AACE MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR MANAGEMENT OF MENOPAUSE

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **CAD** = coronary artery disease; **CI** = confidence interval; **DHEAS** = dehydroepiandrosterone sulfate; **FSH** = follicle-stimulating hormone; **HDL** = high-density lipoprotein; **HRT** = hormone replacement therapy; **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **MPA** = medroxyprogesterone acetate; **RR** = relative risk

MISSION STATEMENT

The American Association of Clinical Endocrinologists (AACE) believes that menopause is a state of hormone deficiency that should be treated. Our mission is to ensure that women receive appropriate guidance and medical management during their menopausal years. The purpose of these guidelines is to provide a reference source for the evaluation and treatment of the menopausal state. In the United States, fewer than 30% of the 35 million postmenopausal women currently receive hormone replacement therapy (HRT) (1).

This document consists of recommendations for the clinical management of menopause and is intended for use by physicians to support their treatment of women's reproductive health issues. We recognize that these guidelines should be used in conjunction with the best clinical judgment and the patient's individual needs. These guidelines will be revised and updated periodically to reflect the latest developments in the management of menopause.

AACE believes that, although a multidisciplinary approach is required to care for the menopausal woman, the clinical endocrinologist is the best trained to evaluate the complex hormonal and medical issues in the management of the menopausal woman.

INTRODUCTION

Menopause is customarily defined, for statistical and epidemiologic purposes, as the absence of menses for 1 year. This definition, however, is merely a guidepost in an ongoing process of declining ovarian function, usually beginning by age 35 to 40 years, with the resultant hormone deficiencies causing progressive systemic damage. Menopause is *adult-onset ovarian failure*, with the loss of estrogens, progesterone, and ovarian androgens. The concept that adult-onset ovarian failure is essentially a permanent state of multiple hormone deficiencies is critical to understanding and managing this disorder from an endocrinologically sound perspective.

The loss of estrogens can lead to vasomotor symptoms, sleep disturbances, mood alteration, depression, urinary tract and vaginal atrophy, and increased health risks for several chronic disorders, including osteoporosis, cardiovascular disease, and loss of cognitive function. Thus, both the organic and the psychologic consequences of menopause must be addressed. Although the pathophysiologic changes associated with estrogen deficiency in postmenopausal women are relatively well understood, the effects of the absence of progesterone and decrease of androgens are not fully appreciated.

Perimenopause is a clinically ill-defined interval that begins with sporadic abnormalities or failure of development and function of the ovarian follicles, corpus luteum, or both. It progresses to persistent anovulation, loss of production of progesterone, and erratic secretion of estrogen. The estrogen secretion may be abnormally high or low at different times. The earliest evidence for ovarian failure is a gradual increase in plasma gonadotropin levels, manifesting as early as age 35 years as a minimal elevation of follicle-stimulating hormone (FSH) on day 2 of the menstrual cycle. Diminution of androgen production is also gradual and begins well before menopause. The time of the transition to the recognizable end-stage of failed ovarian hormone production (that is, menopause) is highly variable.

DIAGNOSTIC EVALUATION

The onset of the perimenopausal state and its evolution to complete ovarian failure vary among women. The timing of medical evaluation and intervention is somewhat arbitrary and dependent on the issues that prompt a patient to seek a consultation. The most common symptoms at the time of initial assessment of perimenopausal patients are vasomotor instability, mood swings, insomnia, decreased libido, and cessation of menses or irregular menses, usually associated with shortening of menstrual cycles. Other patients, because of self-education and media exposure, consult a physician to explore their own risk factors and the preventive health issues that HRT can address. Despite these differences in symptoms and issues of interest to the patient, a standard approach should be used for assessment of the menopausal woman.

The initial consultation is not only the time for eliciting the history, performing a physical examination, and ordering appropriate studies but also an opportunity to educate the patient. To make a rational decision about whether to use HRT, the patient must have a thorough knowledge about the benefits and risks of taking sex hormones. In this context, the patient's knowledge, attitude, and perceptions regarding menopause and perimenopause

as well as her ideas about management must be explored to provide diagnostic perspective, reveal biases, and present a basis for optimizing adherence to eventual recommendations.

History

The patient's current symptoms should be carefully assessed. The most common symptoms attributed to menopause in women are vasomotor instability, insomnia, depression, nervousness, dysphoria, asthenia, decreased libido, dyspareunia, palpitations, formications (crawling sensations), mastalgia, paresthesia, myalgia, headache, and arthralgia.

The history should routinely include the following information:

- A detailed chronologic reproductive history including time of menarche, gravidity and parity, history of breast-feeding, gynecologic surgical history, and a detailed menstrual history
- History of hormonal treatment, including contraceptives (orally administered, injectable, or implant), estrogens, progesterone, and androgens
- Detailed sexual history, including frequency of intercourse, ease of arousal, libido, orgasm, and dyspareunia
- Symptoms of pelvic floor relaxation and bladder dysfunction
- Bone or joint pain, arthritis, fractures, and osteoporosis
- Loss of height
- General current and past personal medical history, family history, and social history
- History of achlorhydria and lactose intolerance
- History of weight fluctuations, physical activity, and exercise tolerance
- Quality-of-life assessment, psychiatric history, premenopausal mood disorders, premenstrual dysphoria (for example, premenstrual syndrome), and cognitive functioning
- Family history, especially of early menopause, cardiovascular disease, osteoporosis, cancer, and dementia
- Dietary history with emphasis on intake of sodium, vitamins (especially vitamin D), and calcium
- Medications (for example, corticosteroids)
- Understanding of fears and expectations surrounding menopause

Physical Examination

As part of the comprehensive physical examination, particular attention should be paid to the following:

- Posture (signs related to osteoporotic compression changes), gait (flexibility), muscle tone, coordination, height, and body proportions
- Body mass index, body composition, and waist circumference
- Breast examination
- Pelvic examination, which should include size and shape of the uterus and adnexal structures, evaluation of estrogenic status of the vaginal mucosa, elasticity and thickness of the vaginal wall (discharge, atrophy), integrity of the pelvic floor (cystocele, rectocele), and levator ani function
- Eyesight and hearing acuity (in terms of fracture risk and quality of life)

Laboratory Studies

Baseline serum chemistry studies, including complete lipid evaluation, should be performed. In addition, a thorough hormonal evaluation and other baseline investigations should be undertaken.

