity of menopausal symptoms and plasma levels of hormones. I most often refer the patient to The North American Menopause Society (NAMS) Web site (www.menopause.org) for patient-oriented literature.

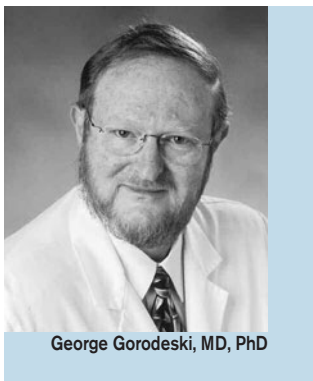
When a decision needs to be made about add-on progestin, I tell my patients that there is no good clinical predictor of which type of progestin will perform best with regard to protecting the endometrium. This effectively rules out salivary progesterone as a measure of progestinic activity.

In my practice, most women who continue to request bioidentical hormone management are those for whom standard HT failed, either because

of a lack of compliance or because of the co-existence of other medical conditions, such as obesity. Some of those patients have left the practice to pursue other modes of treatment, including bioidentical hormones; however, based on conversations with a number of those women, my impression is that their symptoms continued despite the change in treatment.

In summary, lack of appropriate medical evidence precludes me from recommending bioidentical hormones as a way to manage symptoms in menopausal women.

—George Gorodeski, MD, PhD



George Gorodeski, MD, PhD

When women request “bioidentical hormones” and salivary tests of hormone levels,

they provide us an opportunity to teach what we know and don’t know about compounded hormones and salivary testing. Women often request bioidentical hormones because they have heard from their friends or advertising that these products are “natural,” and are therefore safer alternatives than FDA-approved HT. I feel strongly that we, as clinicians, should take the opportunity to educate these patients about the different definitions of “bioidentical” and the availability of FDA-approved bioidentical hormones such as estradiol and micronized progesterone. Since compounded hormones are not regulated by the FDA, it is up to us as experienced and concerned clinicians to teach our patients about the unique potential risks posed by compounded hormones, including concerns about quality control and the lack of scientific efficacy and safety data.

Defining Bioidentical Hormones

The term “bioidentical hormones” refers to exogenous hormones that are biochemically similar to those produced endogenously by the body or ovaries. These include the estrogens estrone, estradiol and estriol, as well as progesterone. The FDA has approved many prescription products that contain bioidentical hormones. However, this term usually refers to custom-compounded hormones made into topical preparations (creams, gels and lotions) or sublingual tablets, subdermal implants and suppositories.

The major difference between the FDA-approved prescription bioidentical hormone products and custom-compounded products is that the former are regulated by the FDA and tested for purity, potency, efficacy and safety. Products from compounding pharmacies are not regulated in this fashion. As a result, dosing and purity can vary, and safety and efficacy are unknown. According to a 2001 American College of Obstetricians and Gynecologists



JoAnn V. Pinkerton, MD

committee review,¹ the FDA analyzed a 29-product sample from 12 compounding pharmacies and found that 34% of them failed one or more standard quality tests. Of those that failed, 90% contained less of the active ingredient than expected. FDA-approved drug therapies have failure rates of less than 2%.¹

Salivary Testing

There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens prepared by compounding pharmacies. Salivary hormone level testing used by proponents to “tailor” HT is not felt to be meaningful because salivary hormone levels vary in each individual woman throughout the day and are not believed to reflect tissue levels of hormone.

Patient Handouts

Because compounded hormone products are not required to give the “black box” warning that all FDA-approved estrogens are required to list, I believe it is the responsibility of menopause specialists to be sure that their patients are adequately educated about the risks and benefits of all types of HT, whether FDA-approved or compounded, as well as the lack of efficacy data and quality control of compounded products. There are two Web

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sites with downloadable handouts on bioidentical hormones: one from NAMS² and one from the National Women’s Health Resource Center.³ We also give our patients considering HT—whether compounded or FDA approved—an educational piece summarizing the current state of research on estrogen and estrogen plus progesterone since the Women’s

Health Initiative (WHI). (We are currently updating this educational piece for 2007; the 2004 version is available at www.healthsystem.virginia.edu/UVAHealth/adult_women/HTFactSheet2004update.pdf).

