Lower Doses of Oral Estrogen and Progestogens as Treatment for Postmenopausal Women

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Semin Reprod Med. 2005;23(2):188-195.
Posted 09/21/2005

Abstract and Introduction

Abstract

Estrogen, with or without a progestin, is effective for the treatment of menopausal symptoms. Larger doses of estrogen/progestin have been used than required for the amelioration of menopausal symptoms. Both positive and negative outcomes of hormone therapy are reported in postmenopausal women. The positive aspects have been those associated with a reduction in menopausal symptoms such as hot flashes, and improvement in vulvovaginal atrophy with maintenance of bone mineral density. The problems have included an increased risk of venous thrombosis and breast cancer. The anticipation is that as the dose of oral estrogen and progestins is lowered, the benefits can be maintained and the side effects reduced. Recent clinical trials have found that lower doses of estrogen and/or progestin reduce or improve menopausal symptoms and maintain bone mineral density. The impact of lower doses of hormones on heart disease, and venous thromboembolism and stroke remain to be determined in future studies.

Introduction

Hormone therapy (HT), consisting of either estrogen alone (ET) or an estrogen in combination with a progestin (EPT), has been provided to postmenopausal women for many years as a treatment for menopausal symptoms. The principal indications for HT approved by the United States Food and Drug Administration (U.S. FDA) are for the treatment of menopausal symptoms, specifically hot flashes and/or night sweats, symptoms of vulvovaginal atrophy (itching, burning, or dyspareunia), and the prevention of bone loss. The standard therapy in the United States for women without a uterus is ET as a monotherapy. A range of estrogen doses and formulations are available and the following are examples of estrogen types and doses. Conjugated equine estrogen (CEE) 0.625 mg, esterified estrogen 0.625 mg, and estradiol-17β (E2) 1.0 mg are available in oral formulations. There are transdermal delivery systems that provide E2 in a variety of doses ranging from 17 to 100 μg/day. Transdermal formulations can be found as adhesive patches, gels, or in liposomes. Estrogens have also been available for local vulvar or vaginal atrophy as creams, rings, and tablets. A recent introduction has been a vaginal ring releasing estradiol acetate that delivers a serum level of E2 sufficient to treat menopausal symptoms. Oral formulations of CEE have been prescribed most in the United States, whereas in Europe, oral E2 at a dose of either 1.0 or 2.0 mg has been prescribed most.

Women who have an intact uterus require the addition of a progestogen. Multiple observational

studies have found an increased incidence of endometrial cancer in women using unopposed oral estrogen therapy.[1] The addition of the progestogen to the estrogen regimen reduces the incidence of endometrial cancer.[1] The prospective, randomized, placebo-controlled clinical trial the Women's Health Initiative (WHI) HT arm has found a protective effect of HT on the incidence of endometrial cancer.[2]

Women who have an intact uterus require the addition of a progestogen to negate the effect of estrogen on the endometrium. This has been termed EPT. The progestogen is administered intermittently for 12 to 14 days each calendar month, once every 3 or 6 months for 14 days (extended regimen), or continuously (daily) with the estrogen.[3-7] An intermittent use of progestin for 3 days and then stopped for 3 days, and repeated with continuous estrogen has been termed cyclophasic or pulsed regimen.[8] The pulsed approach has been used in postmenopausal women as a means of reducing the incidence of endometrial bleeding.[9,10]

The use of EPT continuously (ccEPT) has been in vogue since the late 1980s as a treatment regimen that appears to result in little to no endometrial bleeding as compared with the cyclic use of a progestin, which has a high incidence of withdrawal bleeding.[3,11]

A widely used medication in the United States for ccEPT has been 0.625 mg of CEE plus 2.5 or 5.0 mg of medroxyprogesterone acetate (MPA; PremPro; Wyeth, St. David's, PA).[3] Other ccEPT preparations on the U.S. market have used ethinyl estradiol (EE) 5.0 µg plus 1.0 mg of norethindrone acetate (NETA; FemHRT, Pfizer, New York, NY) and E2 1.0 mg with NETA 0.5 mg (Activella; NovoNordisk, Princeton, NJ).[3,7] The principal continuous oral EPT therapy in Europe has been E2 2.0 mg and NETA 1 mg (Kliogest, NovoNordisk; Bagsverdt, Denmark) although the lower dose E2/NETA 1.0/0.5 mg has been introduced in the last several years.[11-13]

There has been considerable interest in reducing the amount of estrogen and progestin used for HT during the last 8 to 10 years. There are several reasons for this:

1. The U.S. FDA has indicated a need to identify the lowest dose of a medication that is therapeutically efficacious with end points statistically different from placebo.

