Compliance Difficulties With Progestin-Supplemented Estrogen Replacement Therapy

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Forty postmenopausal women were studied prospectively while undergoing estrogen replacement therapy (ERT). Eighteen women with an intact uterus were cycled with additional progestin therapy. All but three women of the estrogen-progestin group elected to discontinue therapy because of undesirable "physiologic" withdrawal bleeding.

Future progestin-ERT recommendations should take these results into consideration. Wide-scale re-education of patients and physicians will be necessary if the existing recommended regimens are to be observed. Alternatively, new or different pharmacologic agents and regimens will be necessary to achieve the postulated benefits of progestin-ERT without undesirable side effects.

Estrogen replacement therapy (ERT) for the postmenopausal woman has been linked to a reduction in osteoporosis,[1] cardiovascular disease,[2,3] and overall risk of death.[4] Many epidemiologic studies have reported that prolonged administration of estrogen to postmenopausal women increases the risk of endometrial cancer.[5-8] It also appears that the monthly addition of a progestin to ERT reduces the incidence of hyperplasia and carcinoma of the endometrium.[9,10] Cyclic vaginal bleeding has been noted to occur in a majority of patients receiving ERT with monthly additional progestin[11]; however, the implications of such regular bleeding on patient compliance with current ERT recommendations have not been previously addressed.

This paper reports findings in 40 postmenopausal women using cyclic estrogen-progestin ERT and followed over 18 months.

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Methods

Forty symptomatic, postmenopausal, sedentary, white women aged 47 to 91 years from a group practice in a major metropolitan area were

studied prospectively over an 18-month period from October 1981 to April 1983. All 40 women were established patients of the practice prior to commencement of the study.

Eighteen of the 40 patients (group A) had an intact uterus, and 22 (group B) had had hysterectomies for nonmalignant pathologic conditions.

Symptomatology included osteoporosis, with or without fractures of hip or vertebrae; atrophy of the genitourinary tract characterized by dyspareunia, dryness, urinary frequency, and urgency incontinence; or severe, protracted vasomotor instability beyond the climacteric. No patients had prior evidence of endometrial hyperplasia, history of myocardial infarction, liver or gallbladder disease, or thromboembolic phenomenon.

All patients in group A received 0.625 mg of conjugated equine estrogens orally for 21 days and 2.5 mg of norethindrone orally from day 12 through day 21. They were given no therapy for seven days thereafter.

All patients in group B received 0.625 mg of conjugated equine estrogens orally for 21 days out of every month.

Group A women who evidenced vaginal bleeding more than once during therapy underwent endometrial biopsy by suction curettage (Vabra). Doses of norethindrone were reduced to 1 mg if bleeding continued after three cycles.

Results

Patients remained on their regimens for at least five months. Of 18 patients in group A, 16 had regular withdrawal bleeding. All bleeding occurred during days 21 to 30 of the treatment cycle. All endometrial biopsies were done between days 22 and 24. All biopsies showed secretory endometrium. Lowering the norethindrone dosage did not change the pattern of withdrawal bleeding. All but three patients in group A elected to discontinue therapy because of the bleeding in spite of reassurances that this was expected and normal. No patients in group B discontinued therapy.

Discussion

ERT has been used since the late 1930s to alleviate the symptoms of the menopausal syndrome. There are over 30 million women in the United States who have reached the age of menopause and who have a postmenopausal life expectancy of 28 years, or over one third of their total life span.

In addition to relieving the discomfort of vasomotor symptoms and genital tract atrophy, ERT has been shown to reduce the risks of pathologic fracture secondary to osteoporosis, a leading cause of morbidity and mortality found almost exclusively in postmenopausal women.

