American Association of Clinical Endocrinologists (AACE) Reproductive Medicine Committee Position Statement on Bioidentical Hormones

Updated on 07/15/07

This statement was developed by the AACE Reproductive Medicine Committee comprised of:

Rhoda H. Cobin, MD, MACE; Chair
Steven M. Petak, MD, JD, FACE, FCLM; Board Liaison

Maya B. Bledsoe, MD, FACE
Walter P. Borg, MD
Steven A. Brody, MD, FACE
Elena A. Christofides, MD, FACE
Rebecca Fenichel, MD
Walter Futterweit, MD, FACP, FACE
Samara Beth Ginzburg, MD
Neil F. Goodman, MD, FACE
Ira Andrew Katz, MD, FACE
Alfred Wayne Meikle, MD, FACE
John Edwin Nestler, MD
Geoffrey P. Redmond, MD, FACE
Arthur G. Shapiro, MD, FACOG, FACE
Keith D. Smith, MD, FACE
Richard F. Spark, MD, FACE
M. Antonia Verso, MD, FACE
Kathleen Louise Wyne, MD, PhD, FACE

Disclaimer:

This statement is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all the facts and circumstances involved in an individual case, and are subject to change as scientific knowledge and technology advance and practice patterns evolve. This statement reflects the views of the Reproductive Medicine Committee of the American Association of Clinical Endocrinologists (AACE) and review of scientific literature as of July 2007.

INTRODUCTION

Several major medical societies have recently published statements reflecting their concern regarding so called "Natural" or "Bioidentical Hormones" (BH) [1], [2], [3], [4]. The terms "***bioidentical," "natural,"*** and ***"compounded"*** sex hormones started to gain visibility in the media a few years ago - mainly due to the enthusiastic endorsements by some celebrities. Despite its outwardly "scientific" appearance, the term "bioidentical hormones" is quite vague, and is used in various contexts. Most commonly, this term denotes plant-derived hormones which are claimed to be "identical in structure" to those produced by the human body. The plant estrogens are not detected by assays for estrone, estradiol and estriol. Estriol has weak biological action and a very short half life. These preparations are compounded by pharmacists - as pills, gels, suppositories, or even injectable solutions [1], [5]. The "compounding process" refers to the creation of a drug by mixing various components by a qualified pharmacist. It is usually done according to a physician's prescription said to be "customized" for every patient. The need for compounding dramatically decreased after the mass pharmaceutical manufacturing process was developed. However, in certain communities, the concept of compounding appears to be experiencing a revival. Moreover, in some instances, treatment with compounded preparations is initiated and directed by a compounding pharmacist, with minimal (if any) involvement of a physician.

The list of compounded hormones includes, but is not limited to: estradiol, estrone, estriol, progesterone, testosterone, and DHEA. In contrast to commercially produced pharmaceuticals, compounded medications are not subjected to stringent FDA oversight. Currently there are commercially manufactured hormones, including estrogen and progesterone, which are, indeed, molecularly identical to hormones produced in human bodies. Those commercial preparations are under the purview of the FDA. In contrast to bioidentical hormones, FDA-approved preparations are reimbursed by most third party payors.

CONCERNS ABOUT "BIOIDENTICAL HORMONES"

AACE expresses concerns about unproven but highly publicized claims about the alleged higher safety and efficacy of compounded bioidentical hormones. In addition, from a clinician's perspective, AACE believes that potentially serious dangers of BH use have not been sufficiently exposed. The primary concern about bioidentical hormone use is patient safety. These substances have not been shown within the medical community to be clinically effective. In addition, utilization of these formulations may be associated with various risks inherent to the compounding process.

The exaggerated claims about efficacy and safety of BH are made despite clear evidences of variability in potency, high potential for contamination and impurity of those preparations. Also, some unorthodox clinical practices utilized by BH promoters are quite worrisome. Those practices include individualized dosing frequently based upon unproven testing methods such as salivary assays, which has not been validated. Finally, the cost effectiveness of this modality requires careful consideration.

