REVIEW

CME CREDIT

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Management of perimenopause: Focus on alternative therapies

ABSTRACT

A variety of herbs and other "natural alternative medicines" are marketed directly to consumers and sold over-the-counter as treatments for perimenopausal symptoms. Far from being innocuous placebos, many of these substances have real physiologic effects, including potential adverse effects and drug interactions. Yet they are largely untested and, by law, totally unregulated. This article reviews a few of the untested substances your patients may be taking, along with established treatments.

KEY POINTS

We try to discourage women from taking "natural" alternative medications, but failing this, we try to monitor their use.

Black cohosh may have actual estrogen-like activity; dong quai may not.

Many women are taking the androgen DHEA, but its safety and role are not known. If patients refuse to discontinue DHEA, we recommend liver function tests and monitoring serum levels of DHEA-S, lipids, and testosterone.

Different women experience perimenopause differently: some have vasomotor symptoms due to estradiol deficiency with resultant surges of luteinizing hormone, but others have surges of estradiol excess with resultant fluid retention. Progesterone deficiency may lead to irregular bleeding.

PHYSICIANS HAVE BEEN CRITICIZED for "medicalizing" perimenopause and menopause. Because the transition is a natural consequence of aging due to ovarian senescence, many women seek "natural" therapies to relieve symptoms. More studies are urgently needed to determine the safety and efficacy of many of these so-called natural formulations. In the meantime, it behooves the clinician to understand perimenopause and to be aware of the use and possible misuse of the many "natural" remedies being marketed to women.

ALTERNATIVE THERAPIES: UNREGULATED, UNTESTED

Alternative therapies include but are not limited to acupuncture, massage, chiropractic, homeopathy, naturopathy, and, most germane to our discussion, a variety of over-the counter products—herbs, supplements, and botanicals. Many of these products are specifically marketed to perimenopausal and postmenopausal women.

More and more patients are using these products, for reasons that include the inability of allopathic medicine to completely control the symptoms of many non–life-threatening ailments, and the appeal of "natural" products.

"Natural" does not necessarily mean safe, however. Many herbs have toxic effects and drug interactions. Many of our contemporary synthetic medicines come from plant sources, and herbs have been used medicinally for centuries, but successful use requires education.

Remarkably, the FDA does not regulate many substances such as herbs (which may or may not have hormone-like effects) and even

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actual hormones such as melatonin, dehydroepiandrosterone (DHEA), and topical progesterone creams. Their manufacture is not standardized, and they are not required to undergo premarket testing for safety and efficacy, as regular pharmaceuticals are.

The loophole that allows these substances to escape government regulation: They are "dietary supplements," a category separate and distinct from either food or drugs. Companies that manufacture and market them cannot make direct claims about curing or preventing disease. Only a few herbs have FDA approval: aloe, cascara, psyllium, and senna (as laxatives); capsicum (as a topical analgesic), slippery elm (an oral demulcent) and witch hazel (an astringent). The FDA has not approved any herb for perimenopausal or postmenopausal use.

There is a crucial need for research and educational programs about these alternative therapies, for both physicians and the public. To this end, the NIH has established the National Center for Complimentary and Alternative Medicine (www.altmed.od.nih.gov/nccam).

Herbs

Many herbs have toxic effects and potential drug interactions

Black cohosh (*Cimicifuga racemosa*), also known as black snakeroot, rattleweed, rattleroot, or cimicifuga, is widely touted in the lay literature as being useful for menopausal symptoms. A German study as reported by Hansel (see SUGGESTED READING) showed this herb to have estrogen-like activity and some efficacy in treating vasomotor menopausal symptoms, possibly by reducing the secretion of luteinizing hormone (LH). Long-term safety of this herb in perimenopausal and postmenopausal women requires additional study.

Dong quai (*Angelica sinensis*) has also been widely touted. However, Hirata et al (a group led by Dr. B. Ettinger, the former past president of the North American Menopause Society) recently conducted a study that found that dong quai, when used alone, was no better than placebo in treating hot flashes.

Phytoestrogens. Plants contain a number of estrogenic substances. Scientific attention has recently turned to both steroidal and nonsteroidal plant estrogens (called phytoestrogens), which are present in soy and legume foodstuffs. These substances may have the beneficial effects of steroidal hormones without some of the risks. Studies are needed to examine red clover (which contains plant phytoestrogens), anise, fennel, black cohosh, ginseng, and some other herbs with potential estrogenic effects with respect to menopausal symptom relief.

