Cardiovascular risk factors in postmenopausal women: effects of estrogen therapy on glucose and lipid profiles

Paola Villa, MD1
Maria Cristina Moruzzi, MD1
Anna Pia Lassandro, MD2
Francesca Sagnella, MD1
Maria Teresa Riccardi, MD1
Lorenzo Vacca, MD1
Giovanna Salerno, MD1,3
Giovanni Scambia, PhD1

1 Department of Obstetrics and Gynecology, Catholic University of Sacred Heart, Rome, Italy
2 Department of Endocrinology, Catholic University of the Sacred Heart, Rome, Italy
3 Department of Obstetrics and Gynecology, AOU Pisa, Italy

Correspondence to:
Paola Villa
Catholic University of the Sacred Heart
Policlinico A.Gemelli,
Lgo A Gemelli 8, 00168 Rome, Italy
E-mail: paolavilla@rm.unicatt.it

Summary
The menopause is associated with unfavorable changes in the lipid profile as well as in glucose metabolism, which may help to increase the incidence of cardiovascular diseases. The metabolic impact of hormone replacement therapy differs in relation to the dose of the estrogen component, the type of progestin, and the route of administration used. Since most studies analyze the effect of combined estro-progestin therapy, the impact of the estrogen component alone is not always differentiable, however the main results are generally consistent. A review of the recent literature was conducted to analyze the impact of estrogen replacement therapy (ERT) on glucose and lipid metabolism and the differences linked to different doses, associations and routes of administration. Studies were selected on the basis of quality of data and relevance to the present topic. Many studies showed that both oral and transdermal estrogen therapy induced positive effects on glucose metabolism, with minimal changes and differences between treatments. A considerable amount of data documented increases in HDL and decreases in LDL cholesterol. Low-dose estrogen therapy showed no negative effect on triglycerides and a neutral effect on the whole lipid panel.
In conclusion, low-dose ERT may prevent the physiological worsening of glucose and lipid metabolism in menopausal women without showing any significant negative effects.

KEY WORDS: estrogen replacement therapy, glucose, hormone replacement therapy, insulin, lipid metabolism.

Introduction
The incidence of cardiovascular diseases increases substantially after the menopause, and the menopause may play a causative role in this increase, even independently of chronological aging. The falling estrogen levels observed in the peri- and postmenopause may be involved in this process, as may the subsequent androgen-dominated metabolic environment (1). The menopausal transition and the menopause itself are associated not only with unfavorable changes in the blood lipid profile (2) and with a deterioration of glucose tolerance and insulin sensitivity, but also with increases in blood pressure, body weight and anthropometric measurements (3). The loss of hormones with the menopause seems to reduce insulin secretion and elimination and increase insulin resistance, thereafter bringing about an increase in the circulating insulin concentration and a higher incidence of both diabetes and metabolic syndrome (4). The increased cardiovascular risk in diabetes is, in part, mediated by the associated dyslipidemia, which is mainly due to the insulin-resistance state. Therefore, hyperinsulinemia and dyslipidemia are classical components of the metabolic syndrome and this syndrome increases with the menopause independently of age, exacerbating the cardiovascular risk in older women. It was long believed that estrogen administration might have deleterious effects on lipid and glucose metabolism, a perception dating back to the steroid composition- and dose-dependent metabolic effects observed in high-estrogen oral contraceptive use (5). In the same way, the metabolic impact of hormone replacement therapy (HRT) differs in relation to the dose of the estrogen component, the type of progestin, and the route of administration used. Current hormone therapy seems to be associated with a decreased prevalence of abdominal obesity and better glucose metabolism, and prior use of hormone therapy has been associated with a lower risk of abdominal obesity and high blood pressure.
Because the majority of studies analyze the effect of the combined estro-progestin therapy, the impact of the estrogen component alone is not always differentiable. Since, according to the latest clinical recommendations, it is opportune to treat postmenopausal symptoms with the lowest effective dose, we reviewed recent literature data on low-dose treatments or on low- versus high-dose replacement therapies. Significant differences seem to exist between oral and transdermal estrogens in terms of...
Estrogens and cardiovascular risk factors in menopause

Estrogens and carbohydrate metabolism

Estrogens play a role in glucose homeostasis, possibly through effects on insulin secretion and clearance. Postmenopausal women had similar glucose and insulin levels to premenopausal women but produced 50% less insulin and eliminated it slowly, thus compensating for the reduced secretion (4).