Exaggerated Claims about Efficacy and Safety

The public has been persuaded that treatment with bioidentical hormones has to be safer, more effective, and free of side effects since those preparations are "natural." Those are the main claims of the proponents of the "bioidentical" approach to menopausal hormone therapy. Those assertions have been made in popular publications or disseminated via the Internet. They have not been properly peer-reviewed or subjected to formal scientific scrutiny. A systematic review of the current scientific literature does not appear to support these notions. Well designed studies in this area are needed. Until evidence-based, scientific studies are available, the existence of meaningful differences between "bioidentical" and conventional hormones remains to be established.

Compounded drugs known as Biest and Triest raise the following concerns. The name Biest, or biestrogen, is commonly used to describe a preparation consisting of 20% estradiol and 80% estriol on a

milligram per milligram basis. Similarly, Triest, or triestrogen, contains a ratio of 10% estradiol, 10% estrone, and 80% estriol. Some compounding pharmacies claim that these mixtures are designed to mimic natural estrogenic activity occurring in young females with intact ovaries. However, the hormonal ratios found in Biest and Triest are not based on each agent's estrogenic potency or individual bioavailablity when given orally, but simply on the milligram quantity of the different agents added together [6]. Estriol is the peripheral metabolite of estrone and estradiol - not a secretory product of the ovary. [7]. Estriol is produced in significant amounts during pregnancy by the placenta. It can be also produced by some tumors. Therefore, concentrations of this hormone are very low in healthy non-pregnant females. In non-pregnant females, the formation of estriol is considered to be an example of metabolic detoxification, i.e., conversion of biologically active material to less active form [7]. Each woman uniquely produces estriol based on individual tissue estrogen metabolism. The enthusiasm about the potential role of estriol in menopausal hormonal replacement therapy may be traced back to past reports that this estrogen limited the growth of breast tumors in the rat model [8]. However, subsequent research did not confirm those initial observations [6], [9].

Estrone is minimally produced by ovarian secretion. Most of it is produced by peripheral conversion from adrenal and ovarian androstenedione, mainly in adipose tissue [10]. However, estrone, as estrone sulfate, a commercially available product, can provide adequate hormonal therapy.

In summary, there is no scientific evidence that specific combinations of oral estrogens provide improved safety or efficacy compared to FDA-approved pharmaceutical products in the treatment of menopausal females. Additional clinical and basic research of this subject is needed.

Variable Potency

There have been instances when patients received compounded preparations containing much larger or much smaller amounts of the active ingredient than was indicated on the label [11]. In addition to clinical reports, limited FDA surveys revealed disturbing inconsistencies in the strength and purity of compounded preparations [12]. Inappropriately high levels of hormonal components in a compounded formulation can cause serious patient injury [11], [13]. This is especially true for compounded injectable depot-testosterone preparations. On the other hand, inappropriately low hormonal content in compounded formulations can result in a situation in which the patient, unbeknownst to the physician, receives suboptimal doses of prescribed medication. In addition, the stability of compounded medication is not known, as each drug is individually formulated. Expiration dates given by compounding pharmacists are often based upon educated guesses.

Impurity and Contamination

The possibility of cross-contamination of compounded preparations with various medications is a valid concern. Such a scenario is particularly likely to occur in smaller pharmacies, where the same compounding equipment is used for preparation of various types of drugs [11], [13], [14]. In addition, assuring the sterility of compounded formulations may be difficult. Most compounded medications are not clinically tested to determine their sterility. Professional Compounding Centers of America and similar organizations have protocols advising stringent sterilization procedures for injectable preparations. However, it is unknown how strictly these voluntary protocols are followed and with what success. There are certain compounding pharmacies that prepare purportedly "aseptic" preparations without the use of the autoclave [11].

Individualized Dosing and Salivary Hormone Testing

Salivary hormone level testing is recommended by many BH proponents as a way of providing patients with "individualized" therapy. Such tests are available to consumers over the Internet. Some of the websites include elaborate questionnaires supposedly designed to establish the type of saliva testing needed [15] . The results of these tests are subsequently used to determine the type and dosage of compounded formulations. Only a few types of salivary hormone testing methods are FDA/CLIA

approved [16]. In fact, the vast majority of the salivary hormone tests results contain the disclaimer that those tests are not FDA/CLIA approved and should be used only for research purposes. Yet such tests are still utilized to support clinical decisions by some supporters of BH.