Hormonal Evaluation

Gonadotropin levels (FSH) should be determined. The measurement of FSH is the key laboratory test for the diagnosis of menopause. Declining ovarian function, which begins in the late 30s, is associated with gradually increasing FSH levels. In women who are continuing to experience menstrual bleeding, whether cyclically or irregularly, FSH determinations on day 2 to 3 after the onset of bleeding are considered increased when levels exceed 10 to 12 mIU/mL, an indication of diminished ovarian reserve. Menopause is associated with substantially increased FSH levels, usually greater than 40 mIU/mL. In perimenopausal women, however, this FSH elevation is often intermittent, and the absolute value cannot be relied on to establish the true onset of menopause (2,3).

In perimenopausal women treated with hormonal contraceptives, the gonadotropins are often suppressed, and the ovarian status (that is, hormone production or likelihood of ovulation) should be evaluated after discontinuation of the hormonal contraception for several weeks to months. During this time, barrier contraception should be used, and the patient's clinical response should be considered with HRT initiated if vasomotor or other menopausal symptoms are present. Under any circumstance, if FSH levels are considerably increased and estradiol levels are low (less than 30 pg/mL), fertility is unlikely and HRT may be started (see upcoming Therapy section). In women of perimenopausal age with signs of estrogen deficiency and normal or low levels of gonadotropins, prolactin should be measured for the possibility of suppression of production of gonadotropins by hyperprolactinemia.

Estrogen, progesterone, androgen, and thyrotropin levels should also be determined, when indicated. Serum estradiol levels are variable in women with normal menstrual cycles and even more variable in perimenopausal women. Levels may range from very low to elevated, as found in the preovulatory time of the cycle. Single estrogen determinations are seldom useful. More information is obtained from FSH and luteinizing hormone levels. The lateral-wall vaginal smear cytology is of use only for detecting major degrees of estrogen deficiency. These cells are highly sensitive to estrogen, and full keratinization is achieved while other cells, tissues, or systems are still hypoestrogenic. Therefore, cytology is of no value for assessing HRT dosage.

Determination of serum progesterone is of no use in amenorrheic menopausal women. In menstruating

perimenopausal women, documentation of ovulation may be of use.

Determination of serum androgens—specifically, testosterone, free testosterone, and dehydroepiandrosterone sulfate (DHEAS)—is indicated in the presence of symptoms of hyperandrogenism. In menstruating perimenopausal women, androgen levels should be measured during the first week of the follicular phase. The usefulness of androgen determinations in women with diminished libido is controversial (see Androgens and Anabolic Agents).

Measurement of serum thyrotropin is indicated because hypothyroidism is a common and correctable disorder in female patients of this age.

Special Baseline Studies

The following studies may be necessary or useful at the time of initial assessment:

- Papanicolaou ("Pap") smears
- Mammography
- Bone density determinations
- Assessment of endometrium, when indicated
- Pelvic ultrasound screening, when indicated

Pap smears and mammography are routinely indicated in this population. In women who have become amenorrheic, or in perimenopausal women, obtaining a baseline bone densitometry is recommended both for documentation and as a tool for improving compliance. For further follow-up of this aspect, see "AACE Clinical Practice Guidelines for the Prevention and Treatment of Postmenopausal Osteoporosis" (4).

Assessment of the endometrium may be accomplished by biopsy or pelvic ultrasonography. Pelvic ultrasonography should be performed in patients who have abnormal bleeding or a pelvic mass.

THERAPY

Background

HRT is underutilized. Data suggest that poor compliance is common. Even among women who elected to begin HRT, and presumably have derived some benefit from such therapy, there is evidence of poor adherence to recommendations: 20 to 30% of women never fill their first prescription, 20 to 30% discontinue HRT within 6 to 8 months, and only 30% of all menopausal women are regular users of HRT at any one time (1).

The cause of this problem may be manifold, but probably the chief reasons are that women are unconvinced about the need, benefits, efficacy, and safety of HRT. They are concerned about bleeding, cancer risks, and the inconvenience of permanent (usually daily) medication. Many either have not been offered menopausal management by their physician or have had such poor communication that their concerns override the physician's advice. Studies have shown that, even among gynecologists, only one-third prescribe estrogen to most of their menopausal patients (5).

All women should consider HRT not only as essential replacement of missing hormones but also as a type of preventive medicine. The risks and benefits of HRT should be individualized on the basis of quality-of-life considerations and a personal risk assessment, with consideration of cardiovascular, osteoporotic, dementia, and cancer risk factors. Therefore, the mission of the clinical endocrinologist should be to educate women and fill this void relative to the health benefits of HRT and to convey the proper balance of risk-versus-benefit information.

HRT is a choice that each woman must address individually. An appropriate decision can be made only by providing as complete information as possible about the benefits and risks of this treatment option. The overriding principle in counseling the patient is the preventive medicine aspects of HRT—such as preventing osteoporosis, preventing deaths from arteriosclerotic cardiovascular disease, preventing dementia and loss of cognitive function, and preventing cancer deaths—in addition to ameliorating existing symptoms (hot flashes, vaginal dryness, and emotional symptoms).