If a patient is convinced that only bioidentical HT will work for her, and she has a reason to take HT (such as persistent hot flashes, bone loss or quality-of-life issues), then I will prescribe compounded HTs such as Triest or Biest. However, a woman with an intact uterus needs adequate endometrial protection with FDA-approved oral, transdermal or vaginal progestogen. Wren et al⁴ conducted a double-blind, randomized controlled trial of transdermal progesterone cream, finding no clinical beneficial effect. Of greater concern, no measurable effect of the progesterone was found on the endometrium, and thus estrogen-induced endometrial proliferation would not be suppressed.

Summary

Prescription FDA-approved bioidentical products are federally regulated. There is no guarantee that compounded products have been tested for purity or potency. There is currently no peer-reviewed, scientific, randomized controlled trial data to suggest that compounded bioidentical estrogen products are safer or more effective than conventional prescription estrogen products. Topical progesterone cream has not been shown to reduce the risk of osteoporosis or breast cancer or to prevent estrogen-induced endometrial hyperplasia.

—JoAnn V. Pinkerton, MD

References

1. American College of Obstetricians and Gynecologists. Committee opinion #322. Compounded bioidentical hormones. *Obstet Gynecol* 2005;106(5 pt 1):1139-40.
2. The North American Menopause Society. *Menopause: bioidentical hormones*. Mayfield Heights, OH: The North American Menopause Society, 2005. <http://www.menopause.org/MN%20En%20bioidentical%20Sept%202005.pdf> [Accessed April 22, 2007]
3. National Women’s Health Resource Center. *Women’s health updates: hormone therapy options: bioidentical hormones*. Red Bank, NJ: National Women’s Health Resource Center, Inc., March 2005. <http://www.healthywomen.org/resources/nwhrcpublications/dbpubs/womenshealthupdateshormonetherapyoptionsbioidenticalhormones> [Accessed April 22, 2007]
4. Wren BG, Champion SM, Willets K, et al. Transdermal progesterone and its effects on vasomotor symptoms, blood lipid levels, bone metabolic markers, mood, and quality of life for postmenopausal women. *Menopause* 2003;10:13-18.

Concerns about the potential harms associated with HT and mistrust of the medical profession and its “collusion” with the pharmaceutical industry have created an environment favorable to a wide range of alternative strategies for the management of the menopause transition. The popularity of “bioidentical” hormones is part of this phenomenon.

When a patient comes into my office with questions about or requesting bioidentical hormones, the first step is to understand what she means by bioidentical hormones. Some women are talking about compounded products containing estradiol, estrone, estriol,

For the woman who wants hormones to treat her menopausal symptoms, I generally start with a low-dose transdermal patch.

—Marcie K. Richardson, MD

progesterone, and sometimes testosterone or dehydroepiandrosterone. I use the term to mean hormones that are found naturally in the human female—and usually estradiol, progesterone and testosterone are the ones I am prescribing.

Discussion of bioidentical and, for that matter, all hormones can be divided into four aspects: symptom management, health maintenance/disease prevention, individualization, and safety and side-effect profile.

Many women hope hormones will address a variety of symptoms that midlife women experience, and some of their expectations are unrealistic. Some women are unabashedly looking for a way to feel good and even stay young. Compounded bioidentical hormones are promoted because they can be individualized and, with unfounded claims about their safety, compared with standard HT.

Each of these areas requires discussion.

