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Menopause *e*-Consult®

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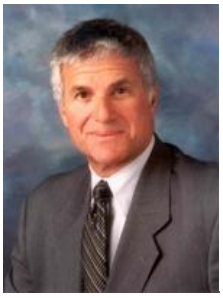
This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Nancy Ann Roberson Jasper, MD, NCMP, the Editor of *Menopause e-Consult*,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

Case

A healthy 55-year-old postmenopausal woman with a history of uterine fibroids and no prior hysterectomy started hormone therapy (HT; transdermal estradiol with daily oral micronized progesterone) for severe menopause symptoms and had good response in reduction of vasomotor symptoms (VMS). She strongly desires continuing on HT but has started to have bothersome breakthrough bleeding. What are management options for women with fibroids having breakthrough bleeding on HT?

Commentary by



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This is not an uncommon situation in clinical medicine for which there is not abundant Level I evidence to guide us, but let me try to reason through how one might approach such a patient.

There really are two main concerns: 1) the exclusion of any serious concomitant organic pathology such as endometrial hyperplasia or cancer, and 2) if the concern for pathology is excluded, we are still left with the nuisance and inconvenience of the bleeding, especially in light of the excellent reduction of VMS.

There are several pieces of information that may be extremely relevant. First, how long has she been on the regimen of an improvised continuous-combined formulation (transdermal estradiol and oral progesterone)? In addition, in what dosages are these preparations being employed?

We know from several studies of continuous-combined HT (none head-to-head) that the incidence of bleeding or spotting in the first 3 to 4 months is not insignificant.

In fact, one arm of a recent trial of a low-dose formulation of 0.45 mg conjugated equine estrogen (CEE) with 1.5 mg medroxyprogesterone acetate daily resulted in approximately a 20% to 25% rate of bleeding or spotting in each of the 4-week aliquots of time.[1]

Thus, in my own practice, when I place patients on any form of continuous-combined HT, I tell them that if they have any bleeding in the first 3 months to ignore it, that that is not unusual, but if it persists beyond 3 months to contact me. This is for patients whether or not they have fibroids.

I have the luxury of doing transvaginal ultrasound in virtually all my patients who

are initiating HT, but especially in a case like this, I would be curious as to how the diagnosis of fibroids was made and where they are located. Is there a submucous component? Was an endometrial echo well visualized, or did the size and or location of the fibroids preclude an adequate assessment?

Still, absent any risk factors concerning for endometrial neoplasia (obesity, nulliparity, diabetes, etc), I would not do anything more invasive (sonohysterography or hysteroscopy). Women on continuous-combined HT are not protected from endometrial cancer. It has long been known that the addition of progestogen simply brings the potential risk of endometrial cancer down to the level of nonusers of estrogen therapy but not to zero.[2]

If bleeding persists beyond 3 to 4 months of a continuous-combined regimen, I would absolutely evaluate the endometrium for organic pathology.[3] I use an ultrasound-based approach using transvaginal ultrasound and saline infusion sonohysterography when necessary.

If the evaluation of the endometrium reveals no pathology and the patient has bothersome breakthrough bleeding, then changing dosages of estrogen or types of progestogen will depend on how bothersome the bleeding is and how fearful the patient is that the new regimen will not be as satisfactory in relieving her VMS.

Alternatively, one could consider the new category of tissue-specific estrogen complexes in which the combination of CEE 0.45 mg and 20 mg of the selective estrogen receptor modulator bazedoxifene reduced VMS from an average of more than ten VMS per day to fewer than three and had a bleeding profile indistinguishable from placebo.[4]

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Disclosures: Dr. Goldstein reports consultant/advisory board or review panel for JDS Therapeutics, Pfizer, TherapeuticsMD, Cook OB/GYN, and Cooper surgical and speakers bureau for JDS Therapeutics and Pfizer.

Question

A woman in midlife presents with new acne issues. What is the best approach to this problem?

Commentary by

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When a midlife patient presents with what appears to be acne vulgaris, the first thing we need to do is determine whether this is indeed late-onset acne vulgaris as opposed to persistent acne. Approximately 12% of women continue to have persistent acne vulgaris into their forties. In contrast, only 3% of women aged

35 to 45 years present with new-onset acne vulgaris.

True acne—acne vulgaris—must be distinguished from other acneiform skin conditions. Acne vulgaris occurs most commonly on the face, then upper back and chest, because it is a follicular eruption involving the pilosebaceous unit, and these anatomic areas contain high concentrations of sebaceous glands.

Individual acne lesions begin as comedones that may rupture, with the formation of papules, pustules, and cysts. Acne vulgaris is distinguished from other types of acneiform conditions by the simultaneous presence of all these lesions seen together on a woman's skin.[1]

Women who present with new-onset acne in midlife may be resistant to recommended treatment guidelines.[2] This should alert one to search for underlying causes of late-onset acne vulgaris.

The target organ for acne vulgaris, the sebaceous gland, is stimulated by androgens, insulin-like growth factor-1 (IGF-1), insulin, and growth hormone.

The new onset of acne, with or without accompanying hirsutism, seborrhea, and androgenetic alopecia, should not be regarded as normal; a search for preexisting or undiagnosed causes of midlife perimenopausal or postmenopausal hyper-androgenism should be considered.

Potential causes of hyperandrogenism include polycystic ovarian syndrome (PCOS), late-onset congenital adrenal hyperplasia (CAH), and androgen-secreting tumors.[3] Although PCOS and late-onset CAH most likely would have been diagnosed earlier in a woman's life, withdrawal of suppressive hormone therapy could lead to a new onset or reappearance of acne vulgaris in midlife. Finding modest increases in testosterone (> 40 ng/dL) in midlife women most commonly is the result of uncovering preexisting conditions (PCOS, CAH).