2. Physicians have also been interested in lowering the dose of hormone(s) from the standpoint of reducing side effects as well as the potential for reducing adverse outcomes, specifically in cardiovascular disease and, potentially, breast cancer.

3. The lower dose is important for the consumer, from the standpoint of fewer side effects and the potential for fewer adverse or harmful events.

The recent approval by the U.S. FDA of lower doses of oral ccEPT than those used in the past has been a signal event that marks the end of many years of clinical investigation. The new lower dose ccEPT consists of four different, continuous, combined doses: CEE 4.5 mg and MPA 1.5 mg, CEE 0.3 mg with MPA 1.5 mg, E2 1.0 mg and NETA 0.5 mg, and EE 5.0 µg and NETA 1.0 mg.[6,7,14]

An additional stimulus to reducing the dose of EPT has been the reports of two randomized placebo-controlled clinical trials of EPT in the United States. The Heart and Estrogen-Progestin Replacement Study (HERS) and the WHI have reported on cardiovascular outcomes in older women using continuous CEE 0.625 mg with MPA 2.5 mg.[15,16] Both studies were neutral regarding an effect of the HT on cardiovascular disease. The WHI added to the controversy with the initial report of its prospective randomized clinical trial that the use of 0.625 mg CEE with 2.5 mg MPA appeared to result in an increase in coronary heart disease events and other

cardiovascular outcomes.[2] This study was performed in older women (average age, 63 years) in whom almost 75% had never used EPT. These women may not be representative of the younger symptomatic individuals who are seen and treated with standard continuous EPT by practicing physicians. The subsequent WHI publication on ccEPT and cardiovascular risk did not find a statistically significant increase or decrease in coronary heart disease outcomes in the women using EPT.[16] A CEE dose of 0.3 mg has been reported to have a reduced relative hazard for coronary heart disease compared with CEE 0.625 mg (not statistically different) in the Nurses' Health Study.[17]

The WHI data have accelerated the movement to lower doses of estrogen plus progestin, with the expectation that the lower doses could have less effect on cardiovascular disease in women. This hypothesis assumes that the lower doses would have comparable effects on menopausal symptoms and other clinical outcomes compared with the higher dose formulations that have been used in the past.

Multiple factors have contributed to and influenced the development of low-dose EPT for the management of symptomatic postmenopausal women. This review presents the efficacy of these lower dose products on the clinical symptoms and findings in postmenopausal women.

Menopausal Symptoms

The most common symptom of the menopause is the hot flush or night sweat. It has been estimated that more than 80% of women experience this symptom. The Study of Women Across the Nation has found that there are ethnic differences in the occurrence and experience of menopausal symptoms.[18] Quality of life is improved in women who use estrogens for suppression of hot flushes.[19] The hot flash is believed to be due to alteration in the hypothalamic thermoregulatory center.[20] Estrogens appear to alter the perception of changes in core body temperature (see Freedman[20,21]).

The U.S. FDA, in its guidance for postmenopausal hormone therapy, has indicated that the medication under study must show benefit in terms of improvement (reduction) in hot flash frequency and severity compared with placebo. It is well known that estrogen treatment, either orally or following transdermal delivery, exhibits a dose-response effect in terms of the amelioration or improvement of menopausal symptoms.[14,22] This dose response has been demonstrated for lower doses of oral estrogen with or without progestin.[14,23-27] A similar dose-response efficacy has been demonstrated using transdermal E2.[22,28] The significant reduction in hot flashes compared with placebo must occur at 4 weeks after initiation of therapy (FDA Guidance at www.fda.gov). Continued use of ET or EPT further reduces hot flash frequency and intensity, reaching a nadir approximately 6 to 8 weeks, with continued suppression for as long as the medication is administered. Placebo use results in a significant improvement compared with baseline levels in hot flashes in all placebo controlled trials.[29,30] It is important to note that complementary and alternative medicines that have been recommended for the treatment or management of hot flashes do not appear to be as efficacious as estrogens.[31,32]

The addition of a progestin to the estrogen is only used for women who have a uterus in place. Recent evidence has shown that the addition of a progestin, either NETA or MPA, synergizes with the estrogenic preparation, resulting in enhanced efficacy in terms of the amelioration of hot flash symptoms.[14,33] This is most apparent in the lower doses of CEE, in which the addition of 1.5 or 2.5 mg of MPA abolishes the dose-response effect found between 0.625, 0.45, and 0.3 mg of conjugated estrogen.[14]