Estrogens may have direct effects on the pancreas and may also influence other hormones which themselves affect insulin secretion or action. Receptor binding for estrogen occurs in the pancreatic islets and at this level estrogen can increase the presence of progesterone receptors, whose activation after progesterone exposure in isolated pancreatic islets increases insulin release (6,7).

The administration of estrogens, especially at high doses, increases glucocorticoid activity and brings about an increase in growth hormone secretion, influencing insulin secretion (8,9).

The possibility that, in humans, estrogens cause glucagon antagonism could provide an explanation for the reduction in fasting plasma glucose often observed in subjects administered estrogens. Estrogen deficiency is associated with reduced glucose tolerance and increased insulin resistance, while estrogen replacement leads to reversal of these effects. Estrogens in excess (high-dose HRT) may also be associated with glucose tolerance deterioration and insulin resistance. These different responses to various levels of estrogens could be linked to insulin receptor gene expression (10).

Clinical evaluation

Because of the substantial and variable uptake of newly secreted insulin by the liver and the short half-life of insulin, pancreatic insulin secretion cannot be assessed through measurement of plasma insulin concentration alone. C-peptide is secreted simultaneously with insulin and in equimolar quantities but does not undergo uptake by the liver. Many models using intravenous or oral glucose tolerance tests have been developed to derive the fraction of newly secreted insulin passing through the liver and the rate of insulin elimination from the general circulation.

Although the glucose clamp technique remains the only direct measure of insulin sensitivity and the gold standard for this measurement, many different indexes of insulin sensitivity have been assessed. The most validated are measurement of the fasting insulin/glucose ratio, evaluation of the glycemic and insulinenic area under the curve (AUC) during the oral glucose tolerance test (OGTT), and the HOMA-IR (homeostasis model assessment) and QUIKI (quantitative insulin sensitivity check index) assessments.

Estrogen replacement therapy and carbohydrate metabolism

The three-year Postmenopausal Estrogen/Progesterin Interventions (PEPI) study was the first placebo-controlled trial to evaluate the effect of postmenopausal hormone therapy on glucose metabolism. The researchers found a statistically significant decrease in fasting glucose levels in patients who adhered to their assigned hormone therapy (11). Two randomized clinical trials, carried out with the primary endpoint of evaluating cardiovascular outcomes, unexpectedly found a significantly lower incidence of diabetes in patients receiving HRT (12,13). The Heart and Estrogen/progestin Replacement Study (HERS) published data on the incidence of diabetes in 2029 postmenopausal women who had coronary heart disease (CHD) and had been assigned to daily estrogen (0.625 of conjugated equine estrogen, CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) therapy or to placebo (12). The incidence of diabetes in this four-year study was 6.2% in the treated group compared to 9.5% in the placebo group (HR 0.65, 95%CI 0.43-0.89).

Along the same lines, the Women’s Health Initiative, which included the study of 8014 healthy women receiving HRT, showed a reduction of the incidence of diabetes possibly related to a decrease in insulin resistance. Data from this trial indicated a small but significant decrease in fasting glucose and fasting insulin levels (13). Margolis et al., using the HOMA-IR calculation to estimate insulin resistance, showed a significant decrease in insulin resistance unrelated to body size (13).

Table 1 shows studies analyzing the effects of low-dose estrogen administration (including ones comparing low and high doses and ones evaluating only low-dose formulations, with or without progesterin) on specific parameters for the evaluation of glucose metabolism. This table highlights differences related to the dose and route of administration used.

Lobo et al. evaluated the effects of low oral doses of CEE 0.45 and 0.3 as compared with 0.625 and found only minimal changes and differences between treatments (14). Further studies showed only minimal positive changes in carbohydrate metabolism (15,16). According to Kajalainen et al., neither oral estradiol (2 mg/day) nor transdermal estradiol (1 mg/day) replacement therapy had any negative effects on glucose metabolism, both treatments being found to induce only a small significant reduction in HbA1 levels and no change in post-challenge glucose and insulin levels (16).

