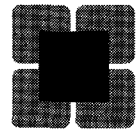

WILLIAM S. WILKE, MD, EDITOR

WHEN AND WHY TO CONSIDER ESTROGEN THERAPY

Only 14% of postmenopausal women who could benefit from estrogen therapy are receiving those benefits. The association between estrogen therapy and endometrial cancer has been disproven, but the lingering fear of risk has deprived many women of therapy that can improve quality of life, lower the risk of osteoporosis and cardiovascular disease, and save more than 280,000 lives annually.

IMPACT ON OSTEOPOROSIS

Nearly half of the 40 million women in the United States over age 50 have some degree of osteoporosis. The annual death toll from hip fractures (more than 50,000) is higher than the mortality associated with breast cancer. The fracture threshold is reached with the loss of 40% to 50% of bone density. If we can maintain bone density above the fracture threshold, and delay hip fractures by 10 years, we can decrease mortality by 60%.

Although lost bone cannot be restored, antiresorptive therapy with estrogen can maintain existing bone density and delay the onset of osteoporosis. Generally, estrogen therapy is continued for 10 to 15 years, but not beyond age 70. With the discontinuation of therapy, bone deterioration resumes.

REDUCED CARDIOVASCULAR RISK

The problem of cardiovascular disease in women is 10 times greater than that of osteoporosis, with a yearly death toll of 500,000. The protective effect of estrogen has been well established. With the onset of menopause, a woman's risk of cardiovascular disease increases by 18 times, compared with a fivefold increase for men of similar age. The Boston Nurses Health Study concluded that women who had ever used estrogen had a 50% reduced risk of coronary heart disease, and for current users the reduction was 70%.

If adequate doses are given, oral estrogen replacement therapy elevates high-density lipoprotein (HDL) cholesterol, lowers low-density lipoprotein (LDL) cholesterol, and lowers total cholesterol. However, the effect on lipid levels accounts for only about 30% of the cardiovascular benefit. Estrogen also relaxes smooth muscle, and it has endothelial effects. It may have an impact on prostaglandin metabolism that results in a shift to prostacyclin vs thromboxane, which decreases platelet adhesiveness and vascular tone.

RISK OF CANCER

It has been shown that women who use estrogen with progesterone have a lower incidence of endometrial cancer than matched controls. The use of unopposed estrogen increases the risk by 500% to 700%, but the addition of progesterone actually lowers the risk. The association with breast cancer is less clearly defined and appears to be dose- and time-related. Conjugated estrogen at the 0.625 dose does not increase risk, but higher doses can increase the risk by 7% to 8%. A recent meta-analysis suggests an annual increased risk of 2% for each year of estrogen therapy. Therefore, 10 years of estrogen therapy would increase the risk of breast cancer by 20%.

MODES OF ADMINISTRATION

Estrogen can be administered orally, transdermally, or by injection. The transdermal therapeutic system is advantageous in that it simulates premenopausal estrogen utilization. It is delivered through the skin, directly into the peripheral circulation, and carried to target tissues without first passing through the liver. Orally administered estrogen is transported by enterohepatic circulation to the liver, where it undergoes first-pass metabolic effects before being transported to peripheral tissue.

Both transdermal and oral estrogen effectively treat major changes associated with estrogen deprivation, including neuroendocrine disorders, urogenital atrophy, androgen excess, skin and hair disorders, osteoporosis, and cardiovascular risk. Transdermal estrogen is recommended for women who smoke; liver metabolism of estrogen in smokers is significantly altered so that

estrogen is converted to inactive catechol estrogens. Transdermal estrogen is also preferable in patients with a history of blood clotting disorders or estrogen-induced hypertension.

Natural estrogens (estrone or estradiol) should be used. Synthetic estrogens in presently available doses are not recommended. Estrone can be administered orally or vaginally. Estradiol can be administered orally, vaginally, or transdermally. Increased doses of 17-beta estradiol are recommended for prevention of osteoporosis.

Although progesterone is definitely needed to prevent endometrial hyperplasia and cancer, its value following hysterectomy is controversial. Available synthetic progestins include medroxyprogesterone acetate, norethindrone, norethindrone acetate, and norgestrel. The starting dose for medroxyprogesterone acetate should be 5 mg/d, compared with 0.35 mg/d for norethindrone and 0.075 mg/d for norgestrel. Women who are overweight and are still producing estrogen may need higher progesterone doses. Norethindrone is marketed primarily as a 5-mg dose, which is 15 times in excess of what is needed. The low-dose progestin-only birth control pills have 0.35 mg norethindrone or 0.075 mg norgestrel, which is the correct starting dose for menopausal women.

TREATMENT REGIMENS

The European dosage schedule for hormonal therapy is now generally recommended: estrogen every day, with progesterone added on days 1 through 12 of the calendar month. This regimen is convenient, easy to remember, and results in predictable mid-month cyclic menstrual bleeding. If bleeding occurs on day 10 or anytime thereafter, then the endometrium has essentially always been secretory and there is no hyperplasia. If bleeding occurs before day 10, then the progesterone dose should be increased. Endometrial biopsy is indicated if bleeding still occurs.

