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Compounded Bioidentical Menopausal Hormone Therapy

Committee on Clinical Consensus–Gynecology. This Clinical Consensus was developed by the American College of Obstetricians and Gynecologists' Committee on Clinical Consensus–Gynecology in collaboration with Amy J. Park, MD, and Belinda Yauger, MD. The American Society for Reproductive Medicine endorses this document.

Summary

Many compounding pharmacies use the phrase "bioidentical hormone" as a marketing term to imply that these preparations are natural and, thus, safer and more effective than U.S. Food and Drug Administration (FDA)–approved menopausal medications that use bioidentical or synthetic hormones or both. However, evidence to support marketing claims of safety and effectiveness is lacking. Compounded bioidentical menopausal hormone therapy should not be prescribed routinely when FDA-approved formulations exist. Clinicians should counsel patients that FDA-approved menopausal hormone therapies are recommended for the management of menopausal symptoms over compounded bioidentical menopausal hormone therapy. If a patient requests the use of compounded bioidentical menopausal hormone therapy, clinicians should educate them on the lack of FDA approval of these preparations and their potential risks and benefits, including the risks specific to compounding. To truly understand the benefits and harms of compounded bioidentical menopausal hormone therapy, high quality placebo-controlled randomized controlled trials with long-term follow-up comparing custom-compounded products with FDA-approved menopausal hormone therapy are needed.

BACKGROUND

Bioidentical hormones are plant-derived hormones that are chemically similar or structurally identical to those produced by the body. These hormones include commercially available products approved by the U.S. Food and Drug Administration (FDA), such as micronized progesterone, estradiol, and dehydroepiandrosterone (DHEA), as well as compounded preparations that are not regulated by the FDA. Other preparations of compounded bioidentical menopausal hormone therapy include estrone, estradiol cypionate, estriol, pregnenolone, testosterone, testosterone cypionate, and testosterone propionate (1). Many compounding pharmacies use the phrase "bioidentical hormone" as a marketing term to imply that these preparations are natural and, thus, safer and more effective than FDA-approved menopausal medications that use bioidentical or synthetic hormones or both. However, evidence to support marketing claims of safety and effectiveness is lacking (1, 2).

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Compounded bioidentical hormones are made from a clinician'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 clinician's specifications. The American College of Obstetricians and Gynecologists (ACOG) recognizes that the use of compounded medications may be appropriate for some patients and in some circumstances. Traditionally, compounding is used to provide treatment for patients when the exact products needed are not commercially available or when different ingredients, preservatives, or routes of administration are required because of patient intolerances (eg, allergy) or needs (eg, inability to swallow an oral pill). For example, there is an FDA-approved progesterone product that contains peanut oil. A prescription to compound progesterone to eliminate the peanut oil can allow a patient with a peanut allergy to use the drug safely. Additionally, cost and access concerns may prompt consideration of compounded vaginal formulations of estrogen or progesterone, for which the quality control regarding potency and vehicle (cream or ointment) should be discussed with the compounding pharmacy. Far removed from the traditional uses of compounding is the practice of blending commercially available drug products in proportions tailored to an individual patient. Many compounded bioidentical menopausal hormone therapy preparations fall into this category. This document focuses specifically on the use of compounded bioidentical menopausal hormone therapy, not compounding for other evidence-based reasons. This topic has been updated to include more recent data and additional therapies, including the use of testosterone for the management of menopausal symptoms.

The Role of the U.S. Food and Drug Administration

Compounding pharmacies that provide drugs based on a patient-specific prescription generally fall under Section 503A of the Federal Food Drug and Cosmetic Act (3). These pharmacies and the drugs that they produce are exempt from the Federal Food, Drug, and Cosmetic Act sections on FDA approval before marketing, current good manufacturing practice requirements, and labeling with adequate directions for use. These products are not reviewed by the FDA for safety, effectiveness, or quality.

