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Sequential Oral Conjugated Estrogen/MPA and 17β-Estradiol Gel/MPA Therapy in Postmenopausal Thai Women : Effects on Hormonal and Lipid Profiles

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ABSTRACT

Objective To compare the effects of oral conjugated equine estrogen (CEE) and transdermal estradiol gel, both combined with an oral progestin, on hormonal and lipid profiles in postmenopausal Thai women.

Design Randomized trial.

Setting Wat Tat-Thong health centre, Chulalongkorn health centre, Institute of Health Research, Chulalongkorn University, Bangkok.

Subjects Twenty-seven naturally menopausal Thai women were randomly allocated to two treatment groups for the period of 12 months. The first group (N = 13) received conjugated equine estrogen (CEE) 0.625 mg/day orally for 21 days. The second group (N = 14) was given estradiol gel (17-β E_2 gel) 1.5 mg/day for 21 days. Medroxyprogesterone acetate (MPA) 10 mg/day was added orally to both treatment groups on the last 14 days (day 8-21) of each cycle of medication. There was a medication free period during the last 10 days (day 22-30 or 31) of each month.

Main outcome measures Blood samples were obtained before treatment and on day 20 or day 21 after 1, 3, 6 and 12 months of therapy for hormonal (FSH, LH, E_1, E_2) and lipid (TC, TG, HDL, LDL, Apo A_1, Apo B) study. Demographic data was analyzed by Unpaired t-test. Friedman test and Mann-Whitney U-test were run on data where it appropriated.

Results Serum estrone (E_1), and estradiol (E_2) increased in both groups with a statistical significance. In the oral (CEE) group the serum estrone (E_1) increased markedly, whereas serum estradiol (E_2) increased more prominently in the gel groups. A higher E_2/E_1 ratio was therefore observed in the gel group. In comparison between the two groups during the 12 months of treatment, the changes of serum E_1 and serum E_2 were statistically significant different at 3, 6 months and at 3, 6, 12 months respectively. Serum FSH and LH were suppressed in both groups significantly with a steeper decreasing trend in the CEE group more than in the gel group. Comparison between serum FSH and LH in both groups were statistically significant different at 3, 6 months and at 0, 1, 6 months respectively. In both groups, most plasma lipids did not change with a statistical significance before and after treatment, only serum total cholesterol (TC) in the CEE group decreased significantly. Comparison of the plasma lipids TC, TG, HDL, LDL, Apo A_1, Apo B between the two groups during the study period did not show statistical differences in all parameters. The clinical response to treatment for climacteric symptoms was the same in both regimens.

Conclusion The estradiol gel groups had higher E_2/E_1 ratio, it showed high bioavailability than in the CEE group. Both therapies had the same effects in relieving typical climacteric in all subjects. However, the insignificance on the positive effect in most lipid profile in both types of estrogen preparations may be attributable to the small population and to large intra-individual of these parameters measured. Further more extensive studies are needed in Asain women setting.

Key words : hormonal replacement therapy, lipids, hormones, menopause

In Southeast Asian countries, homonal replacement therapy (HRT) is increasingly used to alleviate climacteric complaints in postmenopausal women. It is also highly effective in the prevention of osteoporosis.[1] Moreover, it has a positive effect on lipid profile with a reduction in the risk of coronary artery disease.[2] To avoid the increased risk of endometrial cancer associated with unopposed estrogen therapy, the sequential use of a progestin for at least 12 days each month is now recommended.[3, 4]

Peroral estrogen replacement therapy has been shown to have beneficial effect on the lipid profile in numerous studies.[5-12] High oral doses must be used, because metabolism in the gut wall and the liver results in only a transient increase in plasma estradiol and a non-physiological pattern of metabolites.[13]

Transdermal administration of estrogen has the advantage of by-passing the portal circulation. It can deliver low doses of estradiol at a constant rate within the range of early follicular phase.[11,14-17] However, little is known on the long-term effects of transdermal estrogens on the lipid profile.

The purpose of this study was to compare the effects of oral conjugated equine estrogens (CEE) and transdermal estradiol gel, both combined with an oral progestin, on hormonal and lipid profiles in postmenopausal Thai women.