A recent study by our group showed that high-dose oral estrogen therapy (2 mg) caused a slight deterioration in insulin sensitivity. On the contrary, low-dose estradiol unsupported treatment led to an improvement in peripheral in-
sulin sensitivity as shown by an increase in the metabolic index and a decrease in the insulin resistance index (HOMA-IR) (17). Researchers have not found any impairment of carbohydrate metabolism even in the case of low-dose estradiol oral therapy associated with progestin. Some recent studies evaluating the effects of 1mg estradiol/0.5 mg norethisterone acetate (NETA) administration showed a decline in fasting glucose and insulin levels (above all in women with higher basal fasting levels) and an improvement in HbA1c and OGTT challenge in the treated groups (18-21). Similarly, the low-dose estrogen/drospirenone combination therapy did not show any negative effect on carbohydrate metabolism but a slight positive effect on insulin secretion (21). Transdermal administration (50μg/day) to healthy women seems to reduce insulin levels; in one study it seemed to increase pancreatic C-pep response to glucose, whereas in another significant changes were found only in hyperinsulinemic patients (22,23).

Estrogens and lipid metabolism

A large number of studies demonstrated that postmenopausal status is associated with increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a), and decreased levels of high-density lipoprotein cholesterol (HDL-C) (26).

Table 1- Effects of estrogen replacement therapy on glucose metabolism

<table>
<thead>
<tr>
<th>References</th>
<th>No. of subjects</th>
<th>Duration of therapy</th>
<th>Fasting glucose</th>
<th>Fasting insulin</th>
<th>AUC glucose</th>
<th>AUC insulin</th>
<th>HbA1c 1c</th>
<th>Insulin sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral low-dose CEE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobo et al., 2001 CEE 0.3-0.45 mg</td>
<td>95/89</td>
<td>12 months</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Oral estradiol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al., 2003 E2 1mg / NETA 0.5mg</td>
<td>40</td>
<td>12 months</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>=/↓</td>
<td>↑</td>
</tr>
<tr>
<td>Kernohan et al., 2007 E2 1mg / NETA 0.5mg</td>
<td>15</td>
<td>3 months</td>
<td>↓</td>
<td>=</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villa et al., 2008 E2 1mg</td>
<td>48</td>
<td>3 months</td>
<td>=</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td>Bingol et al., 2009 E2 1mg / NETA 0.5 mg</td>
<td>40</td>
<td>6 months</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Villa et al., 2011 E2 1mg / DRSP 2mg</td>
<td>40</td>
<td>6 months</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Transdermal estradiol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cagnacci et al., 1997 E2 50μg</td>
<td>9</td>
<td>2 months</td>
<td>=</td>
<td>=</td>
<td>=/↓</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Cucinelli et al., 1999 E2 50μg</td>
<td>21</td>
<td>12 weeks</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=/↓</td>
<td>=/↑</td>
</tr>
<tr>
<td>Duncan et al., 1999 E2 50μg</td>
<td>22</td>
<td>6 weeks</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Karjalainen et al., 2001 E2 1mg</td>
<td>38</td>
<td>6 months</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=/↓</td>
</tr>
</tbody>
</table>

AUC: area under the curve; E2: estradiol; CEE: conjugated equine estrogen; NETA: norethisterone acetate; DRSP: drospirenone; = : no statistically significant change; ↓: increase; ↓: decrease; *Decrease of insulin in oral glucose tolerance test, no change in intravenous glucose tolerance test.

Some studies exploring the effects of estrogen administration in patients with diabetes or metabolic syndrome showed neither an impact on glucose metabolism nor any improvement of insulin resistance (24,25). The latter study in particular pointed out that transdermal estradiol administration had a more beneficial effect.
they increase the hepatic expression of apoprotein genes and LDL receptors and decrease transcription of the lipoprotein lipase (LPL) gene through ERα. Thus, when estrogen levels decrease after the menopause, an increase in LPL activity is observed and this probably contributes to the increased levels of free fatty acids as well as to the accumulation of abdominal fat. By inhibiting lipogenesis, estrogens alter the expression of hormone-sensitive lipase (29). On the other hand, through ERβ and ERα, estrogens are involved in the proliferation of adipocytes, whereas their reduction increases central obesity which is associated with a more atherogenic profile (30).