METHODS

This Clinical Consensus document was developed using an a priori protocol in conjunction with the authors listed above. The a priori protocol was modeled after the Clinical Consensus methodology; a full description of the Clinical Consensus methodology is published separately (4). The description below is specific to this Clinical Consensus document.

Literature Search

A literature search was performed from 2000 to November 2021 for clinical elements as noted in the outline. ACOG medical librarians searched Cochrane Library, Cochrane Collaboration Registry of Controlled Trials, EMBASE, PubMed, and MEDLINE for human-only studies written in English. MeSH terms and keywords can be found in Appendix 1 (available online at http://links.lww.com/AOG/D389). Search terms for racial and ethnic disparities were incorporated into the literature review, and recommendations were drafted with the intent of promoting health equity and reducing these disparities. A bridge literature search was completed in April 2023. Any updated literature was incorporated into the text and recommendations, as appropriate.

Study Selection

Qualifying studies passed both title and abstract screen and full-text screen and met the following inclusion criteria: conducted in countries ranked very high on the United Nations Human Development Index (5), included female participants, and included all study designs. Studies that passed full-text screen by the authors were included in a summary evidence map (Appendix 2, available online at http://links.lww.com/AOG/D390).

Consensus Voting and Recommendation Development

At a meeting of the Committee on Clinical Consensus–Gynecology, a quorum of two-thirds of eligible voting members was met, and the committee held a formal vote for each proposed recommendation. All recommendation statements met or exceeded the 75% approval threshold required for consensus.

Use of Language

The American College of Obstetricians and Gynecologists recognizes and supports the gender diversity of all patients who seek obstetric and gynecologic care. In original portions of this document, authors seek to use gender-inclusive language or gender-neutral language. When describing research findings, this document uses gender terminology reported by investigators. To review ACOG's policy on inclusive language, see https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language.

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SUMMARY OF CONSENSUS RECOMMENDATIONS

Safety and Efficacy of Custom-Compounded Hormone Therapy

There is a lack of high-quality data on the safety and efficacy of custom-compounded bioidentical hormone therapy for the management of menopausal symptoms. Compounded bioidentical menopausal hormone therapy should not be prescribed routinely when FDA-approved formulations exist.

There is no FDA-approved testosterone formulation for the management of menopausal symptoms. Clinicians and patients should use a shared decision-making framework when considering the use of compounded testosterone for this indication. Based on the lack of safety data and inability to remove the pellet, ACOG recommends preparations other than pellet therapy for the delivery of testosterone.

Accuracy of Hormone Level Testing

Data on the interpretation of adjunct hormone tests for prescribing and dosing compounded bioidentical menopausal hormone therapy are limited; thus, these tests are not recommended for these indications.

Patient Counseling

Clinicians should counsel patients that FDA-approved menopausal hormone therapies are recommended for the management of menopausal symptoms over compounded bioidentical menopausal hormone therapy preparations.

If a patient requests the use of compounded bioidentical menopausal hormone therapy, clinicians should educate them on the lack of FDA approval of these preparations and their potential risks and benefits, including the risks specific to compounding.

ACOG, American College of Obstetricians and Gynecologists; FDA, U.S. Food and Drug Administration.

SAFETY AND EFFICACY OF CUSTOM-COMPOUNDED HORMONE THERAPY

There is a lack of high-quality data on the safety and efficacy of custom-compounded bioidentical hormone therapy for the management of menopausal symptoms. Compounded bioidentical menopausal hormone therapy should not be prescribed routinely when FDA-approved formulations exist.

Evaluation of the published data regarding the efficacy and safety of compounded bioidentical menopausal hormone therapy is hindered by an overall lack of high-quality evidence. Many of the data are based on observational studies without a control group and that predominantly evaluated only short-term outcomes (less than 1 year) and often studied surrogate markers. A 2004 Cochrane Review of menopausal hormone therapy noted a 57.7% reduction in hot flushes within the placebo group alone, demonstrating the necessity of a control group, particularly when studying menopausal symptoms (6). Additionally, due to the inherent nature of custom-compounded medications, there is significant variability in the mixture of hormones included as well as differences in the route of administration and dosing. Many studies included a variety of routes of administration, so outcomes on the efficacy of oral compared with vaginal compared with topical administration, for instance, may be difficult to determine. Due to lack of regulation, the amount of active medication can be highly variable within a specific dose, which has been confirmed with independent testing (7). Finally, there are no requirements for adverse event reporting, which hinders a definitive evaluation of safety.