Materials and Methods

Twenty-seven naturally menopausal Thai women (no menstruation for one year or more) with intact uteri participated in this study. Study was approved by the Human Ethical Committee

of Faculty of Medicine, Chulalongkorn University. All subjects signed an informed consent form. Subjects had climacteric symptoms without contraindications to hormonal therapy (on history of breast cancer or genital cancer), they did not have a history of thrombophelic or thrombo-embolic disease, Women with hypertension, diabetes, hepatic or renal dysfunctions were excluded from the study.

The subject underwent a complete physical examination, Papanicolaou smear and laboratory evaluation, including urinalysis and fasting blood samples for routine chemistry, liver enzymes, glucose, blood urea nitrogen (BUN), creatinine, complete blood count. Complete medical history was taken. No subject had taken any preparation of estrogen or progestin for at least three months prior to the study.

Twenty-seven naturally menopausal women who fulfilled the inclusion criteria were randomly allocated to two treatment groups for 12 months. The first group (N = 13) received conjugated equine estrogens (CEE) 0.625 mg/day orally for 21 days. The second group (N = 14) was given estradiol gel (17 - β E_2 gel) 1.5 mg/day for 21 days. Medroxyprogesterone acetate (MPA) 10 mg/day was added orally to both treatment groups on the last 14 days (day 8-21) of each cycle of medication. There was a medication free period during the last 10 days (day 22-30 or 31) of each month. Blood samples were obtained before treatment and on day 20 or day 21 after 1, 3, 6 and 12 months of therapy for hormonal (FSH, LH, E_1, E_2) and lipid (TC, TG, HDL, LDL, ApoA1, ApoB) study. All patients kept a calendar in which they recorded the frequency and the severity of menopausal symptoms (hot flushes, dysuria, dyspareunia, sweating) and any adverse effects from the medication. The diaries were collected and reviewed by study staff at every each visit of the study.

All lipid measurements and hormonal profiles were performed blindly by the co-investigators from the human reproduction laboratory

Table 1. Characteristics of studied women : (mean ± S.D.)

	CEE + MPA (N = 13)	Gel + MPA (N = 14)
Age (years)	52.5 ± 3.2	50.4 ± 3.2
Weight (Kg)	54.5 ± 8.4	56.3 ± 7.7
Height (cm)	151.6 ± 7.9	153.6 ± 3.1
BMI (kg/m^2)	23.7 ± 2.8	23.9 ± 3.2
BP Systolic (mmHg)	130 ± 10	120 ± 6.3
Diastolic (mmHg)	80 ± 0	80 ± 6.3
FBS (mg/dl)	81.5 ± 32.6	85.8 ± 33.8
SGOT (U/L)	27.5 ± 12.6	22.4 ± 3.9
Cr (mg/dl)	0.9 ± 0.13	0.98 ± 0.01
Hb (gm/dl)	12.01 ± 1.1	11.72 ± 0.92
Urine analysis	Normal	Normal
Pap smear	Negative	Negative

Table 2. Reproductive hormones in CEE/MPA and estradiol gel / MPA (x ± S.D.)