No consensus exists about when HRT should be instituted. Waiting for symptoms to appear is unacceptable: bone loss and cardiovascular disease, for example, are initially asymptomatic. Menstrual irregularity or luteal-phase deficiency may signal a loss of production of sex hormones. In some women, hot flashes may occur even before menstrual irregularity. In other women, changes of mood and affect may be the first indications of hormonal irregularities. In women in their 40s and 50s who are using oral contraceptives, the problem of age-related loss of ovarian function (natural menopause) will not express itself.

Long-Term Goals

The following are long-term goals of HRT:

- Relief of subjective and objective symptoms
- Prevention of osteoporosis
- Prevention of cardiovascular disease
- Prevention of dementia
- Prevention of carbohydrate intolerance

Prevention of Osteoporosis

The role of HRT in the prevention of osteoporosis has been extensively addressed in a previous AACE publication (4).

Prevention of Cardiovascular Disease

Coronary artery disease (CAD) is the leading cause of death among women in the United States. More than 250,000 women die of a myocardial infarction (MI) annually. Among women older than age 65 years, 30% have some manifestation of CAD. Most women do not recognize cardiovascular disease as a major health concern. Several meta-analyses of observational studies have demonstrated a 35 to 50% lower relative risk (RR) of cardiovascular mortality in HRT users relative to nonusers (6,7).

The mechanisms of estrogen-related cardiovascular protection include the following factors (8): (*1*) improved lipid profile, with increased high-density lipoprotein (HDL) cholesterol, decreased low-density lipoprotein (LDL) cholesterol, and decreased total cholesterol; (*2*) potentiation of endothelium-derived relaxing factor (nitric oxide), leading to coronary artery vasodilatation; (*3*) antioxidant effect on LDL cholesterol, reducing plaque formation; (*4*) reduction of serum fibrinogen; (*5*) calcium channel blocking effect; and (*6*) increased prostacyclin biosynthesis. The beneficial alteration of serum lipids has been estimated to account for only about 20 to 25% of the effect on cardiovascular mortality.

Numerous studies attest to the postponement of the first evidence of CAD in users of HRT (9,10). Furthermore, in postmenopausal women with established CAD, many retrospective studies and several prospective studies (11-13) have found that HRT was associated with a reduced recurrence of MI and CAD deaths. Additionally, in women requiring angiography, arterial narrowing was present in 22% of estrogen users and 68% of nonusers; HRT was associated with an 87% reduction in the prevalence of CAD (14). In women with moderate (5 to 69%) stenosis on angiography, the 10-year survival was 95.6% with HRT and 85.9% without HRT. With stenosis greater than 70%, survival for HRT users was 97% in comparison with 60% for nonusers (15). A more recent study of women after a coronary artery bypass surgical procedure showed a 98.8% 5-year survival and 81.4% 10-year survival with HRT, in contrast to 82.3% and 65.1%, respectively, without HRT (15). Similar results were found in women who underwent angioplasty (16).

In contrast, a large, randomized, placebo-controlled study (the Heart and Estrogen/Progestin Replacement Study or HERS trial) of HRT for the prevention of recurrent CAD (17,18) found no beneficial effect of a commonly used HRT regimen during a 4-year period, with respect to nonfatal MI and CAD deaths. Because of the nature of the atherogenic process, no benefit was expected during the first 2 years. In fact, an increased RR of 2.3 was noted during the first 4 months of HRT, 1.46 during the second 4 months, and 1.18 during the third 4 months (overall, 1.52 for the first year). The RR declined to 1.0 during the second year, 0.88 during the third year, and 0.67 during the fourth year. These RRs are not statistically significantly different, but the trend is (P = 0.009 for trend in log relative hazard). In any event, no evidence was seen of a statistically significant beneficial effect of HRT over 4 years.

This group of women had important CAD characteristics: (*1*) the mean age was 67 ± 7 years, about 2 decades postmenopausal; (*2*) major obesity was present (body mass index >27 in 57%); (*3*) 24% were in fair or poor health (10% died before the end of the fourth year); (*4*) 13% were current smokers; and, most importantly, (*5*) 87% had undergone a coronary artery bypass operation or percutaneous arterial revascularization procedure. Up to 78% were using some cardiovascular medication.

The difference between the results of this randomized, placebo-controlled study, which showed no benefit of HRT on preexisting CAD, and the numerous other observational studies that have shown very large decreases in RR remains speculative. Barrett-Connor and Stuenkel (19) recently discussed this controversy.

Prevention of Dementia

Dementia (loss of intellectual functioning) affects 10% of women older than 65 years and 50% of women older than 85 years. Alzheimer's disease is 2 to 3 times more likely to develop in women than in men. The risk of developing Alzheimer's disease is 50% lower in ever-users than in nonusers of HRT (RR −0.5) (20). This effect crosses genetic phenotypes and socioeconomic class; however, lower biologic intelligence increases the risk for Alzheimer's disease. A meta-analysis of the observational studies of the effect of estrogen therapy on the risk for developing dementia did support a 29% decreased risk among estrogen users (21). If validated by scientific studies, the risk reduction would be of major public health importance.

Prevention of Carbohydrate Intolerance

Various studies have shown that HRT is associated with a decrease in the likelihood of developing diabetes by a factor of nearly 5, improves blood glucose control, and is associated with a decrease in the risk of MI in women with diabetes (RR = 0.51; 95% confidence interval [CI], 0.22 to 1.15 overall and RR = 0.78; 95% CI, 0.56 to 1.08 per year of HRT use) (22).

