Compounded bioidentical menopausal hormone therapy

American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and American Society for Reproductive Medicine Practice Committee

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Although improvement in long-term health is no longer an indication for menopausal hormone therapy, evidence supporting fewer adverse events in younger women, combined with its high overall effectiveness, has reinforced its usefulness for short-term treatment of menopausal symptoms. Menopausal therapy has been provided not only by commercially available products but also by compounding, or creation of an individualized preparation in response to a health care provider's prescription to create a medication tailored to the specialized needs of an individual patient. The Women's Health Initiative findings, coupled with an increase in the direct-to-consumer marketing and media promotion of compounded bioidentical hormonal preparations as safe and effective alternatives to conventional menopausal hormone therapy, have led to a recent increase in the popularity of compounded bioidentical hormones as well as an increase in questions about the use of these preparations. Not only is evidence lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal hormone therapy, but these claims also pose the additional risks of variable purity and potency and lack efficacy and safety data. The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and the Practice Committee of the American Society for Reproductive Medicine provide an overview of the major issues of concern surrounding compounded bioidentical menopausal hormone therapy and provide recommendations for patient counseling. (Fertil Steril® 2012;98:308–12. ©2012 by the American College of Obstetricians and Gynecologists.)

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Case Study

A 50-year-old woman experiencing common menopausal symptoms feels embarrassed to discuss these issues with a health care provider and believes that the health care provider's response will be a prescription for risky hormone therapy that will not address her symptoms (i.e., sleep disturbances, weight gain, knee and hip pain, hair loss, low libido, and depression). She finds literature on the Internet promising her that she can regain all of the vigor and fitness of her youth. Furthermore, for the price of a salivary hormone assay by a specialized laboratory, she will be sent a printout of her test results along with a customized list of the natural hormones she needs to feel young again. Although many of these preparations are not covered by insurance, she believes that the cost is less than the cost of a doctor's office visit. She reads that she need only present this list to a health care provider willing to prescribe it, and she will be able to take this safe form of hormones. The given reason that these hormones are so safe is that they are bioidentical to the natural hormones produced by the body and have no reported risks. What should a clinician tell this patient?

Background

Before the publication of the Women's Health Initiative (WHI) findings, it was believed that "replacing" lost ovarian hormones would not only relieve menopausal symptoms but also improve overall health. This belief was dispelled after the WHI reported a lack of cardioprotection and an increased risk of incident breast cancer (1), venous thromboembolism (1), and stroke (2) associated with the use of combined hormone therapy. These findings dramatically changed the indications for menopausal hormone therapy, and secondary analysis of WHI results continues. Although improvement in long-term health is no longer an indication for menopausal hormone therapy, some evidence has supported fewer

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adverse events in younger women (3). This, combined with its high overall effectiveness, has reinforced its usefulness for short-term treatment of menopausal symptoms.

Menopausal therapy has been provided not only by commercially available products, as in the WHI, but also by compounding. Compounding is the creation of an individualized preparation in response to a health care provider's prescription to create a medication tailored to the specialized needs of an individual patient. The WHI findings, coupled with an increase in the direct-to-consumer marketing and media promotion of compounded bioidentical hormonal preparations as safe and effective alternatives to conventional menopausal hormone therapy, have led to a recent increase in the popularity of compounded bioidentical hormones as well as questions about the use of these preparations. In this joint document, the Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and the Practice Committee of the American Society for Reproductive Medicine provide an overview of the major issues of concern surrounding compounded bioidentical menopausal hormone therapy and provide recommendations for patient counseling.

Compounded Bioidentical Hormones

Bioidentical hormones are plant-derived hormones that are chemically similar or structurally identical to those produced by the body. Bioidentical hormones include commercially available products approved by the U.S. Food and Drug Administration (FDA), such as micronized progesterone and estradiol, as well as compounded preparations that are not regulated by the FDA. Many compounding pharmacies use the term bioidentical hormone to imply that these preparations are natural or the same as endogenous substances and, thus, are safe. The phrase bioidentical hormone therapy has been recognized by the FDA and the Endocrine Society as a marketing term and not one based on scientific evidence (4).

