Cardiovascular Changes and Cardiac Morbidity of Menopause. Effects of Hormone Replacement Therapy

Roberto Bassan

Rio de Janeiro, RJ - Brazil

General and epidemiologic considerations

The cessation of cyclic ovulation and consequent interruption of estrogen production by follicular cells in the ovaries is a natural phenomenon in women around 50 years of age, representing the menopause or climacterium. However, menopause can also result from surgical bilateral oophorectomy in a still fertile woman. Independently of its mechanism, menopause causes important metabolic and cardiovascular changes in women, as shown by several case-controlled and cohort studies. These changes do not seem to be due to differences in age or other factors, suggesting that the cause is the reduction in estrogen levels.

During a woman's fertile years, coronary artery disease is rare, with a male-to-female ratio of at least 3:1, for age-matched individuals. After menopause, this ratio progressively decreases reaching 1:1, at the age of 75 and above [1]. A 50-year-old woman has a 50% chance of developing coronary artery disease, and a 30% chance of dying from it during the postmenopausal years [2]. For breast cancer, these ratios are 10% and 3%, and for endometrial cancer 3% and 0.3%, respectively.

Thus, coronary artery disease is the major cause of death in adult woman (as it is for man) in developed countries. Although breast cancer is responsible for 43,000 deaths annually, and lung cancer for 51,000 deaths annually of women in the United States, coronary artery disease causes 236,000 annual deaths, and 87,000 strokes [2,3].

Even though there was a 20% reduction in mortality resulting from coronary artery disease in women from 1979 to 1989, the absolute number of women dying due to this pathology continues to increase. With the progressive increase in life expectancy, the number of women older than 50, and consequently in menopause, is much higher today than in previous decades. In the United States, the average life expectancy for women is around 80, showing not only a higher number of postmenopausal women but also that these women will live more than one third of their lives deprived of estrogen.

Hospital Pró-Cardíaco - Rio de Janeiro
Mailing address: Roberto Bassan – Hospital Pró-Cardíaco – Rua Dona Mariana, 219 – 22280-020 – Rio de Janeiro, RJ - Brazil

Menopause and atherosclerotic disease

From the pathologic point of view, atherosclerotic disease occurs later in women than in men, especially in the coronary arteries. Kayan et al. [4] determined that a 50-year-old woman has 45% of her aorta area and 25% of her coronary artery area affected by the atherosclerotic process, but a man of the same age has 50% and 40%, respectively. At 75 years of age, the figures are 75% of the aorta area and 55% of the coronary artery area for women and 70% and 55% for men, respectively. This shows that for postmenopausal women the speed of coronary atherosclerotic disease development is much higher than for men of the same age group, despite similar aortic involvement.

These data support the Framingham Study, which showed that acute myocardial infarction – a clinical manifestation of coronary atherosclerosis – was rarely found in women before the age of 45, in a ratio of one woman to 40 men [5]. In the age group from 45 to 64 years, the number of infarctions in women was 45 times that of the younger group, but in men it was only 3.5 times, a ratio of 1:3 between the genders. In individuals older than 65, the number of infarctions in women increased 2.3 times, but in men there was no difference, resulting in a ratio of 1:1.2.

Another relevant result of the difference in coronary atherosclerotic involvement in women versus men is women's higher hospital mortality rate due to acute myocardial infarction. Several studies, including ours, have demonstrated that the relative mortality risk for women is 2-3 times higher than that for men [6-8]. Although some studies attribute this higher mortality to the prevalence of more death risk factors, including age – because women's average age is 6-10 years higher than that of men – some authors observed that these variables only partially explain this high mortality [6,7]. This indicates that sexual biological factor might be an independent variable in hospital mortality risk in patients with acute myocardial infarction.

Menopause and blood pressure

Hypertension is a known risk factor for atherosclerotic disease development – especially in the coronary arteries – in both genders [9,10]. Epidemiologic studies have shown that until age 35, the prevalence of hypertension is higher in men

than in women. However, after age 60, this ratio is inverted [11]. Nevertheless, morbidity and mortality for any level of hypertension are always lower in women, including the occurrence of stroke.

