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Menopause *e*-Consult®

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This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Wen Shen, MD, MPH, the Editor of *Menopause e-Consult,* encourages your suggestions for future topics. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Shen.

Case:

A patient requests your advice about testosterone from a compounding pharmacy to supplement her hormone therapy. How should you advise her? Are there any guidelines for dosing testosterone ordered from these pharmacies?

Management issues by:

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The controversy over compounding rages on. It has been aggravated by questions of whether a substantial proportion of compounding is simply manufacturing by a different name, as manufacturing requires FDA oversight. New concerns adding fuel to this fire have been raised over the safety of the practice. Many people have died in several states following the recent fiasco related to mold contamination of epidural methylprednisolone.[1] In the absence of FDA-approved testosterone products for women, many practitioners are faced with similar challenges.

It has been estimated that more than 1.3 million prescriptions for compounded testosterone products were used by women in 2003.[2] Presumably, this approach to the aging US female population and the increasing prevalence of low sexual desire with age[3] augments demand for testosterone products for women.[4,5] As demonstrated in these reviews, evidence documents that testosterone treatment (local/clitoral, vaginal, and systemic) increases sexual desire and genital sensitivity, and might improve the intensity of orgasm. Prospective, randomized, clinical trials of a testosterone patch developed specifically for women demonstrated a statistically significant increase in the number of satisfying sexual events and improved desire, arousal, orgasm, pleasure, responsiveness, and self-image—while decreasing sexual concerns and distress. These findings were consistent in surgically and naturally menopausal women already on estrogen therapy or estrogen and progestogen therapy.[5] The response to this therapy was similar in women taking oral or transdermal estrogen, and in women who were not taking estrogen at all.[6] Safety was demonstrated over as long as 4 years of treatment in a small sample of women from these trials,[7] but despite approval by the European regulatory authorities (MEA), the product was recently discontinued by the manufacturer. An even larger safety study of testosterone percutaneous gel focusing specifically on the risks of breast cancer and cardiovascular disease was recently stopped by the gel manufacturer after 4 years of study, but not because of an increase in breast cancer or cardiovascular events.

Clinicians in the United States who want to provide testosterone treatment to their postmenopausal patients are stuck with no FDA-approved products. Compounded copies of esterified estrogens 1.25 mg and methyltestosterone 2.5 mg or esterified estrogens 0.625 mg and methyltestosterone 1.25 mg continue to be available. Other compounded testosterone therapies remain available and suffer the same vagaries of formulation, delivery, and safety. A reasonable solution for both the patient described above and most US clinicians is to prescribe a reduced dosage of testosterone products that are marketed (and FDA approved) for hypogonadal men. This is an off-label use. As the testosterone production rate in a premenopausal woman is about 10% that of a normal man, efforts to use male products at about 10% the approved male dosage have proliferated. These regimens include: testosterone injections (testosterone enanthate, cypionate, or propionate), 30 mg to 50 mg intramuscularly every 3 to 4 weeks; testosterone in a hydroalcoholic gel (ie, Androgel 1%, not the new 1.62%) from the pump—one depression of the pump twice or three times per week to the leg; or testosterone gel (ie, Testim 1%), 6 drops per day applied to the lower leg. Another option is the crystalline testosterone subcutaneous implant (Testopel). While many have used compounded testosterone pellets for years, these compounded pellets often suffer from spotty sterilization and unreliable absorption. Like the other agents listed above, Testopel is not approved for use in women, but preliminary study results suggest that the proper dosing may be half to one full implant every 4 to 6 months.

So, with regard to the patient in this case, I would first have to confirm that she has a legitimate need for testosterone, as this therapy will not fix severe vulvovaginal atrophy, pelvic pain, a bad marriage, a partner with erectile problems (unless he uses the testosterone for hypogonadism), nor many other reasons for a failed sexual relationship. Once I am sure that a hormonal option may help (a clinical judgment), I usually begin empirically with one of the above options. The major barriers to their use are fear of side effects (eg, hirsuitism, acne) which are rare if used as noted above. The other significant barrier is cost. Off-label use of male products rarely is included in insurance coverage, especially without an approved indication in women. While initial out-of-pocket costs may be high ($300), such prescriptions (a one month's supply for a man) usually last 10 to 12 months.