Examples of compounded hormones include Biest (biestrogen) and Triest (triestrogen) preparations. The name Biest commonly refers to an estrogen preparation based on a ratio of 20% estradiol and 80% estriol on a milligram-per-milligram basis. A similar preparation, Triest, usually contains a ratio of 10% estradiol, 10% estrone, and 80% estriol. These ratios are not based on each agent's estrogenic potency but on the milligram quantity of the different agents added together (5). Other commonly compounded hormones include dehydro-epiandrosterone, pregnenolone, testosterone, and progesterone (6). (See the FDA, "Compounded Menopausal Hormone Therapy Questions and Answers," in the Resources section for additional information.)

Compounding

Compounded bioidentical hormones are made by a compounding pharmacist from a health care provider's prescription and are available in various routes of administration, including oral, sublingual, and percutaneous or as implants, injectables, and suppositories. Unlike drugs that are approved by the FDA to be manufactured and sold in standardized dosages, compounded preparations often are custom-made for a patient according to a health care provider's specifications. Traditionally, compounding is used to provide treatment for patients when the exact products needed are not commercially available or different ingredients, preservatives, or routes of administration are required because of patient intolerances. For example, in the case of menopausal hormone therapy, there is an FDA-approved progesterone product that contains peanut oil. A health care provider's prescription to compound progesterone to eliminate the peanut oil can allow a patient with a peanut allergy to safely use the drug. Far removed from the traditional uses of compounding is the practice of blending commercially available drug products in proportions tailored to individual patient information. Many compounded bioidentical hormone preparations fall into this category. Other potential advantages of compounded hormone therapy compared with FDA-approved conventional hormone therapy include greater dosage flexibility, availability of low-dose preparations, and potential lower cost.

The practice of custom blending commercially available drug products may lack both a strong biological rationale and medical evidence for effectiveness. Moreover, it introduces the possibility of multiple sources for drug effects and adverse effects, making it difficult to identify the active agent responsible. For these reasons, compounded preparations generally are considered inferior to FDA-approved agents, which have much better characterized pharmacokinetic properties.

Lack of U.S. Food and Drug Administration Regulation for Compounded Preparations

Compounded preparations are not regulated by the FDA. Although technically all compounded prescription drug preparations could be considered unapproved new drugs, the FDA has adopted a policy of enforcement discretion, allowing legitimate preparation of compounded formulations to be regulated by state boards of pharmacy, with a provision of stepping in when dangerous practices must be addressed and when drug manufacturing occurs under the guise of compounding. There are currently no specific regulations by the FDA on what constitutes a legitimate claim for compounded drug preparations. In general, states regard compounding to be part of the practice of pharmacy. In addition, individual states' pharmacy acts usually permit other licensed practitioners (e.g., physicians, nurse practitioners, and others with prescriptive authority) to engage in the practice of pharmacy compounding for their own patients.

Regulatory Exemptions for Dietary Supplements

Under the Dietary Supplement Health and Education Act of 1994, compounded hormones applied to the skin are considered to be supplements; the argument being that the hormones came from natural sources and should be considered in a category similar to herbs. Thus, the potential for such agents to cause harm was considered minimal. The Dietary Supplement Health and Education Act exempted remedies that fell into the category of supplements from regulation by the FDA, which requires that, unless a drug is generally recognized as safe, its safety and efficacy must be demonstrated before it can be marketed. Dietary supplements are not required to prove safety or efficacy; hence, there is no major barrier to

marketing them. However, the FDA can remove these supplements from the market and subject them to further testing if there is sufficient suspicion that they are not safe.

Labeling Issues

The FDA requires manufacturers of FDA-approved products that contain estrogen and progesterone to use class labeling (the black box warning indicating a drug with special problems, particularly ones that may lead to death or serious injury) reflective of the findings of the WHI. However, because compounded preparations are not approved by the FDA and have no official labeling (i.e., a package insert), they are exempt from including contraindications and warnings. They also may have additional risks intrinsic to compounding. The lack of even rudimentary pharmacokinetic data for the commonly prescribed bioidentical hormone preparations should cause considerable concern about the prudence of prescribing such medications. In January 2008, the FDA warned seven pharmacy operations that their claims about the safety and efficacy of their bioidentical hormone replacement therapy preparations were misleading and unsupported by medical evidence because the mixtures were not tested for purity, potency, efficacy, or safety (7).

Safety and Efficacy Issues

Because of a lack of FDA oversight, most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, the purity, potency, and quality of compounded preparations are a concern. Over a 6-month period, the FDA performed repeat analytic testing of 29 Internet-ordered samples—including estradiol and progesterone—from 12 compounding pharmacies (8). Although none of the preparations failed identity testing, 10 of the 29 preparations (34%) failed one or more standard quality tests performed, including potency testing. In contrast, the analytical testing failure rate for drug therapies approved by the FDA is less than 2%.

