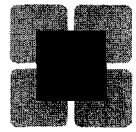

Estrogen supplements in menopause

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■ The number of women aged 65 and older is expected to double by the year 2000, increasing the need for effective management of symptoms related to menopause. Contemporary management of menopause addresses the continuum of events associated with the effects of estrogen deprivation on quality and duration of life, including neuroendocrine changes, urogenital atrophy, sexual dysfunction, skin and hair changes, osteoporosis, and cardiovascular disease. The risks and benefits of management strategies, including hormone replacement therapy, must be weighed carefully by both physician and patient. The use of estrogens and progestins, alternative compounds, dosages, routes of administration, and their advantages and disadvantages must be analyzed.

□ INDEX TERMS: HYPOGONADISM; MENOPAUSE □ CLEVE CLIN J MED 1990; 57:154–160

TODAY, women who are alive at age 50 can expect to live another 36 years, to age 86; women still healthy at age 52 can expect to live to age 91. Although life expectancy for women has increased by 30 years since the turn of this century, to 78.2 years,[1] the average age of onset of menopause—51 1/2—has not changed significantly. One-sixth of the United States population consists of postmenopausal women, and the number of women aged 65 and older is expected to double by the year 2000. This trend will manifest itself in clinical practice with a growing proportion of patients who need management of symptoms related to menopause.

DEFINITION

Menopause begins with the last menstrual period. We can view menopause as a natural phenomenon and argue that an event which occurs in all women, if they live long enough, should not be considered abnormal. We could pose the same argument with diabetes or any other naturally occurring event.

Menopause is the endocrine deficiency disorder of adult-onset hypogonadism. Morphologic and functional changes in the ovary during menopause lead to definitive changes in overall circulating hormone levels. Tissues responsive to specific ovarian hormones undergo changes that result in menopausal symptoms. Premenopausal removal of the ovaries produces these same changes on a permanent basis and replacement of ovarian hormones reverses the symptoms. The climacteric syndrome fulfills these postulates of an endocrinopathy.[2]

Menopause occurs because women outlive their reproductive systems, with decreased ovarian production of estrone and estradiol and depletion of ovarian follicles. The maximum number of primordial ovarian follicles—approximately 7 million—is reached at about 20 weeks gestation. This quantity decreases to about 2 million at birth and only about 300,000 oocytes remain at puberty. Approximately 1,000 oocytes are lost with each menstrual cycle and a minimal number remain at menopause. Histology of the premenopausal ovary re-

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veals multiple follicles, whereas after menopause, only ovarian stroma remains.[3]

ENDOCRINOLOGY

The postmenopausal hormonal profile reveals elevated gonadotropic hormones. These are released in an attempt to drive ovaries that are no longer responsive. There is loss of cyclic ovarian production of estrogens and progesterone,[4] an absolute decrease in total estrogen production, and increased conversion of androstenedione to estrone with reversal of the estrone/estradiol ratio. Elevated levels of luteinizing hormone stimulate increased production of testosterone by ovarian stroma. The progressive decrease in estrone and estradiol leads to neuroendocrine changes, urogenital atrophy, skin and hair changes, osteoporosis, and increased cardiovascular risk. Ovarian and adrenal testosterone induce androgenic effects related to skin and hair changes and cardiovascular risk. Ovarian and adrenal androstenedione is converted peripherally to estrone and testosterone; these are ultimately converted to estradiol, but the dominant circulating hormone in postmenopausal women is estrone. There is also a decrease in sex hormone binding globulin which is significant in androgen-excess skin and hair disorders.

Menopause is a continuum of events. Early changes associated with vasomotor instability and other neuroendocrine changes are the only events that will resolve. All other changes have a period of latency and then continue for the remaining years of life.

Neuroendocrine changes

Neuroendocrine changes precipitate vasomotor instability in approximately 85% of perimenopausal women. Hot flushes continue beyond 5 years in 45% and for 10 years or more in 5% of postmenopausal women.[5] Hot flushes can be disruptive, with decreased job performance in 10% of affected women. Neuroendocrine studies have identified specific neurotransmitter substances related to altered sense of well-being, sleeping disorders, and psychological changes.[6] Menopausal hormone replacement therapy controls these changes effectively in most women.