Theoretically, devising a therapy that provides hormonal effects in certain sites (for example, the urogenital tract) and avoids others (such as unwanted stimulation of breast or endometrial tissue) may be advantageous. Nevertheless, focusing on a particular therapeutic outcome, such as arrest of bone loss, to the exclusion of other hormonal deficiency states, which might require different levels of therapeutic intervention, is to ignore the basic philosophy underlying the optimal management of the menopausal woman. Clearly, because the hormonal deficiencies are permanent, replacement therapy must be permanent also. Although accurate monitoring techniques to determine the adequacy of a specific dose of estrogen on target tissues in individual patients are not available, the goal of therapy is to use doses of estrogen sufficient to treat symptoms as well as prevent bone loss, lower cardiovascular risk, and prevent dementia.

Hormone Replacement Therapy

In a woman with a uterus, HRT must include an estrogen and a progestational agent because the use of estrogen alone can produce endometrial hyperplasia or carcinoma (or both). In the absence of a uterus, a progestational agent is unnecessary.

Estrogens

The following are the most commonly used estrogens:

- Conjugated equine estrogens
- Esterified estrogens
- Estropipate and other estrone sulfate preparations
- Micronized 17β-estradiol
- Ethinyl estradiol
- Transdermal estradiol patches (various brand names)
- Vaginal estrogenic preparations including a vaginal ring

In addition, other available preparations such as estrogen pellets, gels, creams, intranasal sprays, or injections (for example, Depo-Estradiol) have been used. The major differences among these formulations are in the mode of absorption and the pharmacokinetics. Few, if any, clinically significant *qualitative* differences exist between free and conjugated estrogens.

The oral and transdermal routes are the most frequently used. Patient acceptance and prior experience are the major factors in determining the preferred route of delivery. The oral route is distinguished by first-pass enterohepatic removal of a substantial fraction of the estrogen, followed by hepatic metabolism and conjugation to sulfates and glucuronides, which are then excreted through the bile back into the digestive tract. Here the sulfates are deconjugated to some extent and reabsorbed. All drugs subject to the first-pass effect show greater interindividual variability in the blood levels attained. This finding is true of the estrogens—a fact that is of considerable clinical relevance. Furthermore, the high concentrations of estrogen delivered to the liver by the oral route (in comparison with transdermal absorption directly into the peripheral circulation) induce increased synthesis of triglycerides and certain proteins such as cortisol-binding globulin (transcortin), sex hormone-binding globulin, and angiotensinogen. Therefore, transdermal estrogen is preferred in certain clinical situations, such as in women with hypertension, hypertriglyceridemia, and a history of or increased risk for cholelithiasis.

Vaginal administration of estrogen has been used for treatment of vaginal atrophy. Of note, this treatment has more than a local effect. Estrogens are readily absorbed through the vaginal mucosa and result in appreciable blood levels of estrogen.

The dosage of estrogen used to initiate HRT should be individualized because it is strongly dependent on age of the patient and various other factors. In a reproductive-age woman who has had recent bilateral oophorectomy, a larger dosage of estrogen (for example, orally administered micronized estradiol, 2 to 4 mg/day; equine estrogen, 1.25 to 2.5 mg/day; or ethinyl estradiol, 0.02 to 0.05 mg/day) is required than for a woman who has been amenorrheic and symptomatic for a long time (for example, orally administered micronized estradiol, l to 2 mg/day; transdermal estradiol, 0.05 to 0.1 mg/day; equine estrogen, 0.625 to 0.9 mg/day; or ethinyl estradiol, 0.01 to 0.02 mg/day). A patient who has been deprived of estrogens for years is likely to be too sensitive to the usual dosages and should initially receive even lower doses than those used for maintenance therapy. The desired effects of therapy manifest themselves slowly (for example, autonomic symptoms may begin to subside in a week or 2, whereas alleviation of dyspareunia may take months). In this situation, *one dose does not fit all*. Moreover, few dose-response data are available to help determine the optimal (or minimal) dosage to provide cardiovascular protection. Protection against bone mineral loss is clearly dose-dependent, and each patient should be appropriately monitored to determine the adequacy of an administered dose of estrogen.

Measurement of serum FSH levels cannot be used to monitor the adequacy of the estrogen doses the same way that thyrotropin levels are used to monitor the adequacy of doses of thyroid replacement therapy. Use of this determination is inappropriate because estrogen is not the only regulator of FSH secretion; inhibin also has a role. FSH levels may remain increased despite adequate estrogen effect on the target tissues.

Progestins

After a hysterectomy, progestins are unnecessary. In a woman with an intact uterus, the endometrium must be protected against hyperplasia and possible progression to dysplasia and carcinoma by the use of progestational agents. Side effects of progestational compounds are difficult to evaluate and will vary with the progestational agent administered. Some women experience premenstrual-tension-like symptoms, including mood swings, bloating, retention of fluids, and sleep disturbance. Switching among various progestational agents may decrease these symptoms. Studies of the effect of progestational agents on lipids have reported conflicting results. Lipid profiles should be monitored to determine individual risk.

The classic regimen consists of 5 to 10 mg of medroxyprogesterone acetate (MPA) used for 10 to 14 days each month. Levonorgestrel, norethindrone, or micronized progesterone can also be used for this purpose. Cyclic administration of the progestin usually produces monthly menstrual periods. Because persistent menstrual bleeding is often cited as the major reason for noncompliance with HRT, amenorrhea may be achieved by using a low dose of a progestin administered continuously (daily) in conjunction with estrogen. Many women, however, will continue to experience episodes of breakthrough bleeding. Alternatively, a progestin can be administered at 2-, 3-, or 6-month intervals and still prevent endometrial hyperplasia. This nonconventional use of progestins requires careful monitoring of the endometrium with ultrasonography and endometrial biopsy.