Because of variable bioavailability and bioactivity, underdosage and overdosage are both possible. Certain progestin preparations, such as that found in the Mexican wild yam, are not bioavailable to humans and, therefore, patients can believe that they are receiving endometrial protection against hyperplasia when they are not (9). Similarly, underdosing of estrogen can lead a woman to believe that she is protected against osteoporosis when, in fact, bone resorption is progressing. Estriol is substantially less bioactive than estradiol, and large quantities must be used to achieve any biological effect. The potential for overdosage also exists, which can lead to increased risks of endometrial hyperplasia, endometrial cancer, and venous thromboembolism.

Hormone Level Testing and Compounded Bioidentical Hormone Use

Many advocates and compounders of bioidentical hormones recommend the use of salivary hormone level testing (and other proposed mechanisms, such as serum and urine testing) as a means of offering individualized therapy. However, individualized testing only is indicated when a narrow therapeutic window exists for a drug or a drug class. This includes drugs with nonlinear pharmacokinetics, that are eliminated by the kidney as the active drug, that are not metabolized during first pass through the liver, and that have clearly defined therapeutic and toxic concentrations based on large-population pharmacokinetic studies of serum concentrations. Steroid hormones, such as estrogen and progesterone do not meet these criteria and, thus, do not require individualized testing.

There is no evidence that hormonal levels in saliva are biologically meaningful. In addition, whereas saliva is an ultrafiltrate of the blood and in theory should be amenable to testing for "free" (unbound) concentrations of hormones, salivary testing does not currently offer an accurate or precise method of hormone testing (10, 11). There are several problems with salivary testing and monitoring of free hormone levels. First, salivary levels do not consistently provide a reasonable representation of endogenous, circulating serum hormones (12). There is large within-patient variability in salivary hormone concentrations, especially when exogenously administered hormones are given (11, 13–16). Salivary hormone levels vary depending on diet, time of testing, and the specific hormone being tested (11, 14, 17–19). Second, because the pharmacokinetics of exogenously administered compounded hormones cannot be known, it is not possible to estimate with reliability how and when to test saliva to obtain a representative result. Third, saliva contains far lower concentrations of hormone than serum and is prone to contamination with blood, infectious agents, and epithelial cells—all of which may affect the level of hormone to be measured.

Although more sensitive testing is becoming available through the use of mass spectrometry, there are few indications for the measurement of hormone levels to ascertain success of therapy when treating a postmenopausal woman with hormones. If treatment is initiated for symptom control, subjective improvement in symptoms is the therapeutic end point, and there is no need to assess hormone levels. Hormone therapy should not be titrated to hormone levels (serum, urinary, or salivary).

Patient Counseling

Patients should be counseled that menopausal hormonal therapies that are proved to be safe and effective by the FDA are more appropriate for their use than individual pharmacy-compounded preparations. Patients should be educated on the FDA approval status of compounded preparations and their risks and benefits, including the risks specific to compounding. Physicians should exercise caution in prescribing compounded hormones when FDA-approved alternatives exist.

The following preparations are naturally occurring hormones that are ingredients in FDA-approved products:

Estrogens

- Estradiol-17b (transdermal or oral, micronized)
- Estrone (sodium estrone sulfate)—active ingredient in naturally occurring conjugated equine estrogen preparations and in synthetic conjugated estrogen preparations

Progesterone

- Progesterone (oral, micronized or vaginal gel or insert)

Regardless of the type of preparation, the varying formulations available, pharmacodynamics, and individual patient factors must be taken into consideration when using menopausal hormone therapy.

Conclusions and Recommendations

The American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and the Practice Committee of the American Society for Reproductive Medicine make the following conclusions and recommendations:

- Evidence is lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal hormone therapy.
- Customized compounded hormones pose additional risks. These preparations have variable purity and potency and lack efficacy and safety data.
- Because of variable bioavailability and bioactivity, both underdosage and overdosage are possible.
- Conventional hormone therapy is preferred over compounded hormone therapy given the available data.
- Despite claims to the contrary, evidence is inadequate to support increased efficacy or safety for individualized hormone therapy regimens based on salivary, serum, or urinary testing.

Resources

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practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists have approved this report.

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