The effects of conjugated equine estrogens plus cyclical dydrogesterone on serum lipoproteins and apoproteins in postmenopausal women

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Abstract. Serum lipoprotein and apoprotein concentrations were monitored for 24 weeks in 26 postmenopausal women treated with conjugated equine estrogens (0.625 mg/day) with the addition of dydrogesterone (10 mg/day) for the last 12 days of each 28 day cycle. The women had had no previous hormone replacement therapy. The estrogen plus dydrogesterone regimen caused significant ($P < 0.05$) increases in triacylglycerol and HDL cholesterol concentrations. Both HDL2 and HDL3 cholesterol were increased. There were no other significant changes in lipoprotein concentrations. Both apoprotein AI and apoprotein AII concentrations increased significantly ($P < 0.05$) over the study period. The ratios of apoprotein AI to apoprotein AII, apoprotein A1 to HDL cholesterol and apoprotein AII to HDL cholesterol did not change. At the doses employed in this study, the use of dydrogesterone as a progestogen alters the effects of conjugated equine estrogens on lipoproteins and reinforces the view that the effects of a combined HRT regimen cannot be predicted from a consideration of the effects of the individual components.

It is well established that hormone replacement therapy (HRT) relieves the distressing physical symptoms caused by the menopause and prevents the rapid loss of bone which may eventually lead to the development of osteoporosis. Women with intact uteri are usually treated with a cyclical preparation incorporating a progestogen in the latter half of the cycle to avoid the endometrial hyperplasia associated with estrogen only regimens (Sturdee et al. 1978).

Most cyclical regimens to date have used one of the androgenic progestogens, either norethisterone or norgestrel. These progestogens have the disadvantage that they cause adverse changes in lipid (Farish et al. 1983; Hirvonen et al. 1981) and carbohydrate metabolism (Spellacy et al. 1975). For this reason there has been considerable interest in progestogens which do not have androgenic properties. One such progestogen is dydrogesterone (6-dehydro-9ß,10-progesterone) a retroprogesterone which has no androgenic effects (Schöler et al. 1961). Preliminary evidence suggests that it does not affect lipid metabolism (Lacey et al. 1983) when used alone. However, the metabolic effects of a cyclical preparation are difficult to predict from a consideration of the effects of the individual components because the overall effect depends on factors such as the doses and potencies of the hormones used. To our knowledge, there are no reports on the effects of conjugated equine estrogens plus cyclical dydrogesterone on the lipoproteins of postmenopausal women. In this study we have monitored the effects of such a preparation over a period of 24 weeks on the lipoproteins and apoproteins of a group of menopausal women who had had no previous hormone replacement therapy.
Patients and Methods

Twenty-six women attending the menopausal clinics at the Western Infirmary and Stobhill General Hospital, Glasgow, who were suffering from climacteric symptoms, participated in the study. Twenty-three of the women had had a natural menopause and were judged to be postmenopausal by the presence of established amenorrhea and postmenopausal gonadotropin levels. The remaining 3 women had had a surgical menopause. None of the women was taking any drug liable to interfere with lipid metabolism. All had normal renal and hepatic function before and during treatment as indicated by routine biochemical tests and in no case was there any contraindication to hormone replacement therapy. Informed consent was obtained from each subject.

The women (mean age 47.9 ± 4.0 years) who had not received any hormone therapy prior to commencing treatment were treated for 24 weeks with a combined preparation consisting of conjugated equine estrogens (Premarin®, Ayerst, UK), 0.625 mg/day, with the addition of dydrogesterone (Duphaston®, Duphar, UK), 10 mg/day, during the last 12 days of each 28-day treatment cycle.

Fasting specimens of blood for lipoprotein analysis were obtained before commencing and after 8, 16 and 24 weeks treatment. Specimens were therefore taken in all cases at the end of the progestogen phase of the treatment cycle. Serum was separated by centrifuging for 10 min at 1000 × g and stored at 4°C for a maximum of 5 days prior to analysis. Serum triacylglycerol concentrations were measured enzymatically (Bucolo & David 1973) using a Technicon RA1000. Cholesterol concentrations were estimated manually using an enzymatic technique (Allain et al. 1974). VLDL was separated from serum by ultracentrifugation (Airfuge, Beckman Instruments Ltd) as described previously (Farish et al. 1983). HDL and subfractions (HDL2 and HDL3) were quantified using the method of Eyer et al. (1981). LDL cholesterol levels were obtained by calculation of difference. Apoproteins A1 and AII were estimated by an immunoturbidimetric assay (Siedel et al. 1983) using commercial antiserum (Boehringer Mannheim GmbH, FRG) and reference standards (Immuno Diagnostica GmbH, FRG).

The results were analysed by a repeated measures analysis of variance using the Rummage statistics package (Bryce 1980). Differences from baseline were assessed using Bonferroni confidence intervals and normality and constant variance were assessed graphically using relevant residual plots.