Furthermore, ovarian androgen secretion in premenopausal and postmenopausal women depends on luteinizing hormone stimulation; after menopause, the substantially increased gonadotropin levels maintain ovarian androgen secretion despite substantial reduction of estradiol.

Polycystic ovarian syndrome in premenopausal women is associated with metabolic syndrome and risk factors for coronary artery disease (CAD). It is not clear whether there is an association between hyperandrogenism and postmenopausal women's risk of CAD.

Not all acne occurs in the setting of androgen excess. Despite relatively normal levels of androgens, the end-organ sensitivity of an individual woman's sebaceous glands will determine whether the relative change in the ratio of free androgen/estrogens stimulate the formation of acne.

End-organ sensitivity is the genetically determined ability (enzymes and receptors) of a pilosebaceous unit to respond to circulating androgens. Postmenopausal testosterone levels only rarely exceed those found in premenopause; however, a relative androgen excess could lead to new-onset acne vulgaris. This relative androgen excess after menopause is further amplified by a decrease in sex hormone-binding globulin and subsequent increase in free androgens.

Where new-onset acne is sudden and accompanied by other signs of virilization (clitoromegaly, deepening of the voice,

increased muscle mass, decreased breast size), it is important to rule out androgen-secreting adrenal or ovarian tumors, ovarian hyperthecosis (OH), and exogenous androgen administration.

The normal range of dehydroepiandrosterone-sulfate (DHEAS) and testosterone varies with age. Given that a normal range of DHEAS is 500 ng/dL to 2,500 ng/dL (18-244 µg/dL for ages 40-49 y; < 15-200 µg/dL for ages 50-59 y; and < 15-157 µg/dL for ages ≥ 60 y) and testosterone is 20 ng/dL to 90 ng/dL, adrenal tumors have plasma levels of DHEAS greater than 8,000 ng/dL and total testosterone of 100 ng/dL to140 ng/dL to greater than 200 ng/dL. Ovarian androgen-secreting tumors have plasma levels of DHEAS greater than 700 ng/dL and total testosterone levels greater than 200 ng/dL.[3,4] (These levels are examples of what is found in the literature, but levels may vary depending on the lab in which they were tested.)

Ovarian hyperthecosis is a non-neoplastic disorder mainly diagnosed in postmenopausal women, mimicking the clinical manifestations and metabolic sequel of PCOS. It is thought to be related to elevated postmenopausal gonadotropin levels.

Women with OH typically present with a long history of slowly progressive hyperandrogenism, often resulting in virilization. They have a markedly increased serum testosterone level (> 150 ng/dL) in the absence of other elevated androgens and high gonadotropin levels. Most women with OH are insulin resistant, with elevated insulin levels, which enhance ovarian androgen production. They tend to be obese and are at increased risk for type 2 diabetes mellitus and cardiovascular disease. Peripheral aromatization of testosterone to estrogen increases their risk of endometrial hyperplasia and cancer.[5]

Acromegaly caused by a pituitary adenoma secreting growth hormone is uncommon: it can present with new-onset acne vulgaris with or without increase in the size of the hands and coarsening of facial features.

Growth hormone stimulates the liver to produce IGF-1, which sensitizes the adrenal gland to adrenocorticotropic hormone and thus to produce more DHEAS. In the appropriate clinical setting, plasma levels of growth hormone should be drawn and compared to normal values for a woman's age to diagnose acromegaly. Magnetic resonance imaging of the pituitary should be done when appropriate.

Weight gain and diet could induce acne vulgaris in premenopausal women. There is a connection between abdominal obesity, insulin resistance, and hyperandrogenemia. Hyperinsulinemia has been clearly shown to promote ovarian androgen synthesis independent of gonadotropins.

There is an association between acne, increased body mass index, insulin resistance, glycemic load, and skim milk consumption. High glycemic diets and skim milk-containing foods have been shown to exacerbate acne vulgaris in premenopausal women.[6]

Similarly, in a woman with a genetic predisposition to metabolic syndrome, weight gain with an elevation in insulin and IGF-1 might trigger new-onset acne vulgaris. However, studies have shown that increases in IGF-1 potentiates androgen production by the adrenals, and IGF-1 directly upregulates the growth and proliferation of sebaceous glands and sebum production. Acne vulgaris severity correlates with the level of IGF-1.[7]

Various drugs such as exogenous androgens (testosterone, DHEAS, danazol), aromatase inhibitors, certain antiepileptic drugs (phenytoin), synthetic progestins (ie, levonorgestrel), lithium, and isoniazid can induce or exacerbate acne vulgaris.[3]

Certain cosmetics when applied to the skin will induce comedone formation and acne vulgaris. Most cosmetics are extensively tested for comedogenicity. Acne vulgaris can be induced by constant friction or rubbing of the facial skin (acne mechanicum). It can be seen in violin players on the side of the jaw or in those who wear chin straps that rub.

For a woman in midlife presenting with new-onset acne, it is important to exclude various causes: an underlying metabolic abnormality, drugs, end-organ sensitivity, dietary factors, and cosmetics. When a midlife patient presents with late-onset acne, it would be wise not to assume that the problem is only skin deep.

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Do you see many cases of new-onset acne in your midlife women patients? What have you found to be the most common cause? Visit our Member Forum to discuss the November *Menopause e-Consult*.

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