Disclosure: Dr. Simon reports: Consultant/Advisory Board: Abbott Laboratories, Agile Therapeutics, Amgen, Ascend Therapeutics, BioSante, Depomed, Intimina by Lelo, MD Therapeutics, Merck, Novo Nordisk, Novogyne, Pfizer, Shionogi, Slate Pharmaceuticals, Sprout Pharmaceuticals, Teva, Warner Chilcott, Watson Pharmaceutical; Grants/Research Support: BioSante, EndoCeutics, Novo Nordisk, Novogyne, Palatin Technologies, Teva, and Warner Chilcott; Speakers Bureau: Amgen, Merck, Novartis, Novo Nordisk, Novogyne, Teva, and Warner Chilcott; Chief Medical Officer: Sprout Pharmaceuticals.

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Question:

How should you advise a patient concerned about her dry skin, wrinkles, and thinning hair?

Commentary by:

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Why do skin, hair, and nails age? There are several types of dermatological aging that women experience in middle age.

- *Biological aging* is a result of our individual clock and affects the rate at which skin wrinkles, hair thins, and nails thin. DNA is largely responsible these changes.
- *Environmental aging* is due to the daily exposures we encounter, whether wind, cold weather, smoke, sun, or stress. These exposures damage lipids, proteins, and DNA, resulting in stress on the cells and causing premature aging.
- *Mechanical aging* is the result of our repeated behaviors to the outside of our skin such as frowning, smiling, squinting, scrubbing, over-washing, and bruising.

Estrogen has long been known to be a factor of the aging process. Loss of estrogen decreases connective tissue turnover, collagen content, and dermal thickness.[1]

Why is aging skin so important to our patients? Skin is the only organ we can see. A study in the United Kingdom in 2011 reported that 64% of women at a menopause clinic complained of bothersome skin changes, with dryness being the most common problem. We as clinicians may not think that dry skin is a life-threatening issue, but to our patients, physical appearance is often the essence of who they believe themselves to be and affects their social interactions and sense of well-being. Americans spend more than $33 billion on cosmetics and skin products each year. Our patients deserve a serious explanation about skin, hair, and nail issues.

How does skin age? Skin is composed of layers: epidermis, dermis, and subcutaneous. Being the largest of our organs, it is responsible for regulation of heat and cold, storage of water and fat, prevention of loss of water, sensation, and entrance of bacteria into our environment. As skin, hair, and nails age, they lose function, feeling, and color:

- Loss of the moisture barrier from the epidermal lipids results in increased transepidermal water loss
- Loss of collagen causes less elasticity and an increase in extensibility
- Aging blood vessels and glands cause fragility, including noticeable skin tears, poor healing, dryness, itching, and hair loss
- Loss of regeneration of keratinocytes thins the skin and makes it look dull and feel rough
- Hyperpigmentation darkens the skin and nails due to increased melanin

Color changes. Melanin is produced by melanocytes, which are activated by the sun and other inflammatory sources. This inflammation happens evenly or unevenly, causing tanning, wrinkles, and age spots. Other sources of inflammation to the melanocytes that can cause discoloration include antibiotics, nonsteroidal medications, sex steroids, fabric dyes, chemical irritants, plant irritants (eg, poison ivy), chemotherapy, and even physical trauma. Due to the aging process, the melanocytes are more slowly brought to the surface and shed, thus causing more unevenness and prolongation of color changes.