Melatonin

Melatonin is a hormone produced in the pineal gland in response to ambient light-dark cycles. Levels decline with age, and the decline may lead to altered sleep patterns in aging persons. Perimenopause may be associated with sleep disturbances due to vasomotor phenomena (hot flashes, night sweats, palpitations; which may intensify at night), progesterone deficiency, or nonhormonal conditions such as poor sleep hygiene, alcohol or sedative misuse, substance abuse, and obstructive sleep apnea (which is most common in men but also seen in some postmenopausal women).

Unfortunately, the optimum dose of melatonin for replacement or supplementation is unknown. The unregulated manufacture of this hormone, particularly from animal sources, raises concerns regarding purity. In 1989, tainted lots of L-tryptophan (a natural amino acid that was widely promoted as an aid for insomnia, among other ailments) caused death and disability from the eosinophilia-myalgia syndrome. This food supplement disaster reminds us that "natural" substances manufactured or processed in an unregulated laboratory may lead to potentially devastating consequences when ingested.

DHEA and DHEA-S

The androgens DHEA and DHEA-S circulate in levels far exceeding any other steroid. Their exact physiologic roles are not known, but their levels in the human circulation are developmentally regulated. Both decline with age, independently of menopausal status. As the zona reticularis of the adrenal cortex involutes, levels of DHEA and DHEA-S decline in a cortisol-independent fashion. By age 70, levels in both men and women are approximately 10% of the peak, which usually occurs between ages 18 and 25.

It is not known whether this age-related

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decline, which has been dubbed "andropause" is simply a marker of aging or an aging-induced potential steroid deficiency. In animals, DHEA has protean age-attenuating effects, including being an insulin-sensitizing agent, an immune augmentor, an antiosteoporotic factor, a cognition-enhancing substance, and an antiobesity agent. However, recent data have shown that oral DHEA replacement or supplementation in humans may lead to significant decreases in HDL cholesterol levels in the same way that other oral androgens such as methyltestosterone do.

The FDA considers DHEA an investigational drug that has no approved indication. Because investigators lack a clear understanding of the mechanism of action and long-term effects of DHEA, we recommend that it not be used in the routine clinical care of perimenopausal women or any aging person.

Due to media hype and the wide and unregulated availability of DHEA, many patients are using it without proper supervision. Paradoxically and of concern, many perimenopausal and postmenopausal women who are fearful of estrogen replacement therapy, which has been well studied, feel more comfortable using DHEA because it is marketed as a "natural" off-the-shelf food supplement.

If patients refuse to discontinue DHEA, we recommend that the dose be limited on the basis of serum DHEA-S levels, with periodic liver function tests and monitoring of lipid levels and serum testosterone levels (as DHEA can be converted to testosterone if it is not metabolized to DHEA-S).

ESTABLISHED CLINICAL MANAGEMENT OF PERIMENOPAUSE

The orderly and tightly orchestrated hormonal harmony of the menstrual cycle may be disrupted at several points in the perimenopause. Individual women may experience perimenopause differently, depending on constitutional factors, genetic predisposition, diet, and levels of endogenous estrogens, progesterone, and androgen production from nonovarian sources.

Estrogen deficit

Estradiol levels decline in perimenopause, and levels of follicle-stimulating hormone and luteinizing hormone rise, as the pituitary gland attempts to maintain estradiol production in the face of declining ovarian function. Pulses of luteinizing hormone account for the familiar vasomotor symptoms (hot flashes) of perimenopause.

Some women may begin to experience vasomotor symptoms (hot flashes, sweating) while they are still menstruating regularly. In essence, they are menopausal in terms of inadequate follicular estradiol production, but they are not yet menstrually menopausal.

If these vasomotor symptoms cannot be controlled by making environmental changes (eg, turning down the thermostat or sleeping with fewer blankets), avoiding caffeine, taking 400 IU vitamin E orally every day, and physical measures such as exercise and deep breathing, one can prescribe an estrogen preparation in very low doses, such as:

- Conjugated equine estrogen (Premarin 0.3 mg by mouth every day)
- Esterified estrogens (Estratab 0.3 mg by mouth every day)
- Transdermal estradiol (FemPatch 0.025 mg patch, changed weekly; Vivelle 0.0375 mg patch changed every 3 1/2 days; others).

However, such use of estrogen is controversial, in part because many perimenopausal women do not need it.

For vasomotor symptoms, try nondrug therapies first

Estradiol excess

Paradoxically, some perimenopausal women experience the opposite problem—periods of estradiol *excess* as the failing ovary temporarily responds to elevated levels of stimulating gonadotropins with surges of estrogen production. This excess may account for breast tenderness, fluid retention, the tendency for fibroids to enlarge, and heavier menses (particularly if there is an associated progesterone deficiency).