The effect of menopause on blood pressure levels in women is not yet well understood, but some studies seem to indicate a mild and progressive increase with the climacteric years, especially of the systolic pressure [14-16]. However, although age is a known factor responsible for the increase in blood pressure, the role of menopause in pressure elevation occurring in women cannot yet be quantified.

Estrogen affects systemic and local vasodilatation [17,18]. This effect seems to be both dependent on and also independent from the endothelium. Estrogen-receptors are found in artery walls and, when stimulated, they respond with vasodilatation [19]. In addition, estrogen seems to stimulate the endothelial production of nitric oxide and prostacyclin (PGI_2) [20-22], which are strong vasodilating agents, and also to modulate the endothelial production of endothelin [23], a strong vasoconstricting agent. Finally, estrogen also seems to have a blocking effect on calcium channels of the arterial wall [24,25], resulting in vasodilatation. Changes in action and production of these vasoactive substances would be responsible for some vasomotor and pressure changes observed in woman in menopause, among which is paradoxal coronary vasoconstriction (see below).

Menopause and lipid changes

Dyslipidemias, especially those causing elevation of low-density lipoprotein cholesterol (LDL) and reduction of high-density lipoprotein cholesterol (HDL) in addition to the increase of triglycerides, are related to atherosclerotic disease, acute myocardial infarction, and cardiac death [26]. However, in women HDL-cholesterol and triglycerides were the strongest predictive factors of coronary artery disease development, both in the Framingham Study [27] and in the Lipid Research Clinics Follow-up Study [28], but LDL-cholesterol was a strong predictive factor only in the former.

Serum lipid reduction studies have shown a decrease in the risk of coronary events and also the progression of atherosclerosis, even though only a few of these investigations were carried out in women [29-32].

Some studies [33,34] showed that premenopausal women have lower levels of serum LDL-cholesterol than do men. However, after the age of 50, women's levels increase considerably, exceeding those of men of the same age group. With regards to HDL-cholesterol, no significant change was observed in women during pre- and postmenopausal periods, but their serum levels were always higher than those of men.

The Framingham Study also demonstrated that even though total cholesterol progressively increases with age in both genders, the rise was more accelerated in women, especially after 45 years of age [35].

Menopause and carbohydrate metabolism

Diabetes is considered an important risk factor for atherosclerosis and coronary artery disease, as well as for cardiac mortality. In the Framingham Study, diabetes tripled coronary artery disease risk in women, and the same was observed for cardiac mortality [36]. The risk for men seems to be half that for women.

The menopausal effect in carbohydrate metabolism in women is not yet well understood. An increase in serum insulin parallel to a mild glycemic elevation seems to occur, suggesting some degree of tissular resistance to insulin [38,39]. However, an increase in the incidence of diabetes during menopause was not confirmed.

Hormone Replacement in Menopause

Effect in the risk of cardiovascular disease

Several studies of the case-control type suggest an inverse relation between estrogen use and coronary artery disease risk and mortality in menopausal women [40]. However, this type of study is influenced by factors that are difficult to control and can turn into methodological bias that ends up influencing the results as well [2]. Cohort studies are less prone to bias, but only prospective, randomized and controlled studies answer in a more accurate way if a therapeutic form is related to an analyzed event. Unfortunately, so far there is no study of this type that has already been finished and that evaluates hormone replacement benefits in relation to cardiovascular disease risk in menopausal women.

The Framingham Study was the first prospective clinical cohort study to establish a risk correlation between menopause and coronary artery disease independent of the natural or surgical mechanisms of menopause [41].

Less than one decade later, Stampfer and co-workers published their first analysis of the Nurses' Health Study [42], which was later expanded to include a total of 48,000 healthy postmenopausal women followed for a 10-year period [43]. In this prospective cohort study, the authors showed that women undergoing estrogen replacement therapy had a significant 50% reduction in the coronary artery disease development rate (and 50% in the cardiac death rate, as well) when compared to other women who had never used estrogen.