- Symptoms: Review the evidence pertaining to whether HT can effectively treat the patient’s symptoms.
- Health maintenance/disease prevention:

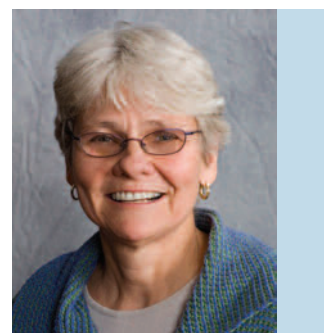
Emphasize that the role of HT in disease prevention is uncertain for most women at this time.

- Individualization: Explain that use of HT requires trial and error, and each woman’s response to it will be different. Monitoring HT with either blood or salivary tests does not make sense, with the possible exception of testosterone. And although serum testosterone measurements in women are notoriously unreliable, salivary testing is not standardized either. The efficacy of HT for the treatment of menopause-related symptoms is best evaluated by the patient’s response (reduction of symptoms)—not hormone levels.
- Safety and side-effects: Explain that although the idea that bioidentical hormones are safer than the WHI-studied hormones is appealing, this notion is unencumbered by data.

For the woman who wants hormones to treat her menopausal symptoms, I generally start with a low-dose transdermal patch. I use 0.025 mg/24 hours of estradiol and give patients a 3-month supply. This is a “bioidentical” regimen. I explain to women that I prefer to use FDA-approved products because of the quality control that is required for their manufacture. Most women have a satisfactory response to lower-than-standard doses of estrogen therapy (ET). We then evaluate the effect, alter the dose, and add progesterone if appropriate. For the woman wanting bioidentical hormones, I use micronized progesterone.

If decreased libido persists as a symptom, compounded testosterone gel can be added as well, although when treating sexual symptoms it is mandatory to consider that factors other than hormones may be contributing.

The conversation that I have with each woman about her menopause is unique. Careful listening, anticipatory guidance and sharing

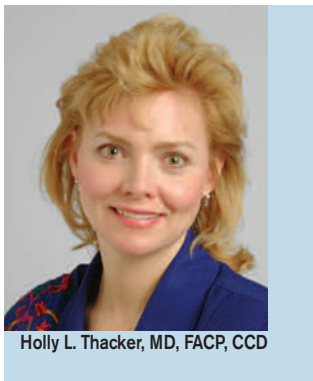


Marcie K. Richardson, MD

of areas of controversy and uncertainty are important. I emphasize that menopause management is a work in progress for each patient and for all midlife women. A discussion of bioidentical hormones fits easily into this framework.

—*Marcie K. Richardson, MD*

I no longer approach women requesting “bioidentical hormone therapy” who also want “salivary levels” in an adversarial manner. In the past, I would launch into a scientific discourse; however, the discussion of the science and the rebuttal of the validity of salivary hormone assessments would inevitably alienate



Holly L. Thacker, MD, FACP, CCD

my patient. My approach quickly changed. Any time a woman asks if I prescribe bioidentical HT, the answer is a resounding “Yes.” I nonjudgmentally ask if they have read Suzanne Somers’s book, and when the answer is invariably “yes,” I then go on to say that Ms. Somers’s message that women deserve to feel

well, look great and enjoy sex is a great message; however, the exact way Ms. Somers proposes to achieve this hormone balance is, well, off-balance. After I have demonstrated respect for and empathy with the symptomatic woman in my office, I find it far easier to begin with a comprehensive menopausal risk assessment and discussion of the myriad HT options, the risks and benefits of treatment, and how we will individualize her regimen and periodically reevaluate it.¹

When presented with salivary hormone levels from an outside source, I give the patient the courtesy of looking at the results while asking questions about her symptoms. If she hasn’t already wasted her money on the non-validated salivary tests, but asks to have them done, I explain that it’s more important to know about the hormone levels in her body tissues—brain, breast, bone and vagina—as opposed to the hormone levels in her blood or

spit. I then go on to explain that we assess these tissue levels by inquiring about symptoms (hot flashes, sleep disturbance and menstrual pattern) as well as assessing bone density, which is an indirect marker of estrogen exposure. I also tell her that it is important to perform a complete physical exam, including a breast exam and inspection of the genitals. I explain that the highest concentration of estrogen receptors is in the lower third of the vagina. Finally, when the woman asks me if I prescribe compounded hormones, my answer is an honest “yes,” as I prescribe off-label compounded testosterone and, prior to the advent of Prometrium, I prescribed compounded micronized progesterone.

