Editorial

Postmenopausal hormone replacement therapy and prevention: no chance for celebration? What should doctors do? A personal opinion

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For many years, conventional wisdom, supported by observational and epidemiological studies, has sustained that estrogen "replacement" after menopause would restore the relative protection from cardiovascular diseases that is enjoyed more by premenopausal women than by men of a similar age. This view was bolstered by evidence of the beneficial effects of oral estrogen therapy (the only type to be used almost constantly) reported by different studies, together with a large body of biological, experimental, observational and clinical data. Recent clinical trials, however, have failed to support the benefits of hormone replacement therapy (HRT) in terms of both secondary and primary prevention. Let's take a critical look at the HRT saga.

The first celebration

The studies on estrogen replacement therapy – the real origin of the saga – started in the '70s. Almost all the information derived from observational and prospective studies. The former were difficult to compare, because of the adoption of different endpoints, while the prospective studies showed a significant reduction in cardiovascular risk. The first and most relevant one was the Lipid Research Clinics Program Follow-up Study[1], in which 2270 women were enrolled. Among these, 593 were submitted to HRT. The study, with a mean follow-up of 8.5 years, showed an approximately 60% reduction in the incidence of cardiovascular mortality. Nevertheless, the most important study was the Nurses' Health Study[2] which was started in the United States in 1976 and involved 121 000 nurses aged between 30 and 55 years. Of these, 32 000 were postmenopausal. In 1991, after 5 years of estrogen replacement therapy, a 50% reduction in the incidence of myocardial infarction was observed for past users and a 70% decrease was noted for current users. In 1996, a reduction in the relative risk was observed and was associated with the increase in the negative effects of estrogen replacement therapy. On the whole, the latter was found to be more beneficial for higher risk women, and to have no effects on the incidence of neither ischemic nor hemorrhagic stroke. The latest data from the Nurses' Health Study revealed that there was a reduction in benefit after 10 years of treatment (relative risk 0.80) because of an increased mortality due to breast cancer (+ 43%)[3].

The observational studies were then taken for consideration in meta-analyses. The most important two were the one by Stampfer and Colditz[4] published in 1991 and the one by Grady et al.[5] published in 1992. Stampfer and Colditz[4] showed an approximately 50% reduction in the cardiovascular risk for women, notwithstanding the use, a bit confounding, of the mean relative risk for their calculations; more definite was the study by Grady et al.[5] who reported, using the coronary artery disease mortality and incidence as endpoints, a relative risk of 0.63 in users versus nonusers. Many other studies regarding this topic

were published in the '90s, all definitively in favor of the effects of estrogen replacement therapy. Among observational studies, our research on 250 women with different risk factors is worthy of mention because of the different type of HRT administered. In fact, transdermal patches containing 17β-estradiol were employed[6]. All women received short-term (24 months) treatment, and the lipid profile and the glucose and fibrinogen levels were determined before and after it. At final observation, a reduction in all the risk factors was found in a subgroup of 75 women with mild to moderate hypertension. Observational studies are nevertheless limited by the well-known bias due to patient compliance, to prevention and to the preponderant recruitment of healthy users. Besides, it is difficult to determine whether the higher number of events in nonusers is a cause or a consequence of drug withdrawal. Further limits of observational studies include the type of therapy, its duration and the administered dosages. The first important randomized study was the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial[7], which tested four different treatments in 840 women (aged 45-64 years). Unopposed estrogen and three types of estro-progestinic drugs were compared to placebo. The follow-up was 3 years, and the endpoints (the limits of the study), rather than events, were the cardiovascular risk factors. The PEPI trial showed a clear benefit of HRT and unopposed estrogens on the lipid profile, and created the so-called "lipid-centered" theory: the increased risk of postmenopausal women for atherosclerosis is due to estrogen deficiency and hence estrogen replacement therapy may contribute to prevention. At this point the enthusiasm for HRT reached its peak, and the old, skeptical Europe was finally convinced.

The delusion

From August 1998 onwards, with the publication of the Heart and Estrogen/progestin Replacement Study (HERS) trial[8] until July 2002, with the Women's Health Initiative (WHI)[9] through the Estrogen Replacement and Atherosclerosis trial (ERA)[10], the Women's Estrogen for Stroke Trial (WEST)[11] and the HERS II[12], HRT has been deemed a total failure by both the scientific arena and public opinion who held that it played no role in primary or secondary prevention. The HERS, a randomized, double-blind, placebo-controlled, multicenter trial, enrolled 2763 women with established coronary artery disease and compared oral conjugated equine estrogen (0.625 mg) and 2.5 mg of medroxyprogesterone acetate versus placebo. The HERS trial reported an increase in the cardiovascular risk, while after 4.1 and 6.8 years of follow-up, HRT had neither increased nor decreased the risk of cardiovascular events in women with coronary artery disease. The HERS investigators hypothesized an early proischemic effect of estrogen with subsequent improvements due to the clear benefits offered by the lipid profile. After 4.1 years, the HRT mortality attributable to breast cancer and cardiovascular factors, ceased to increase. HERS represents a "milestone" in the saga of HRT as it succeeded in drawing attention away from the "lipid-centered" theory and towards the "thrombo-centered" effects of estrogens.