Endorsers of salivary assays quote their positive empiric experience as well as some recent research studies in support of this methodology [17], [18], [19]. There are many troubling aspects of such an approach. First, when talking about the empiric experience, those practitioners simply report anecdotal information such as positive testimonies of their patients, or their own subjective impressions. Therefore, they base their conclusions on non-scientific information, which is not randomized, placebo-controlled data and not peer reviewed [20]. Second, the limited research, although interesting, does not prove that salivary testing can be used as reliable ancillary tests for *clinical* purposes. AACE Protocol for Standardized Production of Clinical Practice Guidelines points out that the physician must frequently act on the basis of incomplete information [21]. In order to help the physician sort through such information, several strength-of-evidence scales have been proposed [22], [23]. Unfortunately, the evidence often quoted by Salivary Test promoters simply do not pass the muster of the level 1 or even 2 of the Level of Evidences (LOE) as endorsed by AACE [21]. The only exception here is cortisol measurement [24], [17]. In contrast to cortisol salivary level, large intra-subject variability has been shown in salivary sex hormone concentrations [24], [1]. Salivary sex hormone levels fluctuate depending upon numerous variables such as diet, hydration status, and circadian rhythm. These conditions are difficult to standardize [1]. Finally, standard blood tests for sex steroids are well established, with the exception of free testosterone measurement [25]. Free testosterone direct analog methods are unreliable for free testosterone. Dialysis methods and calculation methods that have accurate and sensitive assays for blood testosterone such as mass spectroscopy are reliable [26], [27], [28]. Also, venipuncture is a straightforward and minimally invasive procedure. Hence, there is little need to resort to salivary sex hormone testing in the setting of medical practice.

Sex hormones do not belong to a pharmacological class of drugs with clear indications for individualized dosing. From the perspective of clinical pharmacology, individualized dosing is indicated for drugs characterized by a narrow therapeutic window. Drugs with nonlinear pharmacokinetics (those with renal elimination) are good examples. Drugs that are not metabolized during the first pass through the liver, and those with clearly defined (in large population pharmacokinetic studies) therapeutic and toxic concentrations meet the requirements for individualized dosing as well. In contrast, sex hormones do not meet these criteria and dosage is evaluated by clinical response parameters [1].

Cost Effectiveness

The cost of compounded drugs is usually greater than that of traditional preparations and compounded medications are not reimbursed by insurance [2]. In addition, patients pay out of pocket for salivary hormone tests [2], [17]. The budget of an average American family is already tight. Many women are being influenced by the mixture of unsubstantiated promises and scare tactics employed by some BH promoters. Such patients are making choices they probably would not make if presented with scientifically-based information.

CONCLUSIONS

All the information presented here should be carefully explained to patients who request BH Therapy (BHT). Their misconceptions about BHT should be tactfully and thoroughly discussed. The decision to prescribe any type of menopausal hormone therapy should be based upon careful clinical evaluation of risks and benefits of such therapy in a specific patient [29]. Based upon available evidence-based medicine, the safest and most effective hormonal therapy for menopausal women is to utilize FDA-approved commercially available hormonal preparations, following the guidelines published by the various medical societies.

AACE, along with The Endocrine Society, and American Society for Reproductive Medicine, has introduced AMA's recent resolution urging the FDA to increase regulation and oversight of BH [4]. Specifically, AMA asked the FDA to:

- conduct surveys for purity and dosage accuracy of all compounded "bioidentical hormone" formulations;
- require mandatory reporting by drug manufacturers, including compounding pharmacies, of adverse events related to the use of "bioidentical hormones";
- create a registry of adverse events related to the use of "bioidentical hormones"; and
- require inclusion of uniform patient information (warnings and precautions), in packaging of compounded bioidentical hormones.

REFERENCES:

1. American College of Obstetricians and Gynecologists, *ACOG Committee Opinion #322: Compounded bioidentical hormones.* Obstet Gynecol, 2005. 106(5 Pt 1): p. 1139-40.
2. MacLennan AH, Sturdee DW *The 'bioidentical/bioequivalent' hormone scam.* Climacteric, 2006. 9(1): p.1-3.
3. The Endocrine Society, *Bioidentical Hormones*. Position Statement. October 2006.
4. American Medical Association, *FDA Oversight of Bioidentical Hormone (BH) Preparations. Resolution 706 (I06).* in *AMA House of Delegates Meeting*. 2006: Las Vegas, NV.
5. Martin, K.A., H.N. Rosen, and R.L. Barbieri, *Preparations for postmenopausal hormone therapy*, in *Up to Date*, B. Rose, Editor. 2006., Up to Date: Waltham, MA.
6. Boothby, L.A., P.L. Doering, and S. Kipersztok, *Bioidentical hormone therapy: a review.* Menopause, 2004. 11(3): p. 356-67.
7. Speroff, L., *Clinical Gynecologic Endocrinology and Infertility*. 7th ed. 2005: Lippincott Williams & Wilkins.
8. Lemon, H.M., *Estriol prevention of mammary carcinoma induced by 7,12-dimethylbenzanthracene and procarbazine.* Cancer Res, 1975. 35(5): p. 1341-53.
9. Weiderpass, E., et al., *Low-potency oestrogen and risk of endometrial cancer: a case-control study.* Lancet, 1999. 353(9167): p. 1824-8.
10. Grodin, JM, Siiteri, PK, and MacDonald, PC, *Source of estrogen production in postmenopausal women.* J Clin Endocrinol Metab, 1973. 36: p. 207.
11. Hallissy, E and RS, *Who's Mixing Your Drugs? Bad medicine: Pharmacy mix-ups a recipe for misery.Some drugstores operate with very little oversight* San Francisco Chronicle June 23, 2002
12. FDA Center for Drug Evaluation and Research, Report: Limited FDA Survey of Compounded Drug Products. Available at http://www.fda.gov/cder/pharmcomp/survey.htm., 2003.
13. Appleby J., *Safety Concerns Grow over Pharmacy Mixed Drugs.* USA TODAY, 2005.
14. Hileman, B, *Counterfeit Drugs.* Chemical & Engineering News. American Chemical Society., 2003. 81: p. 36.
15. Aetna, *Salivary Hormone Tests.* Clinical Policy Bulletin:, 2006.
16. Food and Drug Administration, *CLIA Electronic Database.* *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/search.cfm.* 2007.
17. Chatterton RT Jr. et al., *Characteristics of salivary profiles of estradiol and progesterone in premenopausal women.* Journal of Endocrinology 2005. 185: p. 77 – 84.
18. Ishikawa, M, et al., *The clinical usefulness of salivary progesterone measurement for the evaluation of the corpus luteum function.* Gynecol Obstet Invest, 2002. 53(1): p. 32-7.
19. Gann, PH, et al., *Saliva as a medium for investigating intra- and interindividual differences in sex hormone levels in premenopausal women.* Cancer Epidemiol Biomarkers Prev, 2001. 10(1): p. 59-64.
20. Ratzan, SC, *The Plural of Anecdote is not Evidence.* Journal of Health Communication, 2002. 7: p. 169-170.
21. AACE Ad Hoc Task Force for Standardized Production of Clinical Practice Guidelines, *AACE Protocol For Standardized Production Of Clinical Practice Guidelines.* Endocr Pract., 2004. 10(4): p. 353-61.
22. Guyatt G. and GRADE Working Group, *Grading quality of evidence and strength of recommendations.* BMJ, 2004. 328(7454): p. 1490-.
23. Liberati A, BR., Grilli R, Magrini N, Minozzi S, *Which guidelines can we trust? Assessing strength of evidence behind recommendations for clinical practice.* West J Med. , 2001. 174: p. 262-265.
24. Nieman, LK, *Measurement of cortisol in serum and saliva.*, in *Up to Date*, B. Rose, Editor. 2006, Up to Date: Waltham, MA.
25. Snyder, PJ, *Clinical features and diagnosis of male hypogonadism in adults.*, in *Up to Date*, B. Rose, Editor.

2006, Up to Date: Waltham, MA.
26. Steinberger, E, et al., *Utilization of commercial laboratory results in management of hyperandrogenism in women.* Endocr Pract, 1998. 4(1): p. 1-10.
27. Ayala, C, et al., *Serum testosterone levels and reference ranges in reproductive-age women.* Endocr Pract, 1999. 5(6): p. 322-9.
28. Goodman, NF, *Hyperandrogenism: Defining the reference ranges for "normal" androgens.* Endocr Pract, 1999. 5(6).
29. AACE, *American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause.* Endocr Pract, 2006. 12(3): p. 315-37.