Urogenital atrophy

Urogenital atrophy is a direct result of inadequate estrogen that leads to vulvovaginal dryness and discomfort as well as urinary frequency, urgency, and incontinence.[7] Dyspareunia and sexual dysfunction can evolve.[8] These symptoms respond well to low-dose systemic hormone replacement therapy and local vaginal estrogen, but treatment must be long-term.

Androgen-excess skin and hair disorders

Skin and hair changes are associated with inadequate estrogen and relative androgen excess.[9] Thinning of skin with dryness, itching, friability, and loss of elasticity are consequences of inadequate estrogen; androgen-excess alopecia and hirsutism are related to dominance of testosterone.[10] Other androgen effects include redistribution of body fat, tendency to gain weight, and deepening of the voice. The ovarian stroma produces approximately one half of testosterone in postmenopausal women, so women who have undergone ovariectomy have fewer androgen-excess problems.

Osteoporosis

Osteoporosis is epidemic in the United States today.[11,12] The marked decrease in use of estrogen about 15 years ago because of fear of endometrial cancer may be an associated factor. Nearly half of the 40 million women in the United States over age 50 have some degree of osteoporosis and suffer 1.3 million fractures per year at a cost of $7-8 billion. Hip fractures alone occur in about 240,000 women with an annual mortality in excess of 40,000 and cost greater than $4 billion. This is comparable to the mortality rate from breast cancer.

Electron microscopy of osteoporotic bone shows that the internal matrix of trabecular bone is lost.[13] Given that regeneration is impossible with presently available therapy, the recent Osteoporosis Study Group concluded that prevention is the only humane and cost-effective treatment.[14] Hormone replacement therapy combined with calcium and exercise will arrest the progression of osteoporosis in most women.[15] Hormonal therapy is continued for 10 to 15 years, depending on the age of menopausal onset, but usually not beyond age 70. Bone density is maintained in women who receive hormone replacement therapy but decreases progressively in controls.[16,17]

Clinical parameters identify women at risk for osteoporosis and bone densitometry is helpful for definitive diagnosis and management.[18] Approximately 25% to 30% of women are high-risk and must be identified and maintained on hormone replacement therapy.[19] Low-risk women do well with calcium and exercise alone but this management will not prevent osteoporosis in women at increased risk.[20]

Calcium absorption decreases with age, so oral intake must increase as women grow older. A total dietary calcium intake of 1200 mg per day is recommended before

age 55 and 1500 mg per day thereafter.[21]

Cardiovascular disease

Osteoporosis has profound significance, but cardiovascular disease is by far the leading cause of death in women in the United States.[22] Cardiovascular disease accounts for 355,000 deaths annually, compared to 40,000 from osteoporotic hip fractures. Premenopausal women are at low risk of cardiovascular disease. The annual mortality in this group—1.3 cardiovascular deaths per 1,000—is less than one third that of men in age matched groups.[23] With the onset of menopause, cardiovascular mortality increases approximately 18 times while cardiovascular mortality in men during the same time interval increases only fivefold.[24] Estrogen thus appears to have a significant cardioprotective effect. Studies supporting this impression include the large Boston Nurses' Health Study,[25] which concluded that women who had ever used estrogen had 50% reduced risk for coronary heart disease and current users an even more dramatic 70% reduction.

Factors that predict risk for coronary heart disease include total cholesterol and high-density and low-density lipoprotein levels.[26] Elevations in total cholesterol and low-density lipoproteins increase cardiovascular risk, whereas elevated high-density lipoprotein is cardioprotective. The Lipid Research Clinics Program [27] found that a 1% reduction in total cholesterol leads to a 2% reduction in coronary heart disease risk. Lowering of low-density lipoprotein was also important, although not as profound as the cholesterol factor. Elevation of high-density lipoproteins independently accounted for a 3% reduction in cardiovascular risk per 1% increase.

Lipid levels have thus been shown to have a significant impact on risk for cardiovascular disease. Oral estrogen replacement therapy elevates high-density lipoprotein, lowers low-density lipoprotein, and, in adequate doses, can lower total cholesterol.[28,29,30] Transdermal estrogen therapy has comparable effects on total cholesterol and low-density lipoprotein, but not on the high-density lipoprotein fraction.[31] The cardioprotective effect of estrogen has thus been documented.