Periodic monitoring of the endometrium is recommended whenever a woman has "unopposed estrogen"—normal or high estrogen levels from endogenous or exogenous sources but low progesterone levels. This situation occurs with chronic anovulation.

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Monitoring is with endometrial sampling or by ultrasound assessment of the endometrial thickness. Once menses have ceased for 6 months, cyclic progesterone therapy should be added.

Progesterone deficiency

More commonly, perimenopausal women have adequate estrogen levels but decreased progesterone. This condition may be manifested by mood changes and menstrual disturbances, particularly heavy bleeding with clotting.

Oral progesterone therapy with micronized progesterone (usual dose 200 mg orally at bedtime with food for 12 days) or synthetic oral progestins can regulate the menstrual flow in this situation. Micronized progesterone is now commercially available as Prometrium in 100 mg capsules.

Progesterone can also reduce fluid retention, because it is a mild aldosterone antagonist and therefore a natural diuretic. Moreover, it has mild analgesic and sedative effects, owing to its central nervous system actions. However, at higher oral doses (> 300–400 mg), progesterone can induce PMS-like symptoms. These symptoms occur more commonly with progestins such as medroxyprogesterone acetate (MPA; available as Provera, Cycrin, or Amen). If medroxyprogesterone acetate has adverse effects on the central nervous system and mood, many women can tolerate norethindrone, which is available as the progestin-only minipill, Micronor.

Women should continue birth control 1 year after menopause

Transdermal progesterone therapy. A transdermal preparation of norethindrone in combination with estradiol is now available (CombiPatch; norethindrone 0.14 or 0.25 mg/day with estradiol 0.05 mg/day).

We do not recommend using progesterone skin creams to oppose endometrial hyperplasia, because they produce only low plasma progesterone levels, and we have no data as yet to show that they actually protect the endometrium. Moreover, topical progesterone creams alone are not enough to treat or prevent osteoporosis. Finally, although many of the over-the-counter "natural progesterone" skin creams do contain a wild yam extract that contains diosgenin (a plant precursor to progesterone), humans lack the metabolic pathway to convert diosgenin into progesterone.

Vaginal progesterone (Crinone gel 4% or 8%) can be used every other day for 14 days to cause a secretory effect in the endometrium. This preparation has the advantage of not undergoing first-pass liver metabolism as oral progesterone does, and may be a good option for perimenopausal women who cannot tolerate oral progesterone or progestins due to mood changes. This new preparation is effective but expensive.

What laboratory tests are needed?

In a perimenopausal woman, it may be helpful to measure the serum levels of:

- Follicle-stimulating hormone (FSH)
- Estradiol (E_2)
- Total and free testosterone.

One can usually infer the adequacy of progesterone secretion from the menstrual history, but progesterone levels can also be assayed.

Of note: all of these fat-soluble sex steroids are bound to protein-binding globulins, and serum measurements reflect only total values and not the active free levels (except for the free testosterone level).

Measurement of salivary hormone levels has been advocated by some but is only available at a few laboratories. Salivary levels of sex hormones are only a small percentage of blood levels. For example, the progesterone level in saliva is about 5% to 8% of the plasma level.

Oral contraceptives during perimenopause

Up to age 50, healthy, nonsmoking perimenopausal women can continue to take oral contraceptives. Oral contraceptives have several benefits, especially for symptomatic perimenopausal women, because they:

- Suppress vasomotor symptoms
- Regulate the menstrual cycle
- Possibly protect against bone loss due to perimenopausal estrogen deficiency
- Prevent conception
- Suppress androgen production and raise sex hormone-binding globulin (SHBG) levels, both of which in turn decrease the propensity to develop acne, hirsutism, and

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androgenic (male-patterned) hair loss. Tri-Ortho-Cyclen has FDA approval for the treatment of acne in women.

However, even the newer low-dose oral contraceptives contain 20 µg of synthetic ethinyl estradiol—four times the amount needed for postmenopausal replacement. Therefore, changing to a progestin-estrogen replacement therapy (PERT) is recommended when the woman goes from perimenopause to postmenopause. The FSH level can be checked on days 5, 6, or 7 of the pill-free (placebo) week. An FSH level over 30 IU/mL usually indicates the menopausal status.

Menopause can only be diagnosed retrospectively, and occasionally ovulation and pregnancy can occur even after the menstrual cycle has apparently ceased and an elevated FSH is measured. Therefore, women who practice birth control should continue to do so for 1 year after the onset of menopause. Hormone replacement therapy cannot prevent these occasional ovulations, because it does not provide high enough levels of hormone to suppress the pituitary gonadotropins.