Shortly after the nurses' study, Bush et al. [44] published findings from another prospective cohort study, the Lipid Research Clinics Study, which included 2270 women, whose ages ranged from 40 to 69 years, and who were either healthy or had coronary artery disease. The authors observed a reduction of more than 60% in coronary mortality in women on estrogen replacement therapy compared to those not using the hormone in an average follow-up of 8.5 years. The reduction was more pronounced in those with known coronary artery disease.

Analyzing all of the prospective cohort studies of estrogen use in menopausal women, Stampfer and Colditz [40] and Grodstein and Stampfer [2] concluded that those undergoing hormone replacement had a 45% reduction in the risk of developing coronary artery disease when compared to those who had used it in the past or had not used it at all (95% confidence interval = 30%; 56%). However, it should be emphasized that in none of these studies estrogen use was randomized.

More recently, Henderson et al. [45] in the Leisure World cohort study showed a significant 50% reduction in the incidence of acute myocardial infarction in almost 9,000 female users and non-users of estrogen replacement therapy. Falkborn et al. also demonstrated a significant 50% reduction in the incidence of infarction with the use of estrogen combined with progesterone and a 26% reduction with estrogen alone [46].

The effect of hormone replacement therapy on the incidence of stroke in menopausal women is not yet well established. This occurrence of stroke has not been modified by estrogen use in the large Nurses' Health study [43] and in the meta-analysis by Grady et al. [47]. This fact is in accordance with the observation of similar prevalences of hypertension among female estrogen users and non-users in the Framingham, Nurses' Health, and Lipid Research Clinics Follow-up studies [48]. However, another cohort study revealed a reduction of almost 50% in the incidence of stroke and mortality due to stroke in female estrogen users [45,49]. Two other studies also showed a reduction in the occurrence of stroke, not only when estrogen was used, but when it was combined with progesterone as well [50,51].

The chronic effects of estrogen replacement therapy on the blood pressure of menopausal women are not yet completely understood. Although some studies show no pressure changes [16,52], others reveal increases [53] or decreases [54,55]. These disparate results are certainly due to study methodological bias (case-control, cohort, and retrospective) clearly indicating the necessity for prospective, randomized, and placebo-controlled studies.

The mechanisms of estrogen therapy that cause beneficial effects in cardiac morbidity and mortality in postmenopausal women are not yet well understood, but there are many explanations for them (table I), which will be discussed in the following section.

Table I - Proposed mechanisms justifying the beneficial use of estrogen replacement therapy in coronary artery disease risk, morbidity and mortality, in postmenopausal women

1. Positive effect on serum lipids
2. Decrease in LDL-cholesterol oxidation
3. Reduction in the tissular resistance to insulin
4. Direct vasodilating effect in the coronaries (estrogen receptors)
5. Endothelium-dependent vasodilating effect (NO, PGI2)
6. Calcium-dependent vasodilating effect (channel block)
7. Reversion of the coronary endothelial dysfunction

Effects in lipid and carbohydrate metabolism

Estrogen replacement causes significant changes in lipid serum levels in postmenopausal women. A 5-10% increase in HDL-cholesterol and a 10-15% decrease in LDL-cholesterol are observed, and VLDL-cholesterol and triglycerides increase 10-15% [56-58]. Furthermore, beneficial effects in Lp(a) apolipoprotein and in LDL-cholesterol oxidation have been seen in some studies [59-61]. It is believed that, in postmenopausal women, 50% of the protective effects against development of coronary artery disease with estrogen therapy are due to these serum lipid changes [62].

Nabulsi et al. [59] observed in a cohort study of almost 5,000 postmenopausal women that those using estrogen had higher levels of HDL-cholesterol and triglycerides and lower levels of LDL-cholesterol than the non-users, indicating a 42% risk reduction for the development of coronary artery disease.