After this discussion, I find it much easier to treat the symptomatic woman. If she wants only estradiol and progesterone, I respect this choice and offer any of the currently available FDA-approved products (oral, patch, cream, vaginal). If she wants flexibility in daily dosing,

Once a woman knows I support her values and preferences, many times she will actually decide to go with a daily combination pill.

—*Holly L. Thacker, MD, FACP, CCD*

I tend to start with the transdermal cream (Estrasorb) or gel (EstroGel). Once a woman knows I support her values and preferences, many times she will actually decide to go with a daily combination pill.

For patient education, I always recommend the award-winning NAMS Web site, as well as my easy-to-read lay book, “Women’s Health: YOUR Body, Your Hormones, Your Choices. A Cleveland Clinic Guide.”²

—*Holly L. Thacker, MD, FACP, CCD*

References

1. The North American Menopause Society. Estrogen and progestogens in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause* 2007;14:168-82.
2. Thacker HL. *Women’s health: YOUR body, your hormones, your choices. A Cleveland Clinic guide.* Cleveland, OH; Cleveland Clinic Press, 2007.

When women come to my practice requesting bioidentical hormones, I first ask them the reason for this request and the source of their



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information. I then review with them their symptoms and also the meaning of “bioidentical,” which for many patients has come to mean compounded hormones made up in a pharmacy. Since this option is expensive and not regulated, I review with them the hormones that are on the market and the issue

of quality control. The marketing associated with compounded bioidentical hormones has suggested that this is a risk-free alternative, but the FDA has, in fact, confirmed that all hormone products should be assumed to have the same risks until research shows otherwise. Compounded hormones do not have to be dispensed with a package insert describing the risks, however, giving a false impression of safety.

Another source of confusion is that compounded bioidentical hormones are “natural.” I explain to patients that all hormones are in fact synthetic, as they may be made from plant sources but they require the extraction of a compound called diosgenin from the plant and further synthetic steps in a laboratory to make estradiol or progesterone. The term “bioidentical” actually refers to hormones similar to those made by the body, for which pharmaceutical products are available with supervised quality control. Patients do not have to turn to customized hormones to allay their concerns.

Another source of confusion is the testing of hormone levels, particularly in the saliva, as a way of customizing treatment and providing optimal levels of hormones. Testing a woman’s hormone levels is not a good way to predict how well exogenous hormones will work in an individual woman. The testing of saliva is thought to give free (unbound) hormone levels that are reflective of activity at the tissue level. This measurement is unreliable as it

represents one-twentieth of circulating levels, and “optimal levels” are not documented in the medical literature.

After reviewing symptoms and available options, I use compounded hormones only if a patient insists, with the understanding that if complications arise (such as bleeding) we will switch to regulated treatment. Doses are sometimes difficult to calculate but the compounding pharmacy will give you the milligram dose if requested. (For example, the popular estrogen formulations Bi-Est (20% estradiol and 80% estriol) and Tri-Est (10% estradiol, 80% estriol and 10% estrone) come in 1.25-mg and 2.5-mg doses. A 2.5-mg dose

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given orally twice daily is said to be equivalent to 0.625 mg of conjugated estrogen.) I do not use progesterone cream, as it is not absorbed through the skin in sufficient amounts to protect against endometrial proliferation.

I refer patients to the NAMS Web site for information, or to other society Web sites such as the Endocrine Society (www.endo-society.org) or the American Society for Reproductive Medicine (www.asrm.org/Patients/mainpati.html) for further reading. Some of the patient education materials available from the Council on Hormone Education are also useful to patients (www.cme.wisc.edu/hormonecme/newsletters1/index.htm).

—Michelle P. Warren, MD