(N)	Basal	1 month	3 months	6 months	12 months	Friedman-Test
CEE/MPA (N = 13)						
FSH (mg/dL)	56.39 ± 24.78 (16.68 - 101.12)	17.92 ± 12.57 (5.21 - 47.88)	16.68 ± 17.15[a] (2.48 - 61.34)	14.55 ± 12.92[c] (1.99 - 42.86)	17.1 ± 14.41 (3.41 - 53.14)	P < 0.001
LH (mg/dL)	40.2 ± 14.94[a] (13.95 - 60.1)	17.28 ± 11.47[a] (3.47 - 38.56)	16.26 ± 18.5 (2.19 - 66.08)	14.27 ± 14.49[c] (1.71 - 55.08)	16.51 ± 10.93 (1.71 - 55.08)	P < 0.001
E_2 (p mol/L)	58.01 ± 21.17 (27.28 - 110.40)	195.18 ± 67.07 (103.31 - 307.2)	255.64 ± 66.06[a] (178.94 - 372.09)	232.36 ± 54.63[a] (165.7 - 352.94)	203.96 ± 65.93[a] (124.6 - 302.35)	P < 0.001
E_1 (p mol/L)	215.31 ± 120.33 (58.64 - 511.38)	494.92 ± 305.29 (180.38 - 1156.52)	706.81 ± 311.30[a] (207.79 - 1446.01)	655.66 ± 285.39[c] (230.15 - 1450.38)	665.55 ± 343.75 (246.17 - 1340.28)	P < 0.001
E_2/E_1	0.27/1	0.39/1	0.36/1	0.35/1	0.31/1	
Estradiol gel/MPA (N = 14)						
FSH (mg/dL)	69.53 ± 22.31 (38.08 - 112.01)	35.87 ± 27.11 (7.06 - 86.68)	34.97 ± 24.29[b] (4.33 - 72.88)	38.19 ± 21.23[d] (7.29 - 69.72)	29.48 ± 23.09 (4.70 - 68.16)	P < 0.001
LH (mg/dL)	62.06 ± 22.63[b] (29.92 - 103.52)	35.49 ± 22.09[b] (7.55 - 63.78)	32.09 ± 23.09 (3.34 - 66.65)	39.82 ± 24.95[d] (7.41 - 80.85)	31.63 ± 25.58 (2.21 - 80.56)	P < 0.001
E_2 (p mol/L)	62.32 ± 24.54 (34.20 - 117.6)	275.85 ± 198.89 (33.32 - 752)	466.92 ± 286.16[b] (103.5 - 1129.52)	471.85 ± 286.12[b] (60.64 - 907.92)	332.22 ± 154.87[b] (100.08 - 625.75)	P < 0.001
E_1 (p mol/L)	228.24 ± 125.45 (39.86 - 399.07)	448.7 ± 286.12 (3.74 - 938.29)	466.92 ± 286.16[b] (103.5 - 1126.52)	384.12 ± 233.02[d] (71.25 - 893.02)	485.88 ± 297.37 (63.09 - 1162.13)	P = 0.02
E_2/E_1	0.27/1	0.62/1	1.06/1	1.23/1	0.68/1	

Mann-Whitney U-test : - a, b - Significant at P < 0.05
c, d - Significant at P < 0.01

Table 3. Mean Plasma Lipid Values in CEE/MPA and estradiol gel/MPA (x ± SD)

(N)	Basal	1 month	3 months	6 months	12 months	Friedman-Test
CEE/MPA (N = 13)						
TC (mg/dL)	264.84 ± 51.66 (195.1 - 378.7)	238.95 ± 46.9 (170.9 - 327.7)	239.57 ± 46.9 (176.2 - 342.3)	257.74 ± 71.68 (193.6 - 438.6)	246.13 ± 47.53 (193.6 - 346.2)	P = 0.02
LDL-C (mg/dL)	182.72 ± 51.42 (116 - 299.7)	164.01 ± 40.92 (103.6 - 242.4)	161.51 ± 44 (103.5 - 249.5)	177.22 ± 61.78 (112.8 - 320.1)	165.72 ± 46.36 (110.6 - 264.1)	N.S.
HDL-C (mg/dL)	50.89 ± 10.63 (29.8 - 64.9)	50.95 ± 8.10 (35.7 - 65.9)	48.29 ± 8.88 (35.3 - 60.5)	48.32 ± 11.19 (32.8 - 65.8)	50.27 ± 9.81 (31.9 - 69.3)	N.S.
TG (mg/dL)	105.66 ± 44.55 (49.2 - 206.6)	109.68 ± 41.22 (46.9 - 180.3)	110.95 ± 47.84 (41.7 - 195.5)	125.39 ± 75.04 (44.9 - 329.2)	102.79 ± 44.51 (46.7 - 179.4)	N.S.
ApoA-1 (g/L)	1.4 ± 0.24 (0.98 - 1.77)	1.34 ± 0.21 (0.8 - 1.61)	1.33 ± 1.6 (1 - 1.58)	1.43 ± 0.24 (1.16 - 1.92)	1.39 ± 0.17 (1.02 - 1.74)	N.S.
ApoB (g/L)	0.88 ± 0.2 (0.58 - 1.26)	0.78 ± 0.13 (0.56 - 1.02)	0.8 ± 0.12 (0.63 - 1.09)	0.87 ± 2.1 (0.64 - 1.39)	0.82 ± 0.13 (0.68 - 1.11)	N.S.
Estradiol gel/MPA (N = 14)						
TC (mg/dL)	257.16 ± 58.23 (167.2 - 388.5)	246.40 ± 51.85 (160.7 - 343.6)	246.52 ± 56.79 (163.3 - 377.5)	242.14 ± 52.558 (160.1 - 379.5)	251.01 ± 51.97 (179.3 - 379.5)	N.S.
LDL-C (mg/dL)	171.64 ± 51.48 (88 - 316.6)	173.66 ± 49.09 (95.50 - 276.3)	167.88 ± 47.46 (108.5 - 266.2)	64.132 ± 43.42 (95.2 - 270)	170.91 ± 41.12 (103.5 - 255.8)	N.S.
HDL-C (mg/dL)	48.19 ± 9.03 (29.5 - 65.4)	47.97 ± 7.99 (40.10 - 64.80)	48.44 ± 6.79 (38.80 - 60.7)	49.23 ± 10.57 (31.7 - 64.1)	47.24 ± 7.06 (34.9 - 58)	N.S.
TG (mg/dL)	95.75 ± 43.64 (38.9 - 164.60)	84.11 ± 39.59 (34 181.50)	87.845 ± 50.55 (32 - 229.5)	97.839 ± 49.22 (32.8 - 218)	96.05 ± 45.66 (32.3 - 196.8)	N.S.
ApoA-1 (g/L)	1.35 ± 0.25 (0.95 - 1.63)	1.25 ± 0.19 (0.84 - 1.52)	1.3 ± 0.17 (0.98 - 1.55)	1.32 ± 0.22 (0.95 - 1.69)	1.29 ± 0.17 (0.97 - 1.56)	N.S.
ApoB (g/L)	0.8 ± 0.19 (0.5 - 1.08)	0.8 ± 0.15 (0.56 - 1.16)	0.79 ± 0.17 (0.60 - 1.28)	0.79 ± 0.19 (0.60 - 1.29)	0.85 ± 0.2 (0.56 - 1.31)	N.S.