There are numerous observational and uncontrolled studies evaluating the effect of compounded bioidentical menopausal hormone therapy, with overall poor study quality and minimal symptom relief. A retrospective survey of women using compounded bioidentical products of many different formulations (n=70) compared with those using synthetic hormone therapy (n=53) reported improvements in sleep problems and dry skin with the use of compounded products (8). However, the study presented no statistical comparison and did not control for differences at baseline. Another survey of 184 patients found that menopausal symptom relief was similar between users of compounded bioidentical menopausal hormone therapy (preparations included estrogen, progesterone, and testosterone, and routes of administration included oral, transdermal, and buccal) and conventional therapy users; however, relief of sexual symptoms was reported more frequently in bioidentical menopausal compounded hormone therapy users than in those using conventional menopausal

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hormone therapy (78% vs 33%, $P<.001$) (9). Another systematic review that identified three randomized controlled trials (RCTs) on the use of bioidentical progesterone cream concluded that available evidence did not support its benefit for management of vasomotor symptoms (10).

Data on the safety of compounded bioidentical menopausal hormone therapy also are minimal and evaluate only surrogate markers. A 2022 systematic review and meta-analysis of only RCTs included studies comparing primarily short-term use of compounded bioidentical menopausal hormone therapy with placebo and found that bioidentical products were not associated with adverse changes in lipid profile or glucose metabolism (11). None of the RCTs (the longest duration of study was 1 year) that assessed endometrial thickness showed a significant difference between compounded bioidentical menopausal hormone therapy and either placebo or FDA-approved products. Compounded DHEA (including both oral and vaginal formulations) was associated with a higher risk of androgenic effects compared with placebo (relative risk 3.87, 95% CI 1.28–11.65). In this systematic review of short-term studies, no other compounded bioidentical menopausal hormone therapy products were associated with an increased risk of other adverse events. However, data were inadequate to assess the risk of breast cancer, endometrial cancer, or cardiovascular disease with the use of compounded bioidentical menopausal hormone therapy.

Studies have attempted to characterize the accuracy of dosing of different hormones within compounded hormone prescriptions. A study that evaluated prescriptions for combined estradiol and progesterone capsules and creams from 13 custom-compounding pharmacies found variability across pharmacies and within batches (12). The majority of products made by the pharmacies were within 10% of the label claim. However, levels could be as much as 26% below label for estradiol and 31% above label for progesterone. Some compounding pharmacies have attempted to standardize compounding of bioidentical menopausal hormone therapy by requiring their participating pharmacies to submit random quarterly samples to an independent third-party testing laboratory. In addition to the variability of dosing, compounded prescriptions include the potential for bacterial contamination (7).

There is no FDA-approved testosterone formulation for the management of menopausal symptoms. Clinicians and patients should use a shared decision-making framework when considering the use of compounded testosterone for this indication. Based on the lack of safety data and inability to remove the pellet, ACOG recommends preparations other than pellet therapy for the delivery of testosterone.

Compounded testosterone often is included in, or is the primary component of, compounded bioidentical menopausal hormone therapy. Currently, there is no FDA-approved testosterone formulation for cisgender women. There is an FDA-approved formulation of DHEA, as well as FDA-approved testosterone products for cisgender men. The American College of Obstetricians and Gynecologists' guidance on female sexual dysfunction notes that short-term use of transdermal testosterone can be considered as a treatment option for postmenopausal individuals with sexual interest and arousal disorders who have been appropriately counseled about the potential risks and unknown long-term effects (13). The most commonly reported adverse events noted with testosterone therapy in cisgender women included hirsutism, acne, and virilization, which may be irreversible. The effects of long-term use of testosterone on cardiovascular disease and breast cancer risk are unknown.