Results

All the data were normally distributed (Table 1). Triacylglycerol concentrations increased steadily over the 24 weeks of the study, the increase becoming significant at 8 weeks. Total, VLDL and LDL cholesterol concentrations did not change significantly. HDL cholesterol concentrations

| Table 1. Lipoprotein, HDL subfraction and apoprotein concentrations (mean ± SD) in 26 postmenopausal women treated with conjugated equine oestrogens (0.625 mg/day) plus cyclical dydrogesterone (10 mg/day for 12 days of each treatment cycle). |
|-----------------|----------------|----------------|----------------|
|                 | Baseline       | 8 weeks        | 16 weeks       | 24 weeks       |
| Triacylglycerol (mmol/l) | 1.44 ± 0.64   | 1.60 ± 0.64*   | 1.66 ± 0.73*   | 1.70 ± 0.66*   |
| Total cholesterol (mmol/l) | 6.18 ± 0.89   | 6.81 ± 1.04    | 6.16 ± 0.97    | 6.09 ± 0.95    |
| VLDL cholesterol (mmol/l) | 0.57 ± 0.33   | 0.55 ± 0.29    | 0.54 ± 0.33    | 0.53 ± 0.33    |
| LDL cholesterol (mmol/l)  | 4.07 ± 0.95   | 3.91 ± 1.13    | 3.90 ± 1.00    | 3.85 ± 0.96    |
| HDL cholesterol (mmol/l)  | 1.58 ± 0.38   | 1.82 ± 0.47*   | 1.82 ± 0.39*   | 1.74 ± 0.37*   |
| HDL2 cholesterol (mmol/l) | 0.51 ± 0.26   | 0.62 ± 0.31*   | 0.58 ± 0.19*   | 0.58 ± 0.19*   |
| HDL3 cholesterol (mmol/l) | 1.07 ± 0.19   | 1.20 ± 0.26*   | 1.24 ± 0.22*   | 1.16 ± 0.22*   |
| HDL2:HDL3 cholesterol (mmol:mmol) | 0.48 ± 0.20   | 0.50 ± 0.25    | 0.49 ± 0.22    | 0.52 ± 0.25    |
| Apoprotein A1 (g/l)       | 1.25 ± 0.15   | 1.37 ± 0.19*   | 1.35 ± 0.17*   | 1.37 ± 0.14*   |
| Apoprotein AII (g/l)      | 0.35 ± 0.04   | 0.42 ± 0.05*   | 0.43 ± 0.05*   | 0.43 ± 0.06*   |
| Apoprotein A1 : apoprotein AII (g:g) | 3.29 ± 0.76   | 3.26 ± 0.70    | 3.11 ± 0.65    | 3.16 ± 0.71    |
| Apoprotein A1 : HDL cholesterol (g:g) | 1.86 ± 0.20   | 1.85 ± 0.22    | 1.83 ± 0.25    | 1.84 ± 0.30    |
| Apoprotein AII: HDL cholesterol (g:g) | 0.56 ± 0.19   | 0.56 ± 0.20    | 0.59 ± 0.18    | 0.58 ± 0.17    |

* Significantly different from baseline *P < 0.05.
were significantly higher during treatment, both HDL2 and HDL3 cholesterol increasing significantly. The ratio of HDL2 to HDL3 cholesterol did not change. Both apoprotein AI and AII increased significantly over the treatment period. There were no significant changes in the ratio of apoprotein AI to apoprotein AII, apoprotein AI to HDL cholesterol or apoprotein AII to HDL cholesterol.

Discussion

The results of this study indicate that the combination of conjugated equine estrogens plus cyclical dydrogesterone primarily affects HDL cholesterol and the HDL associated apoproteins. The only other statistically significant change found was an increase in triacylglycerol concentrations.

Conjugated equine estrogens change lipoproteins in the same manner as do synthetic estrogens (Notelovitz et al. 1983), that is they decrease LDL cholesterol and increase HDL and VLDL cholesterol and triacylglycerols. In a previous study (Farish et al. 1986), we confirmed this and demonstrated that the increase in HDL cholesterol was caused mainly by an increase in HDL2 cholesterol. The effects of non-androgenic progestogens on lipoproteins in menopausal women are not well documented but the evidence available suggests that they have little effect (Hirvonen et al. 1981; Silverstolpe et al. 1979).

Our data shows that the addition of cyclical dydrogesterone alters the previously reported effects of conjugated equine estrogens (Notelovitz et al. 1983; Farish et al. 1986). Although triacylglycerols were increased by the combination therapy, VLDL cholesterol concentrations did not increase suggesting that the composition of VLDL was altered. Total HDL cholesterol was increased, the rise being of similar magnitude as that observed during treatment with conjugated estrogens alone. Both fractions were increased and by proportionally the same amount so that the HDL2: HDL3 cholesterol ratio did not change.

We have found that the combination of conjugated equine estrogens plus dydrogesterone increases apoprotein AI and apoprotein AII concentrations. However, neither the apoprotein AI to AII nor either of the apoprotein to cholesterol ratios changed significantly. This is consistent with the increase in HDL2 and HDL3 cholesterol being proportionally the same since HDL2 has a lower ratio of apoprotein A to cholesterol and a higher ratio of apoprotein AI to AII than HDL3 (Cheung & Albers 1977).

The importance of measuring HDL apoprotein concentrations is not as well established as that of measuring HDL cholesterol, but there is a growing body of evidence that HDL apoprotein concentrations are important with regard to arterial disease. For example, Bradby et al. (1978) found that HDL cholesterol concentrations did not discriminate as well between patients with peripheral vascular disease and controls as did concentrations of apoprotein AI and AII. Similarly Riesin et al. (1980) reported that apoprotein AI and AII discriminated better than HDL cholesterol concentrations between patients with coronary artery disease and a control group. However, although these parameters have been found to be associated with coronary heart disease risk, except in the case of LDL cholesterol, there is no evidence that pharmacologically altering them changes actual risk.

In summary, the results of this study indicate that the use of dydrogesterone as progestogen alters the effects of conjugated equine estrogens on lipoproteins and reinforces the view that the effects of a combined HRT regimen cannot be predicted from a consideration of the effects of the individual components.

References


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