Beginning standard hormone replacement therapy in the perimenopause prior to actual menopause may lead to irregular menses. PERT will not inhibit the hypothalamic-pituitary-ovarian axis as oral contraceptives will. Furthermore, occasionally a perimenopausal woman with secondary amenorrhea is actually pregnant, and one should rule this out before prescribing a progesterone challenge, oral contraceptives, or hormone replacement therapy.

IS TESTOSTERONE REPLACEMENT NECESSARY?

Testosterone is produced both in the adrenal glands and the ovarian stroma in women. Approximately 40% of testosterone is produced by the ovarian stroma. Therefore, menopause induced by oophorectomy or chemotherapy can lead to reduced total testosterone levels and, ultimately, reduced free testosterone levels as well. Oral estrogen supplementation, which increases sex hormone-binding globulin levels, may also contribute to decreased free testosterone levels in perimenopausal women. In addition, a small but definite percentage of perimenopausal women develop fibrosis of the ovarian stroma and have lower free testosterone levels.

Unfortunately, there is no good FDA-approved method of androgen replacement in women. Testosterone patches are formulated for replacement of male androgen deficiency and therefore provide too high a dose for perimenopausal or menopausal women. Oral androgen replacement with methyltestosterone as available in Estratest and Estratest HS (half-strength) may be associated with decreased levels of HDL cholesterol and potential adverse effects on liver function. Therefore, women taking oral estrogen-androgen combinations need to be closely monitored for adverse effects.

Elevating the androgen levels above physiologic levels in women can lead to acne, hirsutism, an androgenic pattern of hair loss, and deepening of the voice. Subdermal testosterone pellets are available but not FDA-approved for use. Depo-Testosterone injections are discouraged in women because they provide supraphysiologic peak levels. Transdermal application of topical 1% testosterone propionate or valerate cream via the labia minora can be prescribed, but exact doses are impossible to give due to variable absorption, which limits this as a routine option. Pharmacists can formulate sublingual testosterone drops but exact dosage is not clear.

Testosterone patches provide too high a dose for women

CONCLUSIONS

The hypothalamic-pituitary-ovarian-endometrium axis is disrupted at the ovarian and endometrial level during perimenopause due to fluctuating gonadotropin and sex hormones levels. At the very least, women should be counseled to adopt a healthy lifestyle with good nutrition, emphasizing fruits, vegetables, and grains and possibly more use of soy products (which contain calcium, protein, and phytoestrogens). Exercise (both aerobic and weight-bearing for bone-stimulating effects), smoking cessation, and stress reduction should be encouraged. Physicians should inquire about alcohol and substance misuse. The proper use of vitamins, antioxidants, and trace

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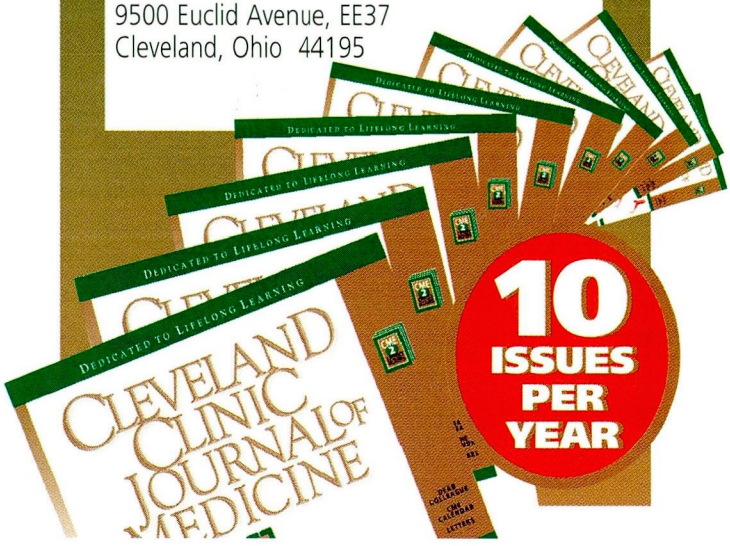

mineral supplements should be reviewed. The patient's use of alternative substances such as herbs and off-the-shelf hormones should be documented and monitored by the clinician. Finally, the rational use of estrogen, progesterone, androgens, and synthetic hormones in the form of oral contraceptives can regulate the menses and provide symptom relief for many women.

SUGGESTED READING

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National Institute on Aging. Pills, patches, and shots: Can hormones prevent aging? (*A patient education handout that briefly reviews how hormones work, DHEA, growth hormone, melatonin, testosterone, and estrogen. For information about free publications from the National Institute on Aging, call: 1-800-222-2225 or visit the web site HTTP://www.nih.gov/nia.*)

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