A 2022 systematic review of RCTs on compounded bioidentical hormone therapy found that testosterone and DHEA, both vaginally delivered, compared with placebo demonstrated a significant improvement in vaginal atrophy in symptomatic postmenopausal women (standardized mean difference −0.66, 95% CI −1.28 to −0.04) (11). Dosages were highly variable, ranging from 300 micrograms to 5 mg; treatment duration ranged from 1 month to 6 months; and follow-up ranged from 2 weeks to 1 year. No significant benefit for bone mineral density was demonstrated. Combining the vaginal testosterone or vaginal DHEA subgroups demonstrated significant improvements in arousal, lubrication, satisfaction, pain, and the overall Female Sexual Function Index score compared with placebo. There was no significant association between oral DHEA and improved total sexual function scores.

An increasingly popular treatment, testosterone pellet therapy, has the potential for better bioavailability and more predictable absorption when compared with intramuscular injection or patches (14). However, unlike other preparations that can be easily discontinued (eg, topical creams and pills), the pellet is not designed to be removed, but instead to dissolve over time. Generally, new pellets are inserted every 3 to 6 months. This route of administration potentially exposes the user to testosterone over a longer period of time compared with oral or topical products. A study of premenopausal (n=108) and postmenopausal (n=192) women treated with compounded testosterone pellet therapy reported statistically significant improvements in each of the 11 Menopause Rating Scale symptom categories over a mean follow-up of 28.1 months compared with pretreatment levels (15). Although data on androgenic adverse effects were not collected by the authors, they reported no adverse drug events. Other studies of testosterone pellets in premenopausal and postmenopausal women have reported adverse effects such as increases in facial hair and acne, perceived voice changes, mood swings, anxiety, weight gain, acute uterine bleeding, and hysterectomy secondary to abnormal uterine bleeding (16–18). In a retrospective analysis of a proprietary compounded testosterone

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pellet product that included cisgender men and both premenopausal and postmenopausal cisgender women (54% were premenopausal), 43% of patients discontinued therapy after the first insertion (14). How the study collected and described data is unclear; however, reported complications from insertion (extrusion, cellulitis, and bleeding) appeared to be low. Unfortunately, adverse effects of testosterone use were not assessed.

A major safety concern about testosterone therapy is a potential increased risk of invasive breast cancer. The effects of long-term use of testosterone on breast cancer risk are unknown, and the limited existing data focus primarily on the risk of estrogen plus testosterone, not testosterone alone (13). A 2006 Nurse's Health Study publication demonstrated a 2.5-fold increased risk of breast cancer in current users of menopausal hormone therapy containing testosterone compared with nonusers (19). At that time, an FDA-approved oral formulation of fixed-combination dosing of esterified estradiol and methyltestosterone was used; however, this medication is no longer available for use in the United States. The risk of breast cancer in users of compounded pellet testosterone therapy is still unclear. A prospective 10-year cohort study reported a decreased incidence of breast cancer in testosterone pellet users compared with patients in a historical control group (SEER [Surveillance, Epidemiology, and End Results] data) (17). However, these data are limited by inclusion of premenopausal and postmenopausal women, the addition of anastrozole to the testosterone pellet therapy (included in 62% of pellets 5 years into the study), significant loss to follow-up (1,267 at initiation, with data analysis on only 407 patients), and lack of standardized breast cancer screening, as well as the use of a historical control group.

ACCURACY OF HORMONE LEVEL TESTING

Data on the interpretation of adjunct hormone tests for prescribing and dosing compounded bioidentical menopausal hormone therapy are limited; thus, these tests are not recommended for these indications.