Associated with the amelioration of menopausal symptoms is the improvement in sleep that has been documented with the administration of estrogen.[26,34-36] There is a reduction in sleep latency and an increase in the percentage of rapid eye movement sleep.[34] These findings, although not

specifically tested with lower doses of EPT, appear to be principally an estrogen-related effect. Recent evidence from a sleep laboratory indicates that the arousal from sleep is not associated with hot flashes.[37]

Vulvovaginal Symptoms

Atrophic changes in the vulvar and vaginal area become apparent usually between 2 and 5 years after the menopause.[38] The symptoms noted by the woman are those of introital burning or itching, or dryness with coital activity. The dryness with intercourse can result in significant dyspareunia that is associated with a discontinuation or reduction in coital activity.[39] The clinical findings of vulvovaginal atrophy are that of a smooth, pale, thin vaginal epithelium lacking rugosity, thinning of the labium minus with fusion into the labium majus, and accumulation of fat in the labium majus. The vaginal pH increases from a normal of < 4.5 to > 6.0, and is usually in the pH 6 to 7 range.[39,40]

Oral estrogen therapy results in a decrease in the vaginal pH.[39] Oral low-dose conjugated estrogen improves the vaginal maturation indices (increases superficial cell counts) and the symptoms of vulvovaginal atrophy.[14,24] This improvement in symptoms is mirrored in the changes in the maturation index using exfoliated vaginal epithelial cells. The effect of estrogen is to increase the superficial cell count compared with the intermediate and basal cell levels. The use of oral estradiol or CEE improves the superficial cell number in the vaginal epithelium.[14,24] The addition of MPA with usual or lower doses of CEE has been shown to reduce but not significantly attenuate the maturation indices of the superficial cells in the vagina compared with estrogen alone.[14] It is apparent, based on these data, that the use of an oral estrogen with or without progestin improves vulvovaginal atrophic symptoms and clinical findings in all instances.

Lipids

The initial results of the WHI and the HERS studies have indicated that EPT results in a increased risk for cardiovascular events in older women with and without evidence of established heart disease.[2,41] It is important to re-emphasize that the final report from the WHI did not find a statistically significant increased risk for coronary heart disease; results indicated a relative hazard (RH) of 1.24 (95% confidence interval [CI], 1.00 to 1.5). The final coronary heart disease outcome in the HERS trial was a relative risk (RR) of 0.99 (95% CI, 0.80 to 1.22).[42] These prospective randomized clinical trials have reported an increase in cardiovascular disease only in the first year of use, with an overall null or no effect at the conclusion of the study.[16,41,42] These data are in contrast to the large observational study of United States Nurses, in which the RR of 0.61 (95% CI, 0.52 to 0.71) for cardiovascular disease supports the contention that hormone therapy is cardioprotective.[17] The ET arm of the WHI also found a RH of 0.91 (95% CI, 0.75 to 1.12) for coronary heart disease, although this point estimate was not statistically significant.[43]

Elevated total cholesterol levels along with a reduction in high-density lipoprotein (HDL) cholesterol and an increase in low-density lipoprotein (LDL) cholesterol are risk factors for cardiovascular disease in postmenopausal women. The administration of CEE plus MPA, E2 plus NETA, or EE plus NETA has been found to result in significant changes in lipid profiles.[7,44,45]

Total Cholesterol

All clinical trials of the three named ccEPT treatment regimens reduced total cholesterol by a varying degree.[7,44,45] The effect of the EPT compared with the ET arm is variable depending on the progestin and the lipid fraction under investigation.[7,44,45] Estradiol and CEE alone have a positive effect (improvement) on cholesterol and lipoprotein fractions, except for the increase in triglycerides, which is seen with all oral estrogens.[7,44-46]

HDL Cholesterol

CEE plus MPA increases HDL cholesterol, although the addition of MPA attenuates the HDL increase compared with the same dose of CEE alone.[44,46,47] Both E2 with NETA and EE with NETA are associated with a minimal increase or a slight decrease in HDL.[7,45] These are thought to be due to the effect of the oral NETA.

