Beneficial effects of low doses of ethinyl-estradiol on the lipid profile in postmenopausal women

M. Minozzi, L. Costabile, E. Cosmi, F. Donadio, E. De Filippis, E. V. Cosmi
II Institute of Obstetrics and Gynecology, University of Rome “La Sapienza” (Italy)

Summary

The purpose of this study was to investigate the beneficial effects of low doses of ethinyl-estradiol on the lipid profile in postmenopausal women. One hundred and five patients (mean age \( \pm S D \) 42.9 \( \pm 5.0 \) years) who underwent a hysterectomy and bilateral salpingo-oophorectomy were included in the study. For the present study serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, apolipoprotein B (apoB), and lipoprotein(a) \( [Lp(a)] \) were investigated. When all patients were considered together (Table 1), EE2 therapy significantly increased serum levels of total cholesterol, HDL cholesterol and LDL cholesterol. The ratio of HDL to LDL cholesterol, \( Lp(a) \) and triglyceride concentrations did not change significantly from the baseline value. Although our study was not randomized or controlled with a placebo, the beneficial metabolic effects of ethinyl-estradiol on lipid patterns should be considered in patients needing hormonal replacement therapy in postmenopause.

Key words: Ethinyl-estradiol - HRT.

Introduction

Several metabolic side-effects attributed to oral contraceptives have been ascribed to the estrogenic component (ethinyl-estradiol). Some of these effects, such as increases in plasma triglyceride and cholesterol concentrations appear to be dose-dependent effects and other metabolic side-effects are progestin dependent [1-4].

After menopause, rates of coronary heart disease (CHD) increase in women until they become similar to the corresponding rates in men of a similar age [5]. This increased incidence of CHD in postmenopausal women has been attributed in part to adverse changes in plasma lipids and lipoprotein levels [6]. Specifically, levels of low density lipoprotein (LDL) increase after menopause. There is evidence that HRT reduces the rate of CHD in postmenopausal women [7, 8].

Numerous estrogen preparations and modes of administration have been developed in an effort to find which will relieve climacteric symptoms and prevent CHD. Orally administrated estrogen is one of the most frequently used replacement therapies.

We chose to evaluate the effect of low doses of EE2 on the lipid profile in women who had undergone a hysterectomy and bilateral salpingo-oophorectomy because this group of patients does not need the progestogen component for hormonal replacement therapy.

Materials and Methods

One hundred and five patients (mean age \( \pm S D \) 42.9 \( \pm 5.0 \) years) who had undergone a hysterectomy and bilateral salpingo-oophorectomy were included in the study. Prior to surgery all patients had normal serum levels of FSH and E2. The women were asked to continue their normal diet, but to exclude alcohol for the entire study duration. The exclusion criteria were: smoking, unwillingness to discontinue use of alcohol, history of carcinoma, gall stones, thrombophlebitis, thyroid disease, diabetes or current taking of medication known to influence lipoprotein metabolism. Patients had not taken hormonal medications, including contraceptive pills, for the previous six months.

Ethinyl-estradiol (0.01 mg daily) which was administered for one year began ten days after the operation.

For the present study serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, apolipoprotein B (apoB), and lipoprotein(a) \( [Lp(a)] \) were investigated.

Assays

Levels of HDL cholesterol were measured in supernatant after plasma precipitation with phosphotungstic acid and Mg2+ (Boehringer Mannheim GmbH, Mannheim, Germany). Levels of total cholesterol and triglycerides were measured by using enzymatic methods (Menarini Diagnostica, Florence, Italy). The LDL cholesterol level was calculated by using the formula of Friedewald et al. Normal lipid values were defined as follows: HDL cholesterol > 50 mg/dl, LDL cholesterol < 160 mg/dl, total cholesterol 120-240 mg/dl, and triglycerides 50-150 mg/dl. Levels of Apo B and \( Lp(a) \) were quantified by performing kinetic immunonephelometry (Array Protein System; Beckman Instruments, Palo Alto, CA).

Statistical Analysis

Results are expressed as means \( \pm SD \). The Kolmogorov-Smirnov statistic with a Lilliefors significance level for testing normality was applied to continuous variables. Logarithmic transformation was used to ensure a normal distribution as needed. Paired t-tests were used to identify the differences between variables at baseline and after 12 months of treatment with EE2. A p-value <.05 was considered statistically significant.
Table 1. — Clinical and biochemical variables in 105 postmenopausal women at baseline and after 12 months of treatment with ethinyl-estradiol.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2±8.8</td>
<td>25.9±7.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>165±30</td>
<td>186±23</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54±13</td>
<td>65±14</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>97±25</td>
<td>105±17</td>
<td>N.S.</td>
</tr>
<tr>
<td>HDL-to-LDL ratio</td>
<td>0.53±0.04</td>
<td>0.55±0.04</td>
<td>N.S.</td>
</tr>
<tr>
<td>ApoB level (mg/dl)</td>
<td>74±13</td>
<td>76±12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>25±26</td>
<td>27±28</td>
<td>N.S.</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>68±50</td>
<td>78±37</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Values are means ±SD. ApoB = apolipoprotein B; HDL = high-density lipoprotein; LDL = Low-density lipoprotein; Lp(a) = lipoprotein(a).

Results

Treatment with EE2 was well tolerated and no patient withdrew from the study. In all patients total cholesterol concentrations were < 240 mg/dl at baseline and after 12 months of treatment with EE2.

Forty-two patients (44.1%) presented with HDL cholesterol levels < 50 mg/dl; in 31 patients these levels normalized after EE2 treatment. Levels of LDL cholesterol were < 160 mg/dl in all patients throughout the study. Only one of 105 patients had increased serum triglyceride levels (215 mg/dl) at the end of the study (at baseline these levels were 165 mg/dl). At baseline 15 patients had Lp(a) levels > 30 mg/dl (which is considered a CHD risk factor); two of these patients also had low HDL cholesterol levels. The increased Lp(a) levels persisted after EE2 treatment in ten patients, but in all of these HDL cholesterol levels increased to normal values.

When all patients were considered together (Table 1), EE2 therapy significantly increased serum levels of total cholesterol, HDL cholesterol and LDL cholesterol. The ratio of HDL to LDL cholesterol, Lp(a) and triglyceride concentrations did not change significantly from the baseline value.

Discussion and Conclusion

It is common knowledge that the reduction of hormone levels in postmenopause causes an increased prevalence of risk factors for cardiovascular diseases, including dyslipidemia.

We evaluated the metabolic effects of EE2 considered to be especially suited to avoiding lipid tolerance abnor-

malties. We used very low doses of EE2 (0.01 mg) equivalent to 0.625 mg of conjugated estrogens. The changes in lipid concentrations among postmenopausal women in our study showed a beneficial effect of EE2 on lipid profiles. On the one hand, serum HDL cholesterol levels increased by a mean of 10 mg/dl after treatment; more than 50% of the patients with initially low HDL cholesterol concentrations experienced normalization of this risk factor for cardiovascular disease. On the other hand, neither serum triglyceride levels nor Lp(a) increased significantly, and although LDL cholesterol levels increased slightly during therapy, these levels were within the normal range both before and after treatment in all patients.

Although our study was not randomized or controlled with a placebo, the beneficial metabolic effects of ethinyl-estradiol on lipid patterns should be considered in patients needing hormonal replacement therapy in postmenopause.

References