The newest approach to replacement therapy is continuous administration of both estrogen and progesterone, which induces endometrial atrophy and amenorrhea. Menstrual periods will cease within 9 months in most women on this regimen, which is a factor in compliance. Many women who discontinue estrogen therapy do so because of continued menstrual bleeding. Progesterone will partly undo the cardioprotective effect of estrogen, although accumulating evidence suggests that the lipid model is less significant than was once believed. A baseline endometrial biopsy must be done before starting the continuous combined regimen because there is no predictable normal pattern of bleeding during the first 6 to 9 months on this schedule.

CONTRAINDICATIONS

Contraindications to estrogen replacement therapy include estrogen-dependent malignancies, undiagnosed abnormal uterine bleeding, possibility of pregnancy, and blood clotting abnormalities. The use of estrogen in a patient with a history of endometrial cancer can be considered, depending on the state and grade of the malignancy and the duration of time since it was treated.

Breast cancer is generally a contraindication to both estrogen and progesterone, although estrogen may be beneficial if the breast cancer is estrogen-receptor negative. Tamoxifen, although relatively expensive, is safe for these patients and confers all of the benefits of estrogen therapy except the resolution of hot flashes; tamoxifen will temporarily increase the frequency of hot flashes.

Although oral estrogen therapy would not be advisable in the presence of an active source of embolization, it can be considered in women who have a long-ago history of one embolic event, and in whom the source is no longer present. These women are particularly good candidates for transdermal administration, which has virtually no effect on blood clotting factors.

STARTING THERAPY

To decide whether to begin estrogen therapy, it is advisable to distinguish between premenstrual syndrome and menopause by measuring follicle-stimulating hormone (FSH) and serum 17-beta estradiol. If the FSH is greater than 40 IU/mL and the estradiol is less than 40 pg/mL, that is consistent with menopause. Some women have significant vasomotor symptoms before the onset of menopause, when the estrogen level is borderline and periodic ovulation occurs. These symptoms can be alleviated with conjugated estrogen, 0.3 mg starting on day 5 and stopping when menses begins.

DELBERT L. BOOHER, MD
Department of Gynecology
Director, Program for Mature Women
The Cleveland Clinic Foundation

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DIFFERENTIATING AMONG RENAL STONES

Renal stone disease is the reason for many patients each year to see a physician or to be admitted to a hospital for treatment or evaluation, so a familiarity with the frequency of the various types of stone disease and their clinical presentation is helpful to the physician.

Renal stone disease is a fairly common cause of hospitalization, accounting for approximately 1 out of 1,000 hospital admissions per year. It occurs most commonly in otherwise healthy 18- to 45-year-old men, and the recurrence rate is almost 100% within 20 years after the first stone. The most common renal stone is the calcium-containing type, found in 75% of all patients with renal stone disease. Less common types include triple phosphate stones (struvite), which occur in 10% to 15% of the cases; uric acid stones, also present in 10% to 15% of the cases; and cystine or xanthine stones, which have a frequency of less than 1%.

CALCIUM STONES

Calcium stones are composed of either calcium oxalate or, less commonly, calcium phosphate. Calcium phosphate stones may indicate chronically alkaline urine, chronic urinary infection, renal tubular acidosis, or primary hyperparathyroidism. Both types of calcium stones occur more frequently in patients who have high urinary concentrations of calcium, uric acid, or oxalate, or a deficiency of crystal inhibitors such as citrate.

It is important to remember that elevated levels of uric acid can be associated with calcium stones as well as uric acid stones. Other risk factors for calcium stone disease include chronic dehydration or low urine volume and inflammatory bowel disease with fluid loss through the gastrointestinal tract.

Idiopathic hypercalciuria, the increased urinary excretion of calcium (>300 mg/24 hours in men, >250 mg/24 hours in women), is the most common of the conditions associated with calcium stone disease, occurring in 60% to 70% of cases. This disease is characterized by low to low-normal levels of serum phosphate and hyperabsorption of calcium from the gut. Less common associated conditions include hyperoxaluria (oxalate excretion exceeding 40 mg/day), hyperuricosuria (uric acid >750 mg/day), and hypocitraturia (<300 mg/day). Urinary citrate, which inhibits calcium precipitation by forming a soluble salt with calcium, tends to exist in higher levels in women than in men. This may account for the increased frequency of renal stone disease in men.

TRIPLE PHOSPHATE STONES

Triple phosphate stones, composed of magnesium ammonium phosphate and calcium phosphate, often appear as staghorn calculi, and they almost always occur in the presence of infection. As a rule of thumb, when the urine is alkaline and its sediment contains white cells and bacteria, the stones are struvite. Infection is rarely the sole abnormality of recurrent struvite stones, however. Usually an anatomical abnormality of the urogenital tract is present.

URIC ACID STONES

There is a common misconception that uric acid stones occur only in patients with a history of hyperuricemia or gout. Although they occur in 22% of patients with primary gout and 42% of patients with secondary gout, this accounts for only a small percentage of the total number of cases. The stones are radiolucent but may present as a filling defect in areas of contrast on an intravenous pyelogram. Patients who have persistently acidic urine (pH<5.0) are especially prone to this disease. The stones will not develop in an alkaline environment.

CYSTINE STONES

Cystine stones form as a result of cystinuria, a genetic disorder (autosomal-recessive) that causes increased urinary secretion of the amino acids arginine, lysine, ornithine, and cystine. Cystinuria can be detected by