The Postmenopausal Estrogen/ Progestin Interventions (PEPI) study is the first large prospective, randomized, double blind, placebo-controlled study that analyses the effects of estrogen replacement therapy, with or without progesterone addition, on morbidity and mortality and in clinical and laboratory parameters of 875 healthy menopausal women. The initial results have shown that all hormone replacement regimens produce beneficial effects in serum lipids [63]. Significant blood pressure changes were not observed in the patients of this study.

The beneficial effects of hormone replacement on carbohydrate metabolism in postmenopausal women observed by Barrett-Connor and Laakso [64] – decrease in insulinemia and glycemia – possibly contribute to the reduction of the occurrence of coronary artery disease, but at this time, this is nothing more than an inference.

The addition of progesterone to estrogen therapy in postmenopausal women tends to reduce the effect of that therapy on the lipid profile [58,63]. However, Nabulsi et al. [59] showed beneficial effects not only in lipidemia but also in insulinemia, when progesterone is cyclically administered.

Effects on coronary atherosclerosis

Some authors investigated the possible beneficial effects of hormone replacement therapy on coronary atherosclerosis.

Adams et al. [65] conducted a randomized, placebo-controlled study of a group of ovariectomized monkeys given a diet rich in lipids and randomized into either an estrogen or a placebo group. A decrease of one half was observed in the grade of coronary atherosclerosis of those given estrogen.

Retrospective case-controlled studies in women using cinecoronary angiography demonstrated that estrogen use was independently predictive not only of the existence of coronary artery disease [66,67] and its higher angiographic severity [68], but also of survival at the end of a 10-year follow-up period in those with coronary obstructions [69].

These pathologic and angiographic studies provide evidence that strengthen the cause-effect relationship between the beneficial changes observed in the lipid profile of postmenopausal women using estrogen and the reduction of coronary artery disease and the incidence of cardiac events observed in cohort studies.

Effects in coronary vasomotion

Some recent evidence suggests that the beneficial effects of estrogen use in postmenopausal women may be due not only to antiatherosclerotic mechanisms.

Studies have demonstrated that estrogen has a direct effect on coronary artery vasomotor function, causing vasodilatation [19,70], as seen in other organs [17,18]. The intracoronary injection of acetylcholine causes a similar effect, which is mediated by the endothelial release of nitric oxide; however, this response turns into vasoconstriction ATT when there is coronary atherosclerosis, characterizing the endothelial dysfunction [71].

Experiments conducted in ovariectomized monkeys, which were chronically fed with a lipid rich diet, showed coronary vasoconstrictive response to acetylcholine administration [72,73]. When these monkeys received an estrogen pretreatment, acutely [73] or chronically [72], the response to acetylcholine was vasodilatation, suggesting that the hormone have a rapid and possibly direct effect in the atherosclerotic coronary arteries, reversing the endothelial dysfunction. However, the idea of an effect mediated by nitric oxide release (or facilitation of its action), or inhibition of vasoconstrictive agents (for example, endothelin), or both can not be discarded [73].

Recently, three placebo-controlled studies carried out during cardiac catheterization in postmenopausal women with coronary atherosclerosis confirmed the previous observations in monkeys, showing reversion of the paradoxical vasoconstriction induced by acetylcholine with acute estrogen use [74-76]. In one of these studies [75], estrogen administration also resulted in coronary vasodilatation and in flow increase at the basal state (preacetylcholine).

These data suggest that beneficial and protective effects of hormone replacement in postmenopausal women may be due, at least partially, to its vasodilating action and coronary vasomotion normalization in cases with endothelial dysfunction.

A small clinical study [77], which supports previous findings, was carried out in postmenopausal women presenting with symptomatic coronary artery disease and ischemic response to exercise. It showed a mild increase in the development time for a 1mm downslope of the ST segment and in the total exercise time with the use of sublingual estrogen, when compared to placebo.

Adverse effects of menopausal hormone replacement

Despite all beneficial effects of estrogen replacement therapy (with or without progesterone) in the cardiovascular system and in the carbohydrate-lipid metabolism of menopausal women, this hormone use can have side effects that should be discussed.