The ERA, an angiographic, double-blind, placebo-controlled study, randomized 309 postmenopausal women with established coronary artery disease. The study showed no effects of estrogen replacement therapy or of HRT versus placebo in the progression of the disease.

The WEST study is a randomized, double-blind, placebo-controlled trial on estrogen therapy that enrolled 664 postmenopausal women who had had an ischemic stroke or transient ischemic attacks. The investigators found no benefit in terms of the total stroke incidence but an increased risk of fatal stroke among women who were assigned to estradiol therapy.

The WHI is a randomized, double-blind, placebo-controlled, primary prevention trial (the first of its kind), with an expected duration of 8.5 years. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women (aged 50 to 79 years) into 40 centers in the United States, in order to observe the clinical effects of a low-fat dietary pattern, calcium and vitamin D supplementation, as well as those of postmenopausal hormone use. A subgroup of 16 608 postmenopausal women (also aged 50 to 79 years), with an intact uterus completed the trial on HRT alone. The main outcome was coronary heart disease, with invasive breast cancer as the principal adverse effect. On May 31, 2002, after an average of 5.2 years of follow-up, the Data and Safety Monitoring Board recommended the cessation of the trial, because the test statistics for invasive breast cancer exceeded the adverse effect limit, and the global index statistics showed that the risks outweighed the benefits.

Considerations concerning the HERS II and WHI trials

The HERS trial. At least the guilty conscience of these authors has prevailed! The decision to continue the observation of the patients in the two study groups (i.e. HRT and placebo) clearly shows that, after all, the criticism made by the entire scientific community was not unfounded. The very same authors, however, still have to explain why the HERS trial was interrupted for no apparent reason when the number of events turned out to be decisively in favor of the placebo group. This interruption resulted in a weakening of a study that, initially, seemed to foresee a very strong design. Since it is now too late to cry over spilt milk, let's have a close look at the HERS II trial, an open study carried out with

the collaboration of general practitioners who, as a matter of fact, decided which therapy the patient was to take by means of an over-the-phone follow-up questionnaire that was made, on average, once every 4 months. And here we are with the remedy being worse than the illness itself!

The clear consequence of this reckless type of study was that it impudently "attacked" the groups observed. Over 50% of the patients under hormone therapy (after being rightly informed that in the early years of experimentation no benefits whatsoever derived from HRT compared to placebo) abandoned the treatment group, while the placebo group patients (who were, besides, also informed of the fact that they were not taking any medication) turned to other forms of medication to deal with their somewhat tormented state of health (by the end of the follow-up, 4% of the placebo patients were on raloxifene). The other problem that should attract the attention of the careful reader is, in our opinion, the concomitant use of statins and other hypolipidemic drugs. This, in view of the fact that in the HERS trial, HRT reduced the cholesterol serum levels by 10-15% compared to those of the placebo group but, by the end of follow-up, the average levels of the total and fractionated cholesterol turned out to overlap perfectly. We believe that this is due to the more widespread use of hypolipidemic drugs in the placebo group, and, even though not statistically significant, is confirmed by the results brought forth.

All these considerations, however, give rise to the legitimate suspicion that two groups of very questionable homogeneity were compared in a – what time proved to be – particularly feeble study design. The authors conclude that there is no convincing evidence that suspending the hormonal treatment actually reduces the cardiovascular risk. However, we still believe that it would have been better to continue the previous study!

Our overall judgment of this experience (including the two HERS studies) is, therefore, totally negative and we retain that its only result was that of confusing the whole matter with absolutely erroneous conclusions.

The WHI trial. This study brings us back down to the arena of meticulously planned and adequately concluded studies. This scheme is the best one imaginable in a study on primary prevention: with a large number of patients, a collegial evaluation of the events and the determination of "the absolute excess of risk" for the treated patients as compared with the placebo group, and the enrolment of relatively young patients of perimenopausal age (from 50 years of age onwards). With all due respect to the reasonable presumption, we assisted, as far as cardiovascular events are concerned, to a premature interruption of the study due to excessive events in the treated group with respect to the control group. We could object that it is only a matter of a small number of events (around 8 more events out of 10 000 women per year) with a very low increase in the absolute risk and a very high number needed in the treatment branch. We could also add that, globally, the number of cardiovascular deaths did not differ between the treatment and control branches and that the increase in coronary risk was due to an irrelevant number of myocardial infarctions (including the perioperative ones and the diagnosis of silent infarctions based solely on ECG and without the use of imaging techniques). Apart from these considerations, the WHI has also been a confirmatory study (of the capacity of estrogens in the treatment of osteoporosis) and has continued to add fuel to old fears and to stir up new hopes (greater protection with regard to carcinoma of the colon despite an increased risk of breast cancer).