Micronized progesterone has been shown to be an effective alternative to MPA in dosages of 100 to 200 mg daily; reported outcomes have included <1% incidence of hyperplasia and improved lipid profiles (23). Some women will experience unacceptable side effects from all oral forms of progestogens. A new vehicle for transvaginal progesterone with improved absorption characteristics with use of a bioadhesive gel may achieve adequate endometrial management with fewer side effects. No studies have as yet described the utility of this progesterone

preparation in HRT for menopausal patients, but it has proved effective in treating infertile women to maintain luteal-phase endometrial integrity for embryo implantation. In addition to menopausal HRT, a progestin can be used for luteal-phase supplementation in perimenopausal patients with irregular menstrual cycles. This treatment protects against endometrial hyperplasia and certain bleeding problems.

The "19-nor" progestins, norethindrone (0.35 mg) and levonorgestrel (0.075 mg), are available as pure progestins (that is, without concomitant estrogen). These agents can be used in place of MPA if endometrial management is unsatisfactory or intolerable side effects develop. Whether any one type of progestin has advantages over another type is unclear. Some patients, however, experience considerable clinical differences and therefore prefer one progestational agent over another.

Other 17-acetoxy progesterone derivatives, besides MPA, are in current use and are potent by oral administration: megestrol and cyproterone. The use of megestrol in the United States has been predominantly in the treatment of neoplasms that have progesterone receptors, such as endometrial carcinoma. In selected patients, megestrol can be an effective treatment of vasomotor symptoms (24).

In menopausal and postmenopausal women whose autonomic symptoms (hot flashes and sweats) are not relieved by tolerable doses of estrogen, supplemental clonidine (0.1 mg or more at bedtime or the transdermal patch), Bellergal (a combination of ergotamine, belladonna alkaloids, and phenobarbital), or fluoxetine or a similar selective serotonin reuptake inhibitor can be used. In addition, Depo-Provera, a microcrystalline suspension of MPA, can be used in special circumstances, as for selected menopausal patients with breast cancer. In these instances, an injection of the contraceptive Depo-Provera formulation (150 mg) or 0.33 mL of the 400 mg/mL formulation (not a contraceptive formulation) is likely to produce dramatic effects within a week. The relief may be permanent or may necessitate repeated injections every 2 to 5 months. This regimen is extremely well tolerated. In rare instances, however, certain patients may have subjective intolerance of all progestins.

Low-dose oral contraceptives are widely used in perimenopausal women to regulate menses as well as to control fertility. Early concerns about increased cardiovascular risk in women older than 35 to 40 years of age have disappeared under critical scrutiny of the early epidemiologic studies and with the accumulation of a very large experience with oral contraceptives containing 30 to 35 μg of ethinyl estradiol. There is no upper age limit for the use of these formulations. They are being used more frequently in postmenopausal women because of better control of menstrual bleeding in comparison with the aforementioned regimens. Women with long-term estrogen deprivation may find these estrogen doses excessive, resulting in mastalgia, bloating, or weight gain. Accordingly, formulations with 20 μg of ethinyl estradiol have been marketed. These formulations are better tolerated by many women but have the disadvantages that intermenstrual bleeding and less abbreviated menstrual flow are more likely to occur than with higher dose regimens, especially with medication omissions leading to breakthrough bleeding. Worldwide experience has shown that the higher bioavailability and longer half-life of levonorgestrel in comparison with norethindrone or its acetate tend to minimize bleeding problems. Comparative studies will be necessary to determine whether this advantage prevails with the 20-μg formulations.

Perimenopausal women using oral contraceptives are generally content to experience cyclic menses, but the alternative of less-than-monthly menstrual cycles is often preferred. Cycle control with contraceptive formulations is such that, eventually, two or three 21-day packages administered back-to-back can be used; the result will be 49- or 70-day cycles, with little or no intermenstrual bleeding. In some women, both perimenopausal and postmenopausal patients, the 7-day interval off hormones is too long, and hypoestrogenic symptoms such as hot flashes and headaches will occur. In such cases, the off-medication interval should be shortened to 5 or even 4 days. Because the endometrium is typically involuted by the oral contraceptive regimen, bleeding is likely to be short and scant. Alternatively, a small dose of estrogen (for example, 0.0375-mg estradiol patch) can be added to the oral contraceptive regimen. When properly explained, this regimen can be seen as a convenience and a benefit.

Women have been exploring complementary and alternative medicine to treat menopausal disorders because of the doubts and concerns surrounding HRT. Reportedly, one in three menopausal women in the United States used alternative medicine therapy in 1990, despite the lack of scientific studies to support the use of various herbs and botanicals rather than HRT. Recommendations for the use of these compounds should be deferred.

Androgens and Anabolic Agents

Does an androgen-deficiency state exist in postmenopausal women? The menopausal ovarian stroma continues to produce testosterone and androstenedione in response to increased pituitary gonadotropin stimulation. With advancing age, however, adrenal androgen production gradually declines. Bilateral oophorectomy in premenopausal, perimenopausal, or postmenopausal women leads to approximately 50% reduction of testosterone levels. The initiation of HRT leads to a suppression of gonadotropins and a decrease in ovarian androgen production. In addition, estrogen stimulates the production of sex hormone-binding globulin and thereby leads to decreased free testosterone. Therefore, menopausal women receiving HRT have a loss of androgen effect in comparison with the premenopausal state. Sexual dysfunction, loss of libido, depression, decreased energy, and other symptoms have been attributed to the loss of androgen production (25). Androgen therapy has been prescribed to alleviate these symptoms, even though the psychologic effects of testosterone are poorly documented. In general, however, clinical studies have not supported the effect of androgen therapy on these symptoms. Observational and cross-

sectional studies of postmenopausal women have generally failed to demonstrate a correlation between circulating androgen levels and libido. A recent 4-year longitudinal study that involved surveillance of 201 women who were 48 to 58 years old concluded that sexual functioning was unaffected by age or endogenous hormone levels (26).