unit at the Institute of Health Research, Chulalongkorn University. The serum lipids (TC, LDL, HDL, TG) were measured by the enzymatic PAP method (BIO Mericux). The ApoA-1 and ApoB were determined by nephelometry (Immunoprecipitation assay). Serum concentration o FSH, LH and estradiol were measured with radioimmunoassay (RIA).[18] Serum estrone (E_1) was measured with specific radioimmunoassay using commercial kits (Wein Laboratories, Inc). Serum chemistry measurement for screening in recruitment was determined from the central laboratory of Chulalongkorn Hospital.

Demographic data was analyzed by Unpaired-t-test. Friedman test and Mann-Whitney U-test were run on data where appropriated.

Results

At baseline, no significant differences between the two groups were detected with respect to age, body mass index (BMI), blood pressure, blood chemistry and urine analysis. All patients had normal Papanicolaou smear test (Table 1). The average mean age in the CEE/MPA and in the estradiol gel/(MPA) groups were 52.5 and 50.4 years, respectively. Thirteen subjects in the CEE group and 14 subjects in the gel groups completed 12 months of study.

Hormonal status

The mean serum follicular stimulating hormone (FSH) and luteinizing hormone (LH) were suppressed in both groups with a statistical significance. The decreased trend was steeper in the CEE group more than in the gel group. Comparison between serum FSH and LH in both groups were statistically significant different at 3, 6 months and 0, 1, 6 months respectively. (Table 2)

The mean serum estradiol (E_2) and estrone (E_1) increased significantly in both groups. In the CEE group the serum estrone (E_1) increased markedly, whereas serum estradiol (E_2) increased more in the gel group. A higher E_2/E_1 ratio at 3 and 6 months was observed to be greater than 1 in the gel group. In comparison between the two groups during 12 months of treatment, the changes of serum E_2 and serum E_1 were statistically significant different at 3, 6, 12 months and at 3, 6 months respectively. (Table 2)

Lipid profile

The results of the lipid study are shown in Table 3. In the CEE groups and in the gel group, most plasma lipid did not change with a statistical significance before and after treatment. Serum total cholesterol and serum LDL-cholesterol in both groups had a decreasing trend, only serum total cholesterol (TC) in the CEE group decreased significantly. HDL-cholesterol at baseline and after 12 months of theray did not change in both two groups. The serum triglyceride levels in the CEE group increased slighly at 1, 3 and 6 months and decreased at 12 months, whereas in the gel group the serum triglyceride decreased at 1 and 3 months and increased closely in the same value at the baseline at 6 and 12 months.