There are many claims regarding the utility of individualizing hormone therapy based on testing of saliva, serum, or blood. However, individualized testing is useful only when there is a narrow therapeutic window for a drug or class of drugs and the serum hormone levels can be reliably assessed, and if the results would change management. This includes drugs with nonlinear pharmacokinetics, that are eliminated by the kidney as an active drug, that are not metabolized by the liver through the first-pass mechanism, or that have clearly defined therapeutic and toxic windows based on data from large population pharmacokinetic studies. As steroid hormones, estrogen and progesterone do not meet these criteria and do not require individualized testing. Although proponents claim that salivary testing can help tailor hormone therapy, salivary testing does not offer accurate or precise assessment of hormone levels. Steroid hormones mostly are bound to albumin, with less than 5% circulating in free form. Estrogen levels are extremely low in saliva, which make it methodologically challenging to measure. Progesterone is present in the saliva at higher levels, but circulating levels do not necessarily reflect the levels present in the tissue (20). Currently, there are no FDA-approved salivary or urinary tests for steroid hormone measurement.

The primary goal of hormone therapy is to alleviate menopause-related symptoms. Most individuals do not require additional ancillary testing of serum levels, and dosing should be titrated to patient-reported menopausal symptom relief. Because compounded bioidentical menopausal hormone therapy products are not tested for efficacy and safety by the FDA, the potency of these formulations may be too high or low, and the pharmacokinetics may be inconsistent. Therefore, if a patient presents already having started compounded bioidentical menopausal hormone therapy, the clinician may consider serum level testing to aid in adequate titration. Generally, a target estradiol level of 40–100 pg/mL is a reasonable range to provide relief from symptoms (21).

For those patients who present for care and are currently using pellet therapy, clinicians can consider testing to rule out supraphysiologic testosterone levels. Testosterone levels can be measured accurately using liquid or gas chromatography and tandem mass spectrometry assays; direct assays for the measurement of total and free testosterone are highly unreliable in the female range. Nevertheless, if liquid or gas chromatography and tandem mass spectrometry assays are not available, direct assays may be appropriate to obtain to evaluate baseline concentrations and to rule out supraphysiologic testosterone levels (22). For individuals on menopausal testosterone therapy, testosterone concentrations should be maintained in the physiologic premenopausal range of 20–80 ng/dL.

PATIENT COUNSELING

Clinicians should counsel patients that FDA-approved menopausal hormone therapies are recommended for the management of menopausal symptoms over compounded bioidentical menopausal hormone therapy. If a patient requests the use of compounded bioidentical menopausal hormone therapy, clinicians should educate them on the lack of FDA approval of these preparations and their potential risks and benefits, including the risks specific to compounding.

Most patients are not aware that there are FDA-approved hormone therapies that are bioidentical. Unlike compounded medications, these products undergo

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Table 1. U.S. Food and Drug Administration–Approved Bioidentical Hormone Therapies	
Hormone	**FDA-Approved Bioidentical Hormone Therapy**
Estrogen	
Estradiol	Oral tablets (0.5, 1.0, 2.0 mg) Transdermal preparations • Patches (14, 25, 37.5, 50, 75, 100 micrograms) • Gels, emulsions, sprays (multiple doses) Vaginal ring (systemic levels for 90 d)
Progesterone	• Oral micronized progesterone (100, 200 mg) • Vaginal progesterone gel (4%, 8%)* • Vaginal progesterone insert (100 mg)*
Combination therapy	Oral estradiol 1 mg and micronized progesterone 100 mg
Androgens	
Testosterone	Testosterone gels†
DHEA‡	Vaginal insert for local therapy (prasterone)

Abbreviations: DHEA, dehydroepiandrosterone; FDA, U.S. Food and Drug Administration.

*Not FDA-approved for menopausal use; approved for support of assisted reproductive technologies.

†FDA-approved preparations dosed for men can be titrated for use in women; no FDA-approved preparation has been formally approved for use in cisgender women.

‡DHEA is an adrenal androgen; in the USA, it is approved for local vaginal therapy.