Blinded, crossover studies of premenopausal oophorectomized women given estrogen, testosterone, or estrogen + androgen (27,28) showed significantly better results with respect to climacteric symptoms and sexual functioning (29) with use of the combination of estrogen + androgen than with the other regimens or placebo. The intramuscular dosage, however, produced supraphysiologic levels of total testosterone (111 to 133 ng/dL); thus, questions about its therapeutic relevance are raised.

Autonomic symptoms not responding to customary doses of estrogen (and which also may not respond to clonidine or Bellergal) have, in blinded, placebo-controlled trials (30,31), benefited from estrogen + androgen combinations; the trade-off with simply increasing the estrogen dose is an individual decision. The orally administered progestins and particularly the injectable MPA (Depo-Provera) are powerful in suppressing symptoms such as sweats and hot flashes, and they represent a nonandrogenic alternative.

Androgens have a role in the prevention of bone loss. A negative correlation exists between bone density and sex hormone-binding globulin, and a positive correlation has been noted between bone density and free testosterone (32). A study of bone markers (33), including urinary deoxypyridinoline and hydroxyproline, osteocalcin, and bone-specific alkaline phosphatase, found that estrogen alone produced a reduction of the bone-formation markers osteocalcin and bone-specific alkaline phosphatase, whereas with estrogen + androgen, all markers of bone formation increased. Davis et al. (34) found significantly greater increases in bone mineral density with use of estradiol + testosterone implants over estradiol alone, but the androgen dosage was supraphysiologic, although patients showed a net decline in total cholesterol and LDL. These findings must be interpreted in light of the other therapeutic options available for the management of bone mineral problems, as addressed previously by AACE (4).

Many studies, blinded and placebo-controlled as well as observational (29,30,35,36), have reported better results in restoring sexual function, particularly libido, with estrogen + androgen than with estrogen alone. The doses administered (usually by implants or injections), however, produced testosterone levels that were multiples of the physiologic range, and side effects of acne, hirsutism, and voice deepening can occur (28) under these circumstances.

When the treatment of sexual dysfunction with androgens is being considered, the premenopausal sexuality of the couple and current marital issues should be evaluated. Physical and psychologic disorders can contribute to sexual dysfunction. In addition, HRT should be optimized because dyspareunia and other climacteric symptoms can adversely influence sexual function.

The androgen preparations commonly used include methyltestosterone, parenterally administered testosterone (injections), transdermal patches, and orally administered micronized testosterone as well as DHEAS. The most widely used oral androgen formulation is methyltestosterone. The 17-alkylated androgens have met with disfavor because, when used in large doses, they have produced hepatotoxicity. No evidence has been found that the doses of methyltestosterone used in HRT (1.25 to 2.5 mg/day) produce hepatic malfunction (37). This compound is available by itself or in fixed combinations with various estrogens.

Micronized testosterone for oral use (2.5 to 5.0 mg in vegetable oil capsules) must be given in substantial amounts; the resultant increases in serum testosterone levels are variable, and no data are available on bioavailability, therapeutic benefit, or side effects. Sublingually administered testosterone (cyclodextrin) potentiates transport across the oral mucosal membrane; although good bioavailability has been reported, no adequate clinical studies have been conducted. Other testosterone products include testosterone gels and creams in a water-soluble base, which provide approximately 10% of the oral dose and have variable absorption.

A transdermal matrix testosterone patch under development for women can achieve physiologic testosterone levels. Clinical studies achieving physiologic replacement levels of testosterone may answer the issue of the efficacy and importance of menopausal androgen replacement therapy (38).

DHEAS has been proposed as a source of androgen. This adrenal steroid, not classified as a prescription drug, is available in health food stores in doses of 25 to 100 mg per tablet. The bioavailability of DHEAS is poor, and tablets from different manufacturers have different bioavailability. DHEAS can be converted to testosterone, and the dosage can be monitored by plasma testosterone determinations (39). No clinical data are available on the effectiveness of DHEAS on libido or sexual functioning; therefore, no recommendations can be made about its value in HRT.

In general, side effects of excessive androgen therapy, including seborrhea, acne, hirsutism, alopecia, and (in extreme cases) voice changes and clitoral hypertrophy, are dependent on the dose, duration, and individual patient. Androgen may alter the HDL/LDL ratio by lowering HDL levels. The side effects are more frequent with intramuscularly administered testosterone compounds.

Androgen replacement has been practiced as long as estrogen replacement (40). Today, four general groups of women are considered candidates for estrogen + androgen therapy: (*1*) women who have had their ovaries removed; (*2*) those who have not experienced relief of vasomotor symptoms with a maximally tolerable dose of estrogen; (*3*) those at risk for osteoporosis in whom other modalities are not satisfactory or suitable; and (*4*) those with unsatisfactory sexual function, especially loss of libido. Because no consensus exists about the use of androgen therapy, the

potential benefits and risks should be explored for each patient (41).

Adverse Effects

Various adverse effects of HRT are described in the Food and Drug Administration-mandated patient information leaflet. Many side effects are well recognized and simple to manage by a change in the dosage, the route of administration, or the prescribed estrogen.

There is a small but statistically increased risk of thromboembolism (estimated at 3/10,000 per year), usually occurring within the first year of therapy, that applies to all forms of estrogen (42). Women who have had documented deep vein thrombophlebitis or pulmonary embolism in the past should, most probably, not be prescribed any form of HRT.