Epidemiological data suggest a role for estrogen replacement in reducing CHD after the menopause, with an improved lipid status supposedly accounting for 25-50% of this protective effect. However, estrogen substitution has both positive and negative effects (31). Negative effects might be: increased occurrence of postprandial hyperlipidemia with increased triglycerides, generation of atherogenous small dense LDL particles, increased risk of inflammatory changes in the vascular wall and procoagulation effects.

**Estrogen replacement therapy and lipid metabolism**

At present most available data document increased HDL and reduced LDL cholesterol as well as lower total plasma cholesterol and sometimes increased triglyceride levels (32-35) following estrogen replacement therapy. However, there remain many differences in the results and conclusions of the different studies (36-38). Table 2 summarizes the main studies on the effect of estrogen replacement on lipid parameters.

Two major placebo-controlled trials document the effects of ERT on lipid metabolism. One study, the HERS, showed that LDL cholesterol levels decreased from baseline in the treated and in the placebo group, while HDL cholesterol levels increased in the treated group and decreased in the placebo group. Mean triglyceride levels increased in both groups (12).

The Estrogen and Atherosclerosis (ERA) trial was a placebo-controlled, randomized trial that examined the effects of conjugated equine estrogen (CEE, 0.625 mg/day) or CEE (0.625 mg/day) plus MPA, (2.5 mg/day) on 256 postmenopausal women with established coronary atherosclerosis (39).

This study showed reduced plasma remnant lipoprotein concentrations in the context of unchanged or raised plasma triglyceride levels as well as significant increases in HDL-C and apo A-I levels.

Variations in treatment effects may be attributable to differences in baseline characteristics among individuals as well as to differences in preparations, doses and routes of hormone administration.

Studies comparing oral low-dose estrogen or estrogen+progestin and standard/high dose hormone therapy showed that CEE often increased levels of HDL cholesterol and reduced levels of LDL and total cholesterol by the same order of magnitude as standard-dose hormone therapy (40-44).

Therefore, different effects on triglyceride levels have been reported.

In some studies triglyceride levels increased significantly with higher doses (0.625 and 1.25 mg), but not with low-dose treatment (CEE 0.3 mg) (40-44); one study showed no difference between CEE 0.3 mg and CEE 0.625 mg doses (43), while others showed that low-dose CEE (0.3 mg) increased triglyceride levels as much as the standard-dose (41,42).

There emerged no dose-related effect on LDL cholesterol or total cholesterol (41). Significantly increased levels of HDL cholesterol and reduced LDL cholesterol and total cholesterol were seen with administration of oral estradiol 1 mg, with or without progestin (45-49).

The effects of estradiol 1 mg on triglycerides were mainly neutral.

In a previous study, we evaluated the different influences of two dosages of oral formulations of unopposed estradiol (1 mg vs 2 mg) compared with a placebo treatment, both on glucose tolerance and lipid metabolism in 48 healthy non-obese normoinsulinemic postmenopausal women (17). We found that the total cholesterol level did not change, after treatment, in any group. Patients treated with 1 mg estradiol showed no increase in triglyceride, HDL cholesterol and VLDL cholesterol concentrations after treatment, while a slight but not significant decrease in LDL cholesterol sub-fractions was observed. This study showed that the low-dose therapy did not adversely affect plasma concentration of triglycerides. On the other hand, the beneficial effect on the lipoprotein profile (increase in HDL cholesterol and decrease in LDL cholesterol levels, with a significant reduction of the LDL/HDL ratio) was observed in the high-dose estradiol treatment only (17). A subsequent study showed that low-dose estrogen (1 mg) in combination with drospirenone (2 mg) can reduce total cholesterol levels as well as the LDL fraction (21).

As regards the route of administration few studies analyzed the effect of transdermal ERT on lipid metabolism in healthy menopausal subjects (50).