Modified from Stuenkel CA. Compounded bioidentical menopausal hormone therapy—a physician perspective. Climacteric 2021;24:11–8. doi: 10.1080/13697137.2020.1825668. Copyright © International Menopause Society, reprinted by permission of Taylor & Francis Ltd, http://www.tandfonline.com on behalf of International Menopause Society.

rigorous assessments of safety and efficacy testing, including potency, pharmacokinetics, and monitoring of adverse effects. See Table 1 for FDA-approved bioidentical menopausal hormone therapies. Compounding pharmacies prepare hormonal products by custom mixing the hormone with inactive ingredients in a pill, cream, or gel form. However, compounded bioidentical menopausal hormone formulations lack rigorous quality control or oversight, which can result in variable absorption and potency (causing too high or low levels), purity, and quality, as opposed to the proven pharmacokinetics of FDA-approved formulations. Clinicians should counsel patients that FDA-approved menopausal hormone therapies are recommended for the management of menopausal symptoms over compounded bioidentical menopausal hormone therapy. Additionally, FDA-approved patches provide an advantage over oral hormones because they provide a more consistent delivery, with a relatively steady level of estradiol, and may have a lower risk of venous thromboembolism (23).

There are good data to support that some formulations of androgen therapy improve symptoms in postmenopausal women with sexual interest and arousal disorders, that vaginal formulations improve vaginal atrophy symptoms, and that implanted testosterone may improve menopausal-related symptoms. See ACOG's Practice Bulletin No. 213, *Female Sexual Dysfunction*, for more information on management of sexual interest and arousal disorders (13). However, as with oral products, implantable formulations are associated with an increased risk of androgenic symptoms that may be severe and potentially irreversible, and the long-term safety of these treatments is still unclear. There currently are FDA-approved formulations of DHEA for the treatment of vaginal symptoms. The risk and benefits of other non-FDA formulations of testosterone to treat menopausal symptoms should be discussed with patients. Based on the lack of safety data and inability to remove the pellet, patients should be informed about the use of preparations other than pellet therapy for the delivery of testosterone.

MARKETING

As noted by the National Academies of Sciences, Engineering, and Medicine, media influences and targeted marketing to both patients and clinicians play an integral role in the popularity of compounded bioidentical menopausal hormone therapy, as well as the unfounded perception that they are safe and effective (1). Patients, many of whom may not know that there are FDA-approved menopausal hormone therapies that are bioidentical, may seek compounded products based on the perception that they are more "natural" and therefore safer than FDA-approved medications. Pharmacies that compound bioidentical hormones are neither required to report adverse events to the FDA nor provide the labeling, with data on safety and effectiveness, as well as warnings, that

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accompany FDA-approved medications. This lack of information on safety also may contribute to the perception that these drugs are safer than FDA-approved medications.

The American College of Obstetricians and Gynecologists advocates that obstetrician–gynecologists should not sell or promote agents or devices as being therapeutic without an adequate evidence base for medical benefit. Physicians who dishonestly market a product as medically beneficial may compromise public trust in physicians' clinical advice (24). Clinicians should engage in individualized, patient-centered shared decision making when discussing the benefits and risks of available treatment options in the context of a patient's values and priorities (25). This is especially essential when data are lacking on the benefits and harms of a medication or device.

FURTHER RESEARCH

To truly understand the benefits and harms of compounded bioidentical menopausal hormone therapy, high-quality placebo-controlled RCTs with long-term follow-up (more than 2 years) comparing custom-compounded products with FDA-approved menopausal hormone therapy are needed. Long-term data are needed on adverse effects of testosterone, including cardiovascular disease and breast and endometrial cancers. Studies are needed on the comparative effectiveness of compounded testosterone products with FDA-approved medications, such as testosterone gel. Additionally, future research should focus on the safety and efficacy of testosterone pellet therapy.

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Appendices

Supplemental Digital Content

1. Literature Search Strategy: http://links.lww.com/AOG/D389
2. Evidence Map: http://links.lww.com/AOG/D390

CONFLICT OF INTEREST STATEMENT

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