Estrogen use without progesterone in nonhysterectomized women has a dose- and time-dependent risk of endometrial cancer 2-4 times higher than that observed in hormone nonusers [3,78-80]. This relative risk seems to be reduced to very low values when progesterone is added, and this reduction seems also to be dose- and time-dependent [3,81,82]. In addition, some case-control studies revealed less aggressiveness and a lower mortality rate from endometrial carcinoma occurring in estrogen users, when compared with non-users [3].

So far, the researchers have not agreed on a possible risk of breast cancer development in estrogen replacement users [3,78,83-86]. Although a meta-analysis of case-controlled studies did not show a higher risk [84], another study [85] revealed a relative risk of 1.3 after 15 years of continuous estrogen use. In another study by Bergkvist et al. [87], despite the higher incidence of breast carcinoma observed in hormone replacement users, the breast cancer mortality was similar to or lower than that of non-users, supporting other study results [45,86]. Use of progesterone in conjunction with estrogen has also shown inconsistent results regarding the incidence of cancer [3].

Other undesirable side effects of estrogen use in postmenopausal women are the development (or recurrence) of gallstones and acute cholecystitis, and the reappearance of vasomotor headache [58].

Finally, estrogen use significantly reduces the incidence of osteoporosis and, consequently, the fractures often observed in postmenopausal women [58].

Hormone replacement therapy: risks *versus* benefits

As already seen all the beneficial and harmful effects of estrogen use associated or not with progesterone in postmenopausal women were obtained by cohort or case-controlled observational studies and their meta-analysis. Even though several authors had tried to avoid the influence of methodological bias in their studies, attempting to control some confusing variables, adjusting them to the results, or both of these, it is necessary to be cautious in the final interpretation. Therefore, only by means of prospective, randomized, double blind, and placebo-controlled studies will it be possible to know if hormone replacement therapy actually has beneficial effects on morbidity and mortality in postmenopausal women, and also the risks deriving from its use. In order to answer these questions, some studies are being carried out and results have recently been published [63], but some years will still be necessary before the presentation of the effects on morbidity and mortality.

Meanwhile, some authors using data derived from cohort studies estimate the effects of hormone replacement therapy on mortality. Henderson et al. [88] applied relative risks of estrogen use of 0.5 for coronary artery disease

development, of 0.4 for osteoporotic fractures, of 1.1 for breast cancer, of 1.5 for cholelithiasis, and of 2.0 for endometrial cancer. Based on these risks, they estimated mortality in women taking 0.625mg of conjugated estrogen daily, at the age of 50 and being observed until the age of 75. The mortality variation with estrogen use compared to that of nonuse was -5250 deaths due to coronary artery disease in 100,000 treated women, -563 deaths due to osteoporotic fractures, +187 deaths due to breast cancer, +2 deaths due to cholelithiasis and +63 deaths due to endometrial cancer. The algebraic sum of these figures gives a variation of the estimated global mortality of –5561 (or –41%) with the use of estrogen. This dramatic reduction in global mortality would be due not only to the elevated number of coronary artery disease cases observed in these women, but also to the elevated mortality of the coronary artery disease itself, causing a relative risk of 0.5 to be translated into a huge number of spared lives. Even though endometrial cancer has a relative (but inverse) risk similar to that of coronary artery disease, it causes a number of deaths 100 times lower, because of its lower occurrence relative to coronary artery disease.