General considerations

The idea (which is quite reasonable) that estrogens can act as a false therapy but as a real prophylaxis, has been mostly, if not completely, unhinged by the WHI. Recreating an estrogen-rich environment in the immediacy of the postmenopause does not yield in terms of the prevention of cardiovascular events. In spite of the criticism that can be made about the study (not so much, to be honest) we are obliged to ask ourselves how this could have happened. The answer to this question implicates an even more clinically relevant one: whether or not HRT can possibly have a future in clinical practice. In our opinion, as it is conceived today, it represents an approach that purports great risk and insinuates a somewhat dubious usefulness. It would be opportune, at this point, to take a look back in time, at least in order to explain the origin of modern hormone therapy.

During the '80s, ischemic heart disease unveiled the importance of the lipid profile which has subsequently become the main target of therapy (above all for the secondary prophylaxis of ischemic cardiomyopathy). Something similar happened with the development of a class of molecules, the statins, with favorable clinical characteristics and associated with an elevated therapeutic index, thus contributing to the creation of that "lipid-centered" theory that had thence taken root. It is reasonable to believe that orally administered estrogens were chosen in the study that involved HRT only because they represented the most effective defense when dealing with the reduction in the serum levels of cholesterol. In the meantime, there was still a conflict concerning the progestogens, responsible for the negative modification of the lipid pattern towards an increase in total cholesterol and a decrease in HDL cholesterol. During the '90s, the "lipid-centered" theory was partially abandoned when the theory that atherosclerosis constituted a very real chronic inflammatory disease was widely accepted[13]. The conclusions drawn up by the authors of HERS were that estrogens exerted posi-

tive and significant effects on lipids, but caused increased cardiovascular events as the result of a proinflammatory effect.

The other concept that has entered the scene of the history of atherosclerosis in very recent years deals with the role of the endothelium. The experimental and clinical function begins with the axiom that an integral endothelium impedes the development of any anatomical-pathological manifestation of the atheromas. Once again, this leads to the choice of orally administered estrogens as the substance most suitable in determining an improvement in the endothelium-dependent vasodilation in postmenopausal women. Furthermore, in an attempt to respect such an assumption, investigators developed research protocols whereby the dosages of progestins used were drastically reduced (medroxyprogesterone acetate, for example, was administered in some reports at a dosage of 10 mg/die for 12 days of the cycle, for a total of 120 mg/month; in others, at a dosage of 2.5 mg/die continuously, for a total of 75 mg/month). In fact, many undertakings where estrogens have been shown to improve the lipid configuration and the endothelial function exist. On the other hand, the exact opposite is true for progesterone. But, once again, we must pose the question as to whether or not the lipid and endothelial alterations are actually useful from a clinical point of view.

The results of the HERS and WHI trials would seem to confirm that this is not the case or that, anyhow, the benefits gained in terms of an improvement in the endothelium-dependent vasodilation and in the lipid profile are outweighed by the negative effects provoked by other factors.

Among the latter factors, some authors mention the proinflammatory and procoagulant effects. Considering the importance of inflammatory processes in contributing to the growth and instability of the plaque, the hypothesis that any therapy equipped with proinflammatory capacities could increase the clinical manifestations of atherosclerosis is quite understandable. As a consequence, if this were the case, it could be argued that the activation of the inflammatory process would be much more conspicuous as opposed to the reduction in the serum cholesterol and to the improvement in endothelial function, at least in terms of clinical events.

It must be borne in mind that a "well-nourished" series of researchers was involved in establishing whether or not the increase in biochemical inflammation indexes (such as C-reactive protein) was actually associated with a "molecular" expression of inflammation. That is to say, whether an increase in C-reactive protein was associated with an increase in the plasma concentration of interleukin and with the expression of endothelial inflammatory receptors. As things stand, this long line of research had a negative outcome, since it demonstrated that at a molecular level estrogens have an anti-inflammatory effect. There are, however, no doubts as to the fact that estrogens increase the plasma concentration of C-reactive protein[14].