Skin cancer. Regarding abnormalities of the skin, one must consider the possibility of skin cancer when someone presents with a rough,

dry, brown patch. Actinic keratosis is a crusty rough skin patch usually found on sun-exposed areas. These patches can be very small and not seen but felt, and come in a variety of colors including brown, red, pink, and tan. There may be a prickly sensation or tenderness when touched. These patches are an indication of skin damage and are the most common precursor to all skin cancers: 10% progress to squamous cell cancer. There are many topical treatments for keratosis on the market including 5-Fluorouracil cream, Imiquimod 5%, diclofenac acid, and hyaluronic acid gel. Surgical removal or freezing are also options. Decreasing sun exposure by staying covered and using sunscreen will help delay the occurrence as well as other sun-damaging effects like wrinkles. Skin cancers have not been found to be affected by hormone use.

Hair loss. Hair loss is due to the aging follicle. A switch from estrogen dominance to androgen dominance affects growth and results in typical male pattern hair loss and growth of facial hair. Loss of estrogen affects fine hairs, resulting in loss of leg, arm, and pubic hair. If hair loss is sudden then androgen-secreting tumors or other metabolic causes such as thyroid disease and metastatic tumors of the breast need to be considered. Excessive hair pulling in the dementia population must also be considered. Tinea capitis (a fungal overgrowth) has also been increasing worldwide. Hair loss due to autoimmune diseases often decreases after menopause.[2] Antifungals, treating the underlying medical problem, and anti-androgens such as finasteride or dutastide and minoxidil produce mixed results. Decreased shampooing (once a week is enough with mild hydrating shampoo) and hydrating with oil-based rinses will help protect the follicles and result in less breakage of the hair and more shine.

Oxidative stress. Research has shown that oxidative stressors add to the loss of function and integrity of connective tissues, hence skin, hair, and nail changes. Oxidative stress increases with smoking, loss of hormones, intense exercise, poor fruit and vegetable intake, and stress. Dietary antioxidants have been studied as preventatives. Higher levels of isoprostanes—measured in the urine as indictors of stressors—cause more stress upon and inflammation of connective tissues including skin, hair follicles, and blood vessels. Emerging treatments for skin and hair are those products that lower these markers.

What can be done? In some small, short-term studies, hormone therapy (HT) has been shown to improve the quality of skin, hair, and nails. A few studies of women with dry eye showed decreased complaints in those treated with transdermal estrogen compared to placebo.[3] However, other studies have reported more complaints of dry eye in women using HT compared to placebo. Estradiol and genistein treatment increase hyaluronic acid concentrations (a precursor to collagen) in facial skin.[4] In vitro studies on cultured skin cells show a decrease in reactive oxygen species when exposed to 17β-estradiol, but long-term safety is unknown and skin treatment is not an approved indication for HT.

Conclusion. Educate your patients with skin, hair, and nail concerns about prevention. Eliminate offensive stressors: smoking, too little or too much exercise, scrubbing, over-washing, sun damage, ignoring medical problems, dehydration, and lack of hormones. Present your patients with options, screen for treatable diseases, encourage healthy nutrition, and send to a dermatologist for follow-up when you encounter issues beyond your clinical expertise.

Disclosure: Dr. Saunders reports: none.

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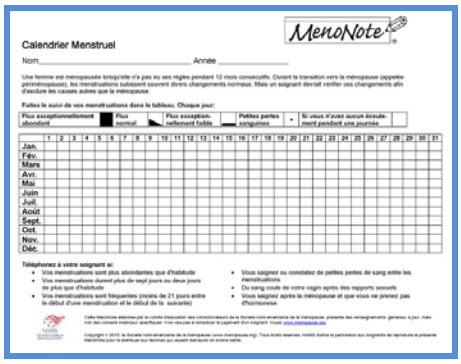
Accurate, Concise Summaries About Menopause
MenoNotes

Six free handouts summarize some of the most confusing menopause-related topics. Hot flashes, vaginal dryness, bioidentical hormone therapy, and a menstrual calendar (in English, French, and Spanish) are clearly explained with the most up-to-date information. More topics will be added regularly so check back often.



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