In a similar way, utilizing a meta-analysis of the different published studies, Grady and co-workers [47] estimated the gain in years of life with hormone replacement therapy. These authors predicted that a 50-year-old white woman would have a 46% chance of developing coronary artery disease during the rest of her life and 31% of dying from it. Estrogen replacement therapy would reduce mortality in such women by ATT 45%. These figures are compared to those estimates of other pathologies related to menopause and hormone replacement. Thus, stroke would occur in 20% of these women and stroke mortality would be 8%, but estrogen therapy would not change these numbers. In regard to osteoporotic fracture (hip fracture), the risk would be 15%, and mortality 1.5%, and hormone replacement would reduce both by ATT 25%. For breast cancer, its probability of occurrence in these women would be 10% and mortality 3%, and the hormone replacement therapy would increase both to 25%. Finally, the development rate of endometrial cancer would be 2.6% and mortality 0.3%, and estrogen use without progesterone would increase the risk by ATT 800% and the mortality by ATT 300%. Based on these numbers, the authors estimated that a white woman who enters menopause and does not have cardiac or gynecologic risk factors would have an average life expectancy of 82.3 years. With estrogen replacement, she would gain 0.9 years. However, a woman with coronary artery disease risk factors would have an average life expectancy of 79.6 years and would gain 1.5 years with estrogen replacement therapy and 1.6 years with estrogen in combination with progesterone. Finally, a woman known to have coronary artery disease would have an average life expectancy of 76 years and would gain 2.1 years with estrogen use and 2.2 years when an association of estrogen and progesterone is used. Even a woman with breast cancer risk (strong family history, risk around 20%) and with an average life expectancy of 82.3 years, would gain 0.7 years with estrogen therapy and 0.8 years with combined estrogen and progesterone.

Final conclusions

All data discussed above strongly suggest that hormone replacement therapy in postmenopausal women has significant beneficial effects on morbidity and mortality, especially that with coronary causes, that supercedes the risk of harmful side-effects. The dramatic reduction in cardiac mortality seems to have a significant impact on general mortality, despite the increased chances of endometrial and breast cancer development. This impact is maximal in women with high risk of coronary artery disease or in those already with the disease. The global mortality reduction would manifest itself in the form of an increase in life expectancy of treated women. However, it is important to emphasize that these data are based on knowledge obtained from studies considered sub-optimal, from the methodological point of view. Despite this, their results are consistent enough to allow the recommendation of estrogen replacement, with or without progesterone, in postmenopausal women, especially for those considered at high cardiac risk [89]. Prospective, randomized and controlled studies that are currently underway should bring, in the coming years, final data on this subject so anxiously awaited.

Addendum

After the submission of this manuscript, results from the Heart and Estrogen/Progestin Replacement Study (HERS) were published (Hulley et al. JAMA 1998; 280: 605-613). This prospective, randomized, single-blinded, placebo-controlled trial compared the combined use of 0.625 mg of estrogen and 2.5mg of progesterone in 2,763 postmenopausal women (mean age = 66.7 years, mean last menstruation = 18 years ago) with known coronary artery disease. The study subjects were followed for four years. No significant differences in cardiac and non-cardiac death, non-fatal acute myocardial infarction or need of myocardial revascularization was observed between treated and non-treated patients. Also, no significant increase in breast or endometrial cancer rates was seen in treated patients, but a significantly increased rate (3-fold) of thromboembolic phenomena was detected in the treated group versus the placebo group.

The negative results of this first randomized trial of secondary prevention indicates that up to four years of hormonal replacement in elderly postmenopausal women does not change the natural history of their coronary artery disease. However some questions can be raised: 1) Would four years of late hormonal replacement be enough to disclose beneficial effects?; 2) Can the results of HERS be extrapolated to a younger group of postmenopausal women with coronary artery disease in whom life expectancy is greater than that of the study population?; 3) Would the tendency of a lower rate of non-fatal infarctions seen in treated patients in the last two years of the study turn out to be significant with a longer follow-up, therefore also changing cardiac mortality?

HERS brings out important information for cardiologists and gynecologists, but also raises questions about the validity of transposing these data to clinical practice where physicians usually deal with younger women with recent onset of menopause and, consequently, with short exposure to reduced levels of estrogen (and its adverse cardiovascular actions). Even if coronary artery disease is already established, it is possible that in this group of women the hormonal therapy will have a more favorable effect than the one seen (or not seen) in the elderly women with significant coronary disease studied in HERS. It is also expected that a greater life expectancy (and, consequently, a longer follow-up) may be necessary to demonstrate a positive effect of estrogen therapy in women with coronary artery disease.

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