MENOPAUSAL HORMONE REPLACEMENT THERAPY

The estrogen deprivation of menopause impairs both quality and duration of life, and improvement of both is a goal of management. Only 10% of women who could benefit from hormone replacement therapy are receiving these benefits.[32] The major reason is fear of cancer,[33] but conclusive studies have shown that women who use estrogen and progesterone have a lower incidence of endometrial cancer than matched controls.[34,35] Breast cancer has been the other major area of concern but, with control for other variables of breast cancer risk, there is little evidence of increased breast cancer risk related to use of menopausal hormone replacement therapy.[36,37]

Indications

The indications for menopausal hormone replacement therapy include hot flushes, urogenital atrophy, sexual dysfunction, neuroendocrine changes, psychological problems, and androgen-excess skin and hair disorders. Hormone replacement therapy is also cardioprotective and will delay the progression of osteoporosis. Used with progesterone, hormone replacement therapy reduces the risk of endometrial cancer. Moreover, menopausal hormone replacement therapy can dramatically improve quality of life.

Contraindications

Contraindications to menopausal hormone replacement therapy include estrogen-dependent malignancies, undiagnosed abnormal uterine bleeding, possibility of pregnancy, and blood-clotting abnormalities. Use of hormone replacement therapy after treatment of endometrial cancer can be considered on an individual basis related to stage and grade of malignancy and period of time since treatment.[38] In this circumstance, progesterone should be used in combination with estrogen. Breast cancer is generally a lifelong contraindication to both estrogen and progesterone, although estrogen may be considered if the breast cancer is estrogen-receptor negative.

Oral estrogen is inadvisable in the presence of an active source of embolization, but it can certainly be an option in a patient who had a single embolic episode years previously and the source of embolization is no longer present. These women are particularly good candidates for transdermal estrogen administration which has essentially no effect on clotting factors.[31]

Estrogen

Estrogen can be administered transdermally or orally. Transdermal administration has the advantage of estrogen delivery through the skin directly into peripheral circulation; it is carried to the target tissue without first passing through the liver and therefore simulates premenopausal estrogen utilization.

Estrogen administered orally is transported by enterohepatic circulation to the liver where it undergoes