LDL Cholesterol

LDL cholesterol levels are reduced in all published data from clinical trials using ccEPT preparations.[2,7,41,44-46,48]

Triglycerides

Triglyceride levels are elevated with oral estrogen, and a comparable elevation is seen with CEE plus MPA.[44,46,47] The addition of NETA to either EE or E2 does not increase serum triglycerides.[7,45]

Lower levels of CEE and MPA are found to reduce the increase in HDL found with CEE alone in a dose-response manner.[44] These lower doses of CEE and MPA reduce LDL cholesterol levels, clearly in a dose-response manner (the lower the dose, the less reduction in LDL cholesterol), and have a minimal effect on triglyceride levels.[44]

These findings, in terms of lipid changes, would argue that there should be improvement in coronary heart disease or the prevention of atherosclerosis. Based on recent evidence in women, the addition of E2 1.0 mg oral prevents carotid intima-medial thickness from developing in women in their 50s, whereas in older women (average age, 70) the use of CEE plus MPA (0.625 mg plus 2.5 mg, respectively) had no effect on established atherosclerosis.[49,50] These conflicting data emphasize the problem associated with the clinical findings of coronary heart disease in women. It is possible that the early onset of use of HT in postmenopausal women can reduce or retard the development of atherosclerosis.[51] Wagner and Clarkson[52] find the data for this in the article in this issue. These data using the *Cynomolgus macaque*, together with the findings from the Nurses' Health Study, present a rationale for the early use of estrogen or EPT in the postmenopause for cardioprotection.[53,54] The definitive answer to this clinical question has yet to be found.

In summary, it has been hypothesized that early-onset use of estrogens with or without a progestin in early postmenopausal women should improve or retard the development of atherosclerosis. The current prospective randomized clinical trials have failed to show an improvement in cardiovascular outcome principally in the first year of EPT use. The divergence in relative hazard between ET and EPT in terms of coronary heart disease requires further elucidation.[16,43] Even more important in the determination of who develops coronary heart disease is the role of socioeconomic status and/or exercise, which might explain the discrepancy between the Nurses' Health Study and the WHI results.[55-58]

Endometrial Hyperplasia

The use of unopposed estrogen in postmenopausal women with a uterus has been found to result in a significant incidence of endometrial cancer.[59] Endometrial cancer occurs in approximately 1 per 1,000 cases per year and the incidence increases as women age. The relative risk for endometrial cancer in ET users averages 2.8 and is not increased in women using EPT (RR, 1.0).[59] Endometrial cancer has a low incidence in the general population, thus the end point in clinical trials has been the occurrence of endometrial hyperplasia. Simple endometrial

hyperplasia does not appear to be a risk factor for endometrial carcinoma, whereas atypical endometrial hyperplasia is associated with endometrial cancer.[59-61] The incidence of endometrial hyperplasia in women using ET vs. EPT has been used to document the efficacy of the progestin to prevent development of endometrial cancer.

Unopposed CEE or E2 or EE results in an occurrence of endometrial hyperplasia at 1 year of somewhere between 12 and 30%.[62-64] The addition of a progestin reduces this occurrence to less than 1.0%.[7,62,64-67] For E2 1.0 mg/NETA 0.5 mg, the incidence of endometrial hyperplasia after 1 year is less than 1%.[62] For EE 5 µg/NETA 1.0 mg, the incidence of hyperplasia is less than 1%.[7] This same finding has also been reported for CEE 0.625 mg/MPA 2.5 or 5.0 mg.[63,65]

Reducing the dose of conjugated estrogen to 0.45 or 0.3 mg in association with either 2.5 or 1.5 mg of MPA results in a similar incidence of hyperplasia of less than 1% in published trials.[66,67] These data highlight the fact that all U.S. FDA-approved continuous combined HT regimens appear to inhibit the development of endometrial hyperplasia.

Endometrial Bleeding

The need to use EPT in postmenopausal women who have a uterus is obvious from the above description of the increased incidence of endometrial cancer in women with an intact uterus who were using estrogen only. The use of EPT in the postmenopausal woman with a uterus results in a high incidence of endometrial bleeding. Unexpected endometrial bleeding and/or spotting (B/S) leading to unblinding to the attending gynecologist occurred in approximately 40% of women receiving CEE 0.625 mg/MPA 2.5 mg in the WHI study compared with 7% in the placebo group.[2] Endometrial bleeding also has been reported in postmenopausal women using placebo. There are two placebo-controlled trials of ccEPT using EE 5 µg and NETA 1.0 mg and the lower doses of CEE plus MPA.[7,68] These studies found a 10 to 30% occurrence of endometrial bleeding in the placebo arms during the first 1 to 3 months of the study. This high incidence of endometrial bleeding decreases to approximately 6 to 7% of the participants by the end of one year of placebo use.