One of the few studies that did compare the effects of oral and transdermal (0.05 mg) estradiol on lipids was conducted in postmenopausal women with type 2 diabetes. A non-significant increase in HDL and a decrease in LDL cholesterol and no significant triglyceride changes were observed following transdermal therapy (24). Also in the study by Chu et al. (25), conducted in patients with metabolic syndrome, transdermal therapy showed an overall neutral effect. These results in pathological subjects have been also confirmed in a wide and accurate meta-analysis (51).

**Concluding remarks**

Significant differences appear to exist between oral and transdermal estrogens in terms of hormonal bioavailability and metabolism, with implications for the clinical efficacy, potential side effects, and risk profile of the different hormone therapy options, but neither the results nor the designs of the various studies are uniform.

Overall, HRT has been shown to improve insulin resistance in postmenopausal women. Randomized studies...
Table 2 - Effects of estrogen replacement therapy on lipid metabolism

<table>
<thead>
<tr>
<th>References</th>
<th>No. of subjects</th>
<th>Duration of therapy</th>
<th>LDL</th>
<th>HDL</th>
<th>Trigl.</th>
<th>Apo-A1</th>
<th>T-chol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral low-dose CEE or low-dose CEE+MPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanada et al., 2003</td>
<td>18</td>
<td>3 months</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Mercuro et al., 2003</td>
<td>25</td>
<td>3 months</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lobo et al., 2001</td>
<td>124</td>
<td>3 months</td>
<td>=</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Wakatsuki et al., 2003</td>
<td>25</td>
<td>3 months</td>
<td>=</td>
<td>↑</td>
<td>=</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>Schlegel et al., 1999</td>
<td>13</td>
<td>6 months</td>
<td>↓</td>
<td>↑</td>
<td>=</td>
<td>=</td>
<td>↓</td>
</tr>
</tbody>
</table>

| Oral estradiol              |                 |                     |     |     |        |        |        |
| Loh et al., 2002            | 48              | 6 months            | ↓   | =   | =      |        | ↓      |
| Hodis et al., 2003          | 150             | 12 months           | ↓   | ↑   | (E2group) | =   | =      |
| Alexandersen et al., 2001   | 50              | 12 months           | ↓   | ↑   | =      | =      | ↓      |
| Bruhat et al., 2001         | 137             | 6 months            | ↓   | =   | =      | =      | =      |
| Davidson et al., 2000       | 67              | 6 Months            | ↑   | ↑   | ↑      | ↑      | ↑      |
| Kernohan et al., 2007       | 15              | 3 Months            | =   | =   | =      | =      | ↓      |
| Villa et al., 2008          | 48              | 3 months            | =   | =   | =      | =      | =      |
| Bingol et al., 2009         | 40              | 6 months            | ↑   | =   | =      | =      | =      |
| Chu et al., 2006            | 25              | 3 months            | ↓   | ↑   | =      | =      | =      |
| Villa et al., 2011          | 40              | 6 months            | ↓   | =   | =      | =      | ↓      |

| Transdermal estradiol       |                 |                     |     |     |        |        |        |
| Chu et al., 2006            | 25              | 3 months            | ↓   | =   | =      | =      | =      |
| Araújo et al., 2002         | 10              | 6 months            | =   | =   | =      | =      | =      |
| Callejon et al., 2010       | 30              | 12 months           | =   | =   | =      | =      | =      |

CEE: conjugated equine estrogen; NETA: norethisterone acetate; DRSP: drospirenone; MPA: medroxyprogesterone acetate; Prog: progesterone E2: 17-beta-estradiol; E2V: valerate estradiol; T-chol= total cholesterol; Trigl: triglycerides; =: no statistically significant change; ↓: increase; ↓: decrease.
have already demonstrated a reduced incidence of diabetes in patients receiving standard/high-dose HRT but these treatments may sometimes reduce insulin sensitivity. Conversely, low-dose estradiol replacement therapy showed neutral or positive effects on glucose metabolism often improving insulin sensitivity or reducing basal levels of glucose or insulin. From the perspective of lipid metabolism, both oral and transdermal delivery systems seem to have beneficial effects on the HDL/LDL ratio, while the transdermal system has more favorable effects on triglycerides. The incidence of metabolic syndrome and weight gain appears to be slightly lower with a transdermal delivery system. This review confirms that low-dose estrogen therapy not only has no direct negative effects on glucose and lipid metabolism but actually shows some positive effects, suggesting that its administration might be warranted in selected subjects with pre-existing metabolic risk factors.