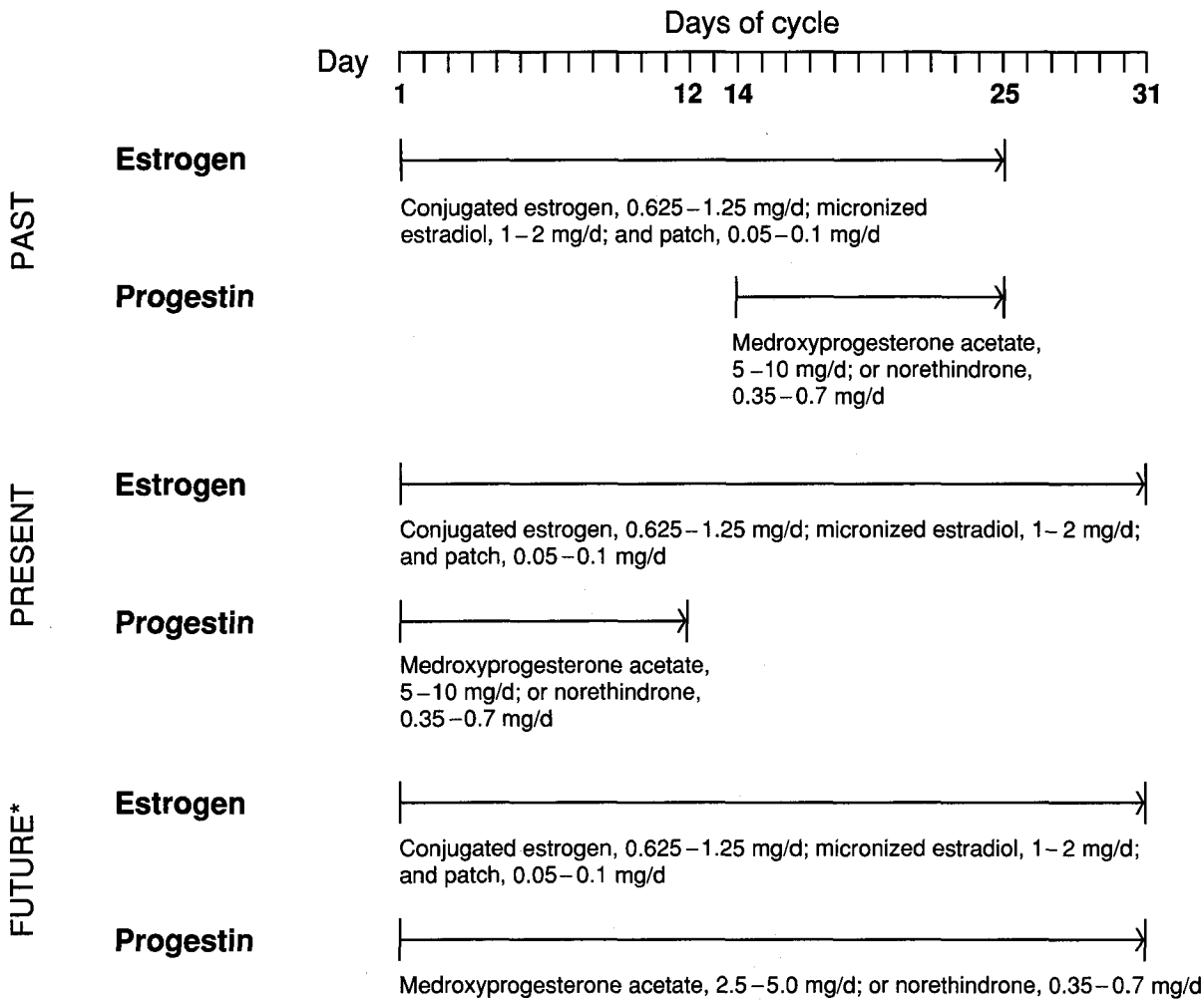

FIGURE 1. Comparison of hormone replacement regimens.

first-pass hepatic effects before being transported to peripheral tissues. First-pass liver metabolism has a beneficial effect on lipids, while its effect on factors that regulate blood pressure and blood clotting is detrimental. Transdermal estrogen administration can avoid these detrimental effects.[31,39,40]

Both transdermal and oral estrogen administration are effective in treating major changes associated with estrogen deprivation in postmenopausal women, including neuroendocrine disorders, urogenital atrophy, androgen-excess skin and hair disorders, and cardiovascular risk.[41] Transdermal estrogen reduces low-density lipoproteins and total cholesterol, but has less effect on high-density lipoproteins and may thus be less cardioprotective than oral estrogen. However, recent studies indicate an additional cardioprotective effect of estrogen that is mediated through the direct effect of estrogen on vasoactive peptides[42] and prostaglandin metabolism. Cardiovascular risk is thus multifactorial, and it involves factors other than the lipid model.

Osteoporosis prevention with transdermal estrogen has promise, pending the results of ongoing clinical trials.[43,44] Because transdermal estrogen has minimal effect on liver production of sex hormone binding globulin, there is relatively more free circulating testosterone.[45] Oral estrogen may therefore be more effective in treating androgen-excess skin and hair disorders.

Progestin

The use of progesterone in menopausal hormone replacement therapy is controversial. The need for progesterone to prevent endometrial hyperplasia and cancer is well established if the uterus is present.[35,46] Progesterone can be associated with premenstrual syndrome symptoms and has a detrimental effect on cardiovascular risk mediated by lipid metabolism.[47] Progestational agents exhibit androgenic effects that vary depending on the agent, dose, and route of administration.[48]

Whether to use progesterone after hysterectomy is the pertinent question. Gambrell has shown that women using estrogen and progesterone had a lower incidence of breast cancer than those who took estrogen alone,[34] but the patients in his study were not randomized. Patients with risk factors for breast cancer were put in a control group, which therefore had a higher incidence of breast cancer than either hormone-treated group. The validity of this study has been questioned.

Schiff and associates subsequently stated[49] that upon recalculation of Gambrell's data,[50] they found no statistically significant difference between groups treated with estrogen only and estrogen in combination with progesterone-treated groups, and do not recommend progesterone after hysterectomy. Their opinion also was the consensus opinion of the Fifth International Menopause Symposium.[51]

Treatment regimens

The older schedules of cyclic estrogen with or without cyclic progesterone have been refined and the European schedule of continuous estrogen with cyclic progesterone is now recommended. Progesterone for 12 days is indicated to prevent endometrial hyperplasia.[35,46] Progesterone administered from day 1 through 12 of each calendar month has excellent patient acceptance. Menstrual bleeding occurs midmonth.