The incidence of irregular B/S occurs in 20 to 50% of the participants during the first 1 to 3 months in published clinical trials of continuous EPT.[6,7,68]

The U.S. FDA has requested that we use cumulative amenorrhea as a descriptor to compare different HT regimens. Cumulative amenorrhea is defined as the percentage of women who stop B/S in a trial and never again experience any B/S throughout the remainder of that trial. The number (percent) of women who stop B/S and do not experience any B/S throughout the trial increases each month. All published studies of ccEPT have found that at the end of 1 year, approximately 90% of women have achieved no B/S status.[6,7,68] Although this information can be used as a comparator between therapeutic interventions, a more important factor is the incidence or number of women bleeding each month. Irregular bleeding is the main reason for discontinuation of the ccEPT.[6]

Lowering the dose of CEE in the ccEPT results in an increase of at least 15 to 20% in the incidence of amenorrhea.[68] The greatest improvement occurs in the first 1 to 3 months of treatment, but the gain in numbers (percent) of cumulative amenorrhea persists throughout the study. Similar reductions in the incidence of endometrial bleeding are found with the use of lower doses of E2 and NETA 1.0/0.5 mg, although there are no head-to-head comparison trials with the higher dose E2 formulation.[6,69,70-72]

The use of a lower doses of E2 (1.0 mg compared with 2.0 mg) with different progestins (either MPA or dydrogesterone) is associated with less endometrial bleeding.[71-74]

The major finding of these clinical reports is that lowering the dose of estrogen improves (reduces) the incidence of endometrial B/S in postmenopausal women using ccEPT.

Bone

Estrogen therapy has been shown to prevent bone loss, whether it be CEE, E2, EE, or esterified estrogen.[7,75-80] Estrogen has been reported to reduce bone loss no matter the age of the individual or the duration of time from menopause.[79,81] Women taking CEE 0.625 mg with MPA 2.5 mg in the WHI study were found to have a statistically significant reduction in fracture risk, and an increase in bone mineral density in a subpopulation of participants who had dual-energy x-ray absorptiometry performed.[82] It should be noted that this group of women was not specifically at risk for osteoporotic fracture based on bone mineral density scores. A similar reduction in fracture incidence at the hip has been found in the participants of the CEE-only arm of the WHI.[43] These data indicate that use of ET or EPT can increase bone mineral density and reduce the occurrence of fractures in postmenopausal women.

Lowering the dose of E2 below 2.0 mg or esterified estrogen less than 0.625 mg has been shown to maintain bone density.[75,76,80] A low dose of CEE 0.3 mg with MPA 2.5 mg has been reported to maintain bone mineral density in women with an average age of 64.[79] Lowering the dose of CEE to 0.45 or 0.3 mg with MPA 2.5 or 1.5 mg reduces the loss of bone.[78] EE at a dose of 10 µg was found to prevent bone loss, whereas lower doses of 1.0 and 5.0 µg did not show a difference compared with the baseline findings after 1 year of treatment.[7]

Conclusions

The need to reduce the dose of ET or EPT for postmenopausal therapeutic intervention is apparent. The dictum of lowering the dose of a medication to achieve comparable outcomes with fewer side effects is consistent with the tenets of medicine. Lower doses of estrogen, specifically CEE 0.45 and 0.3 mg with MPA 2.5 or 1.5 mg, has been shown to have comparable effects in terms of lipids, menopausal symptoms, superficial vaginal cell counts, and endometrial hyperplasia, compared with the higher dose of CEE 0.625 mg with MPA 2.5 mg currently marketed in the United States. Clinical trials with direct comparison of lower doses of estradiol 1.0 mg with NETA 0.5 mg vs. the estradiol 2.0 mg and NETA 1.0 mg of have not been reported. The lower dose E2 1.0/NETA 0.5 has definitely been shown to have less frequent adverse clinical effects. Lower doses of EE are found to have differential effects on bone and bleeding outcomes in the EE plus NETA trial and therefore the best regimen was selected using EE 5 µg and NETA 1.0 mg.

Overall, the reduction in the doses of estrogen and progestin appears to reduce the incidence of unwanted uterine bleeding and the adverse clinical side effects. Breast tenderness, one of the most common clinical side effects of HT, has been reduced with lower doses. Lower doses of EPT have maintained efficacy in terms of the relief of menopausal symptoms improvement in vulvovaginal atrophic changes and prevention of bone loss.

Summary

Lower doses of EPT are to be preferred for the initiation and maintenance of HT in postmenopausal women who are having menopausal symptoms. These lower doses result in improvement in menopausal symptoms and vulvovaginal atrophy while having a positive effect on bone, with no evidence of endometrial hyperplasia. The occurrence of endometrial bleeding, although troublesome at the beginning of treatment, rapidly wanes, and at the end of 1 year the incidence of no B/S is approximately 90% for all ccEPT preparations.

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