In women who use orally administered estrogens, a statistically increased risk of cholelithiasis has been found.

The risk of endometrial cancer due to prolonged use of "unopposed" estrogens (that is, without progestins) should no longer be an issue. Current therapeutic regimens adding progestins to the estrogen therapy (continuously or intermittently) have essentially reduced this risk to somewhat less than the spontaneous occurrence of endometrial cancer in nonusers of HRT. Nevertheless, monitoring of the endometrium by transvaginal ultrasound study or endometrial biopsy is indicated, especially in women who have an abnormal bleeding pattern.

Endometrial effects (both estrogenic and progestational) are best evaluated by endometrial biopsy, a simple, infrequently painful, in-office procedure with modern cannulas. The endometrial end point of progestational therapy is the absence of hyperplasia. The histologic findings of secretory, proliferative, or atrophic endometrium are sufficient evidence of endometrial protection. Alternatively, the endometrial effects of HRT can be estimated by transvaginal ultrasound measurement of endometrial thickness. In many studies that have correlated endometrial thickness and risk of endometrial hyperplasia or neoplasia, an endometrial thickness of 5 mm or less has constituted virtually no risk (43). In the case of women receiving HRT who do not tolerate progestational compounds, and in whom repeated endometrial biopsies become unacceptable, transvaginal ultrasonography is an important option.

The issue of increased risk of breast cancer is a major factor in nonuse or nonadherence to HRT recommendations. Although the issue is unlikely to be resolved for a variety of reasons, women should know that of 55 observational studies of this question between 1974 and 1996, 90% failed to demonstrate an increased risk of breast cancer. For each study that shows a statistically significant increased risk with duration of use, a comparable published study does not come to this same conclusion.

In 1997, the Oxford Group (44) reanalyzed the actual data sets from about 90% of the worldwide published (and two unpublished) studies on this issue. RRs and 99% CIs were calculated. Among the studies included in the meta-analysis that demonstrated the strongest statistical power were 6 prospective studies, 10 data sets of case-control studies with population controls, and 6 data sets from case-control studies with hospital controls. None of these studies yielded results that reached statistical significance based on a 99% CI that included 1. Nevertheless, calculation of the overall data showed an RR of 1.023 (99% CI, 1.011 to 1.036). Therefore, the findings drawn from the meta-analysis demonstrating an increased risk of breast cancer in estrogen users may not be conclusive and may be open to questions of statistical inaccuracy.

The Oxford Group (44) also concluded that this statistically significant risk increases with the duration of use, especially long-term use, and disappears after 5 years of nonuse. Nevertheless, several other investigators, including Newcomb et al. (45), have failed to find such an increase with duration of use.

Clinical studies evaluating estrogen and breast cancer mortality have demonstrated a significant decrease in death rates from breast cancer in estrogen users. An American Cancer Society 9-year prospective follow-up documented a 16% reduced risk of fatal breast cancer (46). A National Cancer Institute study (47) examined breast cancer mortality among women who were diagnosed with axillary lymph node-negative and node-positive breast cancer according to the currency of estrogen use at diagnosis. Patients with breast cancer who were using replacement estrogens at the time of diagnosis had lower breast cancer mortality than did those who were not. Reduced breast cancer mortality in current estrogen users at the time of diagnosis was also reported in the Iowa Women's Health Study (48).

The occurrence of breast cancer after exposure of male-to-female transsexual individuals to estrogen has rarely been reported (49).

Sellers et al. (50) found no influence of a family history of breast cancer on HRT users. Finally, no study of breast cancer recurrence has shown any effect from a pregnancy (with its enormous estrogen output) after primary treatment of the cancer. These observations have led to a reappraisal of the use of HRT in breast cancer survivors, with several large multicenter studies under investigation.

The role of alcohol consumption in relationship to the possibly increased risk of breast cancer in estrogen users has been receiving increased attention. When the data from the Nurses' Health Study were reevaluated for alcohol consumption, the increased incidence of breast cancer was limited to those estrogen users who consumed substantial amounts of alcohol (51).

The Women's Health Initiative, an ongoing randomized study of HRT with more than 27,000 participants, is designed to provide definitive answers to the question of breast cancer risk with HRT. The important factor for the patient to understand is the benefit-to-risk appraisal. Several decision analyses that considered the worst-case estimate of breast cancer risk affirmed that the benefits outweigh the risks (52,53). This examination of the risk-to-benefit issue is the heart of the endocrinologist-patient educational relationship and must be individualized for

each patient. Mortality from all causes is diminished with HRT to a degree that outweighs the worst-case estimate of an increase in breast cancer mortality.

In addition to the aforementioned adverse effects, systemic lupus erythematosus and Raynaud's disease can be exacerbated by HRT. Meier et al. (54) found an increased RR of 2.8 (95% CI, 0.9 to 9.0) for the development of systemic lupus erythematosus in patients with 2 years or more of HRT. Fraenkel et al. (55) reported an RR of 2.5 (95% CI, 1.2 to 5.3) for estrogen users and an RR of 0.9 (95% CI, 0.3 to 1.6) for HRT users for the development of Raynaud's phenomenon.

Contraindications

A history of breast or uterine cancer is still the main contraindication to HRT, except in special circumstances (for example, ongoing investigational studies). The conventional prohibition against HRT in survivors of breast and endometrial cancer is currently being reexamined.

Previous venous thromboembolism is a relative contraindication to use of HRT, but the reality of the thrombotic event must be evaluated. The clinical diagnosis, without definitive testing, is incorrect in more than 50% of cases, and many "silent" events are not clinically recognized. In some instances, evaluation of coagulation factors such as activated protein C resistance, Leiden factor, protein S, or antithrombin II may be justified.