The newer approach to replacement therapy is continuous administration of both estrogen and progesterone.[52] This schedule induces endometrial atrophy and amenorrhea,[53] and avoids the side effect of menstrual bleeding. Endometrial atrophy develops only after 6 to 9 months of therapy, during which there is no "normal" pattern of uterine bleeding. Therefore, endometrial biopsy is necessary before starting the combined schedule. Hormone replacement schedules are compared in *Figure 1*.

TABLE 1
SELECTED ESTROGENS AND PROESTINS

Name	Ingredients	Recommended starting dose (mg/d)
Oral estrogens		
Estrace	Micronized estradiol	1.0
Estraderm	17-B estradiol, percutaneous patch	0.05
Estratab	Esterified estrgen	0.625
Ogen	Estropipate	0.625
Premarin	Conjugated estrogens	0.625
Progestins		
Amen	Medroxyprogesterone acetate	5.0*
Curretab	Medroxyprogesterone acetate	5.0*
Cycrin	Medroxyprogesterone acetate	5.0*
Micronor	Norethindrone	0.35
Nor Q.D.	Norethindrone	0.35
Ovrette	Norgestrel	0.075
Provera	Medroxyprogesterone acetate	5.0
Natural progesterone		300.00

*1/2 of 10 mg tablet.

Recommended estrogens. The natural estrogens, estrone[54] or estradiol,[55] should be used in postmenopausal women. Both forms can be administered orally or vaginally; estradiol can be administered transdermally as well. Vaginal administration is satisfactory only for urogenital atrophy; after recornification of the vaginal epithelium, absorption is reduced and unpredictable.[56] Transdermal estrogen is recommended for women who smoke in order to circumvent first- pass liver metabolic effects.[57,58,59] Liver metabolism of estrogen in smokers is significantly altered, such that estrogen is converted to inactive catecholestrogens. Transdermal estrogen is also preferred with a history of blood clotting abnormality or estrogen-induced hypertension.[31,41] If osteoporosis prevention is the treatment goal, then increased doses of 17-B estradiol are recommended.[15,17] Dosage recommendations are listed in *Table 1*.

Recommended progestins. Available synthetic progestins for menopausal hormone replacement therapy include medroxyprogesterone acetate, norethindrone, norethindrone acetate, and norgestrel. Medroxyprogesterone acetate, a 21-carbon compound, is the least androgenic, followed by norethindrone and then norgestrel, but the androgenic effect is dose-related.[48] The recommended starting dose for medroxyprogesterone acetate is 5 mg per day, compared to 0.35 mg

for norethindrone and 0.075 mg for norgestrel. Dosage can be increased if bleeding control is inadequate.[35] Norethindrone is marketed primarily as a 5-mg dose, which is 15 times more than needed for menopausal hormone replacement therapy. The correct starting dose for menopausal women can be found in low-dose, progestin-only birth control pills, which have 0.35 mg norethindrone or 0.075 mg norgestrel.

Natural progesterone does not cause premenstrual syndrome symptoms or impair the beneficial effect of estrogen on cardiovascular risk,[60] but high doses are required to achieve serum levels adequate to prevent endometrial hyperplasia; and androgenicity has yet to be determined. All progestational agents can contribute to androgen-excess skin and hair disorders. Therefore, the lowest effective dose of the least androgenic progestational agent adequate to control menstrual bleeding is recommended. Comparable doses of recommended progestational agents are listed in *Table 1*.

BENEFICIAL IMPACT

The beneficial impact of menopausal hormone replacement therapy on the care of mature women is significant. Henderson and associates[61] concluded that hormone replacement therapy would reduce mortality from cardiovascular disease in postmenopausal women by 5,250 per 100,000 per year, which could save approximately 250,000 lives annually from heart attack and stroke. Delay of hip fractures for 10 years would reduce the incidence by 75% and save approximately 30,000 lives per year and $3 billion.[14,15]

Quality of life cannot be measured in numbers or dollars, but involves sense of well being, cognitive function, day-to-day coping, functioning on the job, self-perception, and perception of others. Providing quality life for the increasing population of postmenopausal women certainly justifies our concern and involvement in the care of this group of women.

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