References

26. Demissie S, Cupples LA, Shearman AM et al., Estrogen receptor-alpha variants are associated with lipoprotein size distribution and particle levels in women: the Framingham Heart Study, Atherosclerosis 2006;185:210-218
30. Mayes JS, Watson GH. Direct effects of sex steroid hor-
mones on adipose tissues and obesity. Obes Rev 2004;5:197-216
31. Bruschi F, Meschia M, Soma M, Perotti D, Paolotti R, Cro-
signani PG. Lipoprotein(a) and other lipids after oophore-
tomy and estrogen replacement therapy. Obstet Gynecol 1996;88:950-954
32. Paganini-Hill A, Dworsky R, Krauss RM. Hormone replace-
ment therapy, hormone levels and lipoprotein cholesterol 
33. Farish E, Spowart K, Barnes JF et al. Effects of post-
menopausal hormone replacement therapy on lipoproteins 
including Lp(a) and LDL subfractions. Atherosclerosis 1996;122:153-162
34. Miller VT, Muesing RA, LaRosa JC, Stoy DB, Phillips EA, 
Stillman RJ. Effects of conjugated equine estrogen with 
and without three different progestogens on lipoproteins, 
high density lipoprotein sub-fractions, and apolipoprotein A1. 
Obstet Gynecol 1991;77:235-240
35. Grodstein F, Stampfer MJ, Colditz GA, et al. Post-
associations of estrogens and progestins with cardiovascular 
of estrogen replacement on the progression of coronary-artery 
38. Sanada M, Higashi Y, Nakagawa K, et al. A comparison of low-
dose and standard-dose oral estrogen on forearm endo-
thelial function in early postmenopausal women. J Clin Endocrinol Metab 2003;88:1303-1309
GM. Lipid profiles and endothelial function with low-dose 
esterone replacement therapy in postmenopausal women 
at risk for coronary artery disease: a randomized trial. Int J 
Cardiol 2003;89:257-265
40. Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower 
doses of conjugated equine estrogens and medroxyproges-
terone acetate on plasma lipids and lipoproteins, coagula-
41. Wakatsuki A, Okatani Y, Ikenoue N, Shinohara K, Watanabe 
K, Fukaya T. Effect of lower dose of oral conjugated equine 
estrogen on size and oxidative susceptibility of low-density 
lipoprotein particles in postmenopausal women. Circula 
tion 2003;108:808-813
Eckardstein A. The effects of six months of treatment with a 
low-dose of conjugated oestrogens in menopausal 
women. Clin Endocrinol (Oxf) 1999;51:843-851
43. Bruhat M, Rudolf K, Vaheri P, Kanulalinen P, Timonen U, Vi-
ilainen A. Effective bleeding control and symptom relief by 
lower dose regimens of continuous combined hormone re-
placement therapy: a randomized comparative dose-rang-
44. Hodis HN, Mack WJ, Asen SP, et al. Hormone therapy and 
the progression of coronary-artery atherosclerosis in post-
45. Loh FH, Chen LH, Yu SL, Jorgensen LN. The efficacy of two 
dosages of a continuous combined hormone replacement 
regimen. Maturitas 2002;41:123-131
estrogen and estrogen-progestin replacement regimens on 
cardiovascular risk markers in postmenopausal women. 
Arch Intern Med 2000;160:3315-3325
47. Callejon DR, Rios DR, Franceschini SA, Toloi MR. Transder-
mal estradiol and lipid profile: effects on a specific group of 
Brazilian postmenopausal women. Arq Bras Cardiol 2009;93:571-575, 617-622
48. Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, 
Salpeter EE. Meta-analysis: effect of hormone-replacement 
therapy on components of the metabolic syndrome in post-
menopausal women. Diabetes Obes Metab 2006;8:536-554