So, is it possible to explain the excess of events shown by recent studies only and exclusively by taking into consideration the increase in C-reactive protein determined by estrogens? The answer, as far as we are concerned, is yes, and this can be perceived when illustrating all the proatherogenic effects that C-reactive protein (a new and ruthless vascular killer) is capable of achieving. In the meantime, alluding to the fact that C-reactive protein was rediscovered (together with the complement proteins) in the field of atherosclerotic plaques of various zones (including the coronary one) and in the infarcted myocardium of patients who deceased as a result of heart failure is meaningless. Furthermore, C-reactive protein has direct proinflammatory effects; that is to say, it stimulates the production of mediatory, inflammatory molecules (intercellular adhesion molecule, vascular cell adhesion molecule and selectin E) which directly activate complement and the inositol phosphate pathway. It must also be pointed out that patients with more elevated C-reactive protein levels present with endothelial dysfunction, as opposed to individuals with normal C-reactive protein levels. It is quite reasonable, therefore, to think that the chronic increase in C-reactive protein levels creates a highly proatherogenic environment.

From a procoagulant point of view, it is well-known that an increase in the hepatic synthesis of proteins follows hepatic estrogenization. Besides fibrinogen, unerring increases in the serum levels of factors II and VII have been recorded. This is partly counterbalanced by an increase in the fibrinolytic potential mediated by estrogens through an increase in plasminogen activator inhibitor-1. With regard to such modifications of the coagulation profile (besides being caused by local factors such as the dilation of the capacitance vessels associated with venous stasis), reference could be made to the greater incidence of deep venous thrombosis and pulmonary embolism caused by orally administered estrogen.

So, has the estrogen era come to an end?

Should we, as a result of the excessive cardiovascular risk involved, resign ourselves to not prescribing these molecules (which have even been shown to have positive effects)?

The answer cannot be no. Hence, here is where research has to step in and test different dosages of hormones and different ways of administering them.

Two interesting leads have appeared on the horizon: transdermal estrogens and the use of higher dosages of active-progestinic drugs. A harvest of data regarding transdermal estrogens has, by now, been gathered and would really merit being recognized as the basis of a controlled trial in which this pharmaceutical preparation is compared to a control group with the aim of testing its effects in terms of cardiovascular events. The pharmacokinetic properties of these drugs, as com-

pounds, have characteristics which are completely different from those of their orally administered active relatives. It is well-known that the lack of hepatic estrogenization results in a lessened hepatic synthesis of procoagulant proteins, of proteins capable of transporting lipids and of angiotensinogen. Consequently, with transdermal estradiol, we will neither have an increase in HDL (transporting centripetal cholesterol) nor in LDL (transporting triglycerides), and we will significantly decrease the procoagulant effect. Larger studies demonstrated the lack of any effect on HDL levels, but showed modest reductions in the serum levels of LDL and lipoprotein(a), as well as a consistent fall in triglyceride levels[15,16]. This effect on triglycerides is, in theory, desirable. Despite claims that transdermal estradiol exerts less effects on the plasma markers of endothelial function in comparison with oral therapy[17], studies on the beneficial effects of transdermal estradiol in improving forearm blood flow[18] and coronary vasomotion[19] have been performed. It must also be pointed out that transdermal estradiol can reduce blood pressure[20] and, in our experience, attenuates the target organ damage. Thus, it promotes a reversal of left ventricular hypertrophy[16,21].

The C-reactive protein aspect is worthy of a separate consideration. Some researches have shown that transdermal estrogen exerts a "neutral" effect on C-reactive protein levels[22,23]. Other studies[24], including our own experience[25], have even registered a significant reduction in C-reactive protein levels in patients treated with transdermally administered natural estradiol.

If the conjectural statements (atherosclerosis as an inflammatory disease and C-reactive protein as a substance that induces plaque instability) are accurate, then, with the use of transdermal estrogen we should expect that so yearned for reduction in coronary events.

As for progestins, their role as physiological antagonists of estrogens must be borne in mind. Their limited action with regard to the increase in the serum levels of C-reactive protein (stimulated by orally administered estrogens) was highlighted in two studies that, in our opinion, had an excellent design[26,27]. This aspect, if examined more deeply, could turn out to be quite useful when it comes to limiting the proinflammatory effects (in the sense of an increase in the serum levels of C-reactive protein) of estrogens. We must, therefore, increase the dosage of the progestins to be used in HRT and/or move over to different ways of administering estrogens, most probably both and, perhaps, even something else. It is important to break the silence that has fallen on the history of the killer-estrogen (killer of the cardiovascular apparatus) and roll our sleeves up. Once again, by simply counting the events in a treated population, it has been shown that the cultural conjectures on which the postulated efficiency of estrogen therapy was based, clashes with clinical practice.

Let's write new and more effective theories and go on experimenting!

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