Newer and even more profound benefits are suggested by recent observations on reduced risks of cardiovascular disease[2,3] and prolongation of life span[4] without increased risk of hypertension or cerebrovascular accident.[12] An inverse relationship between high-density lipoprotein cholesterol (HDL-C) and coronary mortality has been described particularly among older women.[13] The postulated mechanism of protection offered by ERT against cardiovascular disease is related to the decrease in levels of low-density lipoprotein (LDL) and the increase in HDL cholesterol in women taking low doses of estrogen.[14]

Despite these benefits, ERT application has been tempered by reports linking the use of estrogens to the development of endometrial carcinoma.[5-8]

To avoid this complication of ERT, the addition of cyclic progestin has been advocated and demonstrated to reduce the risk of endometrial cancer to levels even below those of untreated women.[9,10] Progestins oppose the actions of estrogens by reducing the number of estrogen receptors in the endometrium,[15] increasing the rate of endometrial conversion of estradiol to the biologically weaker estrone,[16] and increasing the rate of sulfurylation of estrogen in the endometrium.[17]

The addition of progestin to ERT has raised new questions about its safety, appropriate treatment regimen, and the effect of unwanted withdrawal bleeding.

Progestins have been shown to reduce HDL-C concentration and increase LDL values,[18-20] the opposite of the beneficial effects on these lipid concentrations attributed to low-dose estrogen use. The potential for increasing the risk of death from ischemic heart disease[3] has led the National Institutes of Health to caution against the widespread use of additional progestins to postmenopausal ERT.[21]

Uncertainty exists as to the optimal type of pro-

gestin, its dosage, and its duration of therapy.

The type of progestin may be important in that the nortestosterone derivatives (eg, norgestrel, norethindrone, and norethisterone) appear to lower HDL-C more markedly than the nonandrogenic 17x-hydroxy progesterone derivative, medroxyprogesterone acetate.[18,22,23]

The duration of progestin therapy also appears critical, since the incidence of hyperplasia is reduced to zero only if progestin usage is extended to 13 days per cycle.[24]

The optimal dose of progestin is also unclear in that data have shown little if any loss of progestational biochemical effect on the endometrium when the daily dose of norethindrone was reduced from 10 mg to 1 mg or of D/L-norgestrel from 500 mg to 150 mg.[25] These lower doses still equalled or exceeded the effects of normal secretory phase progesterone when measured in terms of deoxyribonucleic acid synthesis suppression and nuclear estradiol receptor reduction.[25]

The findings of this study demonstrated that 16 of 18 patients on cyclic progestin ERT had regular withdrawal bleeding when 0.625 mg of conjugated estrogens and norethindrone was administered in a cyclic basis. The Nachtigalls[11] noted similar withdrawal bleeding in 60 of 84 patients treated prospectively for ten years with 2.5 mg of conjugated estrogens and 10 mg of medroxyprogesterone.

Conjugated estrogens given in 0.625-mg daily doses appear as effective as 1.25-mg doses in inducing nuclear estradiol and progesterone receptors,[25] while a further reduction in estrogen to 0.3 mg daily is associated with a loss of suppression of vasomotor symptoms and with a loss of prevention of osteoporosis.[26] These findings imply that the lower therapeutic limit for the estrogen component in ERT is approximately 0.625 mg of conjugated estrogens or its bioequivalent.

Studies by Flowers and Wilburn[27,28] suggest that withdrawal bleeding is a "physiologic" response to cyclic estrogen-progestin ERT in that 15 to 20 days of treatment with conjugated estrogens (1.25 mg/d) results in an endometrium that resembles the normal mature proliferative endometrium, whereas 7 days of additional treatment with either medroxyprogesterone acetate (10 mg/d) or norethindrone acetate (2.5 mg/day) is associated with morphologic changes characteristic of days 19 through 21 in the normal cycle.

Atrophic postmenopausal endometrium responds to sequential estrogen plus progestin by developing proliferative, secretory, and bleeding phases similar to those found in normal ovulatory cycles. It is therefore not surprising to note the high incidence of withdrawal bleeding in progestin-supplemented ERT.

These findings suggest that this regular withdrawal bleeding, no matter how "physiologic" and despite reassurances from providing physicians, was responsible for discontinuation of ERT in 15 of 18 postmenopausal women in this study. If this observation validly reflects widespread dissatisfaction with the phenomenon of withdrawal bleeding with progestin-supplemented ERT, the public health implications for continued safe use of ERT are considerable.

In view of the scarcity of data concerning optimal type, dose, and duration of supplemental progestin, it is hoped that further research may yet yield a combination that will continue to minimize the risk-benefit ratio for ERT. In addition, widescale education and reorientation of patients and physicians concerning the significance of withdrawal bleeding in progestin-supplemented ERT may become necessary.

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