Undiagnosed genital bleeding necessitates diagnostic evaluation before initiation of HRT. Unexpected uterine bleeding or spotting during HRT is common and is managed by appropriate changes in therapy, not by discontinuation of HRT. Diagnostic procedures such as endometrial biopsy or ultrasonography were outlined earlier in this report.

Gallbladder disease may be increased by orally administered estrogens; however, estrogens may be beneficial in chronic active hepatitis (56). Previous hepatic disease is not an evidence-based contraindication. Previous jaundice of pregnancy may be a warning of possible adverse effect.

Hypertension may be aggravated or reduced by HRT. If aggravated, the result of withholding further HRT should be evaluated, and the effect of reinstitution should then be observed. Transdermal estrogen may be the preferred route of administration; it avoids first-pass hepatic effects and the resultant production of angiotensinogen.

Migraine and other *headaches* may be alleviated or worsened. The appropriate clinical maneuvers (withholding and then restoring HRT for assessment of effects) should be instituted. Estrogen-deprivation headache, caused by rapidly varying levels of serum estrogen as occurs with skipping doses, should be recognized when it occurs.

Uterine fibroids are rarely stimulated by the doses of HRT currently prescribed.

Patient Compliance

Adherence of the patient to treatment recommendations remains the Achilles heel of HRT. It is fundamentally dependent on the physician-patient dialogue, as outlined in the following 10 basic principles of menopause management:

- Recognize that menopause causes a permanent deficiency of estrogen.
- Understand the system, organ, and tissue consequences of this deficiency.
- Appraise the benefits and risks of the treatment options.
- Educate women about the nature and consequences of permanent estrogen deficiency.
- Engage in interactive discussions about the benefits and risks of therapeutic intervention. Provide printed materials and, if possible, videotapes to reinforce the verbal information. Address specifically the issue of breast cancer, which is uppermost in many women's minds.
- Implement an acceptable course of action.
- Evaluate promptly the real and perceived consequences of the intervention.
- Reevaluate the real and perceived benefits as well as the disadvantages and risks at regular intervals.
- Be aware of and discuss information and misinformation patients may have received through such sources as media reports, advocacy groups, and well-meaning friends.
- Raise the level of information, concern, and involvement in the medical community.

The low percentage of menopausal women electing to use HRT and the poor compliance of those using HRT seem to indicate that women are unconvinced about the need, benefits, efficacy, and safety of HRT. They are concerned about bleeding, cancer risks, and the inconvenience of long-term treatment. Women must be educated to understand that HRT is a permanent commitment, similar to thyroid treatment in hypothyroidism or insulin in type 1 diabetes mellitus, and that cessation of use results in rapidly accelerated bone loss, loss of cardiovascular and cognitive protection, and genitourinary atrophy. The range and degree of benefits, obvious and implicit, must be clarified for the patient.

Management When HRT Cannot Be Used

Alternatives are available when HRT is contraindicated or not tolerated. Some options are discussed in the following paragraphs.

Selective estrogen receptor modulators have a selective estrogen-like activity on some tissues and antiestrogen activity on other estrogen-responsive tissues. Raloxifene has been approved for the prevention and treatment of osteoporosis in postmenopausal women. In the Multiple Outcomes of Raloxifene Evaluation (MORE) study (57,58), approximately a 50% reduction in vertebral fractures was noted at 24 months and a 40% reduction at 36 months in women with osteoporosis. The study was not statistically powered to assess hip fracture. Like estrogen, raloxifene lowers LDL levels; however, unlike estrogen, raloxifene does not increase total HDL levels or triglycerides. Cardiovascular disease prevention trials are

currently being conducted (for example, the RUTH trial—Raloxifene Use for the Heart) to determine whether raloxifene reduces the risk of cardiac events. Early studies (59) suggest that raloxifene may significantly reduce the risk of breast cancer. A comparison study with tamoxifen is under way to analyze these findings further. Unlike tamoxifen, raloxifene does not stimulate the endometrium and can be used by itself in menopausal women with an intact uterus. Raloxifene does not relieve hot flashes and, in fact, may increase their occurrence; therefore, it will not benefit perimenopausal women with vasomotor symptoms. The incidence of deep venous thrombosis associated with use of raloxifene is similar to that with estrogen; thus, raloxifene is contraindicated in women predisposed to deep venous thromboses.

Phytoestrogens may act as selective estrogen modulators and are currently being studied.

Among osteoporosis-specific medications, alendronate is a bisphosphonate that has been shown to decrease significantly the risk of osteoporotic fractures in the hip and spine. In the Fracture Intervention Trial (FIT) (60), a 40 to 50% decrease in spine, hip, and wrist fractures was noted at 3 years in women with previous fractures given alendronate (61).

Calcitonin is available in nasal spray form for treatment of osteoporosis. In the current Prevent Recurrence of Osteoporotic Fractures (PROOF) Study, a 37% reduction in vertebral fractures was noted at 5 years in postmenopausal women with osteoporosis (62).

In general, sufficient calcium, vitamin D, and exercise are important factors in helping to maintain bone density. Exercise is also important for maintaining muscle tone and helping to reduce the risk of falling. For a further discussion on the prevention and treatment of osteoporosis, the AACE Osteoporosis Guidelines (4) are a useful resource.

CONCLUSION

In the use of these guidelines to assess and manage perimenopausal and menopausal women, the primary goal of the endocrinologist should be to inform the patient as completely as possible about the benefits and risks of HRT. Although HRT is preventive medicine at its best, its use—like all issues in preventive medicine—is elective. Menopausal women will comply with HRT if they are confident in their decision, receive continued support and encouragement for adherence, and accept the potential adverse effects and risks as minor in comparison with the benefits.

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