ApoA-1, the principle protein component of HDL was unchanged by both therapy. ApoB, the principle protein component of LDL was lower in the CEE group than in the estradiol gel group. Comparison of the plasma lipids TC, LDL, HDL, TG, ApoA-1 and ApoB between the two groups during study period did not show statistical differences in all parameters.

Climacteric symptoms

The common climacteric symptoms of all subjects were dizziness, tiredness, palpitation, forgetfulness, hot flushes, vaginal dryness and dyspareunia. From recorded diaries viewed at each visit by study staff showed the improvement

of clinical response to the treatment for those climacteric symptoms were the same in both regimens.

Discussion

There is a few data on hormonal and lipid profile studied in Southeast Asian postmenopausal women during hormonal replacement therapy. Steingold et al[19] demonstrated that transdermal estradiol significantly reduced the number of objectively measured hot flushes compared to placebo. In our study the estradiol gel group had higher E_2/E_1 ratio, especially at 3, and 6 months of therapy the E_2/E_1 ratio was greater than 1, it showed high bioavailability than in the CEE group. However, both therapies had the same effects in relieving typical climacteric in all subjects.

After menopause, atherosclerotic diseases become major causes of morbidity and mortality among women.[20] Postmenopausal women have higher plasma levels of total cholesterol (TC), triglycerides (TG), Very-Low-Density Lipoprotein (VLDL) cholesterol, as well as LDL cholesterol. High-Density Lipoprotein (HDL) cholesterol either does not change or is marginally decreased in estrogen-depleted women.[21,22] The impact of estrogen-progestin therapy on the health of postmenopausal women will be largely determined by its effect on cardiovascular diseases (CVD), which is mediated, for the most part, by changes in the serum lipid and lipoprotein levels.[23-27] In general, an orally administered estrogen therapy decreases the level of total and LDL cholesterol and increases the level of HDL cholesterol. Although such alterations in the lipid profile are consistent with a reduction in the risk of coronary artery diseases, plasma concentration of triglycerides may be concomitantly elevated.[9, 28]

Several studies[5-12] have shown the lowering effects of oral estrogen on total cholesterol and LDL-cholesterol. In our study, only total cholesterol decreased significantly in the CEE group, LDL-cholesterol and Apo-B tended to decrease slightly. However, we did not find any significant changes on HDL-cholesterol and ApoA-I inconsistent with previous reports.[29-32]

In this study, the estradiol gel had the similar effect in lowering total and LDL-cholesterol, and Apo-B. HDL-cholesterol and ApoA-I also did not change. Opposite results in measuring plasma triglycerides, tended to decrease in the estradiol gel group but tended to increase in the oral CEE groups as reported by Stern et al[33] and Elkik.[34]

There is no substantial epidemiologic data describing the effect of combined estrogen plus progesterone replacement therapy on CVD, but progesterone seems to attenuate some of the positive effects of estrogen.[35] However, progesterone are structurally heterogenous : C-21 derivatives, such as medroxyprogesterone, which was used in this study, seem to cause fewer adverse effects on the lipid profile than the C-19 nor-derivatives.[36] In our study, the addition of medroxyprogesterone to both types of estrogen (CEE and gel) seemed to have no counteract on the positive effects of estrogens on the lipid profile.

Lipid and lipoprotein metabolism is complex and influenced by numerous factors, including, sex, race, diet, obesity, excercise, life-style, smoking, alcohol consumption, socioeconomic status and a variety of drugs.[37] Studies done in the Western countries[38-41] have shown that some climacteric symptoms (e.g. hot flushes) to be more severe in the Western women than in the Asian women.[42-45] This could be attributed to the different life styles. Southeast Asian women have Asian race, less fatty food intake or diet, less smoking and alcohol consumption habits. These

factors might influence the lipid metabolism and make the difference between Western and Southeast Asian women. However, the insignificance on the positive effect in most lipid profile in our study in both types of estrogen preparations may be attributable to the small population and to large intra-individual variations of these parameters measured. In solving these problems more extensive studies are needed in Asian women setting.

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