Int J Fertil, 46(5), 2001 p. 248–256

Comparative Cardiovascular Effects of Different Progestins in Menopause

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ABSTRACT: Progesterone receptors are present in the arterial wall and it is, therefore, likely that the arterial effects of progestins are mediated through progesterone receptors as well as through down-regulation of the estradiol receptor. Progestin therapy affects arterial function, as it can stabilize arteries in a state of vasomotor instability, but may also induce vasoconstriction of estrogenized vessels. Thus, the cardiovascular effects of progestins may influence the cardioprotective effect of estrogens.

There has been some concern that a combined estrogen-progestogen therapy may attenuate some of estrogen's beneficial effects on cardiovascular health. This is a reflection of the past epidemiologic studies which have used primarily unopposed estrogen. The PEPI trial is the only large-scale, long-term study to compare directly the effects of different combined hormone replacement therapy regimens upon plasma lipids in healthy women. This study has shown that the adjunctive clinical impact of different progestogens on the beneficial effect of estrogen replacement therapy is trivial. It has never been proved that in normocholesterolemic women, e.g., those included in the PEPI trial, the increase in HDL reduces cardiovascular mortality or morbidity. Based on the results of PEPI, hormone replacement therapy has positive effects on key heart disease risk factors and endometrial tissue, and the magnitude of those effects does not differ significantly across the hormone replacement therapy regimens used.

At present there are only few and inconclusive data available on the vascular effect of progestins in menopausal women. Some studies found that progestins reduced the beneficial effect of estrogens, while others did not. Our group has recently shown that different estrogen-progestin treatments have different effects upon vascular reactivity and that a careful selection of the progestin to be added to estrogen is of capital importance to preserve, or even enhance the positive vascular effects of estrogens.

Few epidemiological studies have investigated the effect of adding a progestin to estrogen therapy upon cardiovascular mortality and morbidity, and all have suggested that hormone replacement therapy may be more effective than estrogen replacement alone in reducing cardiovascular events in primary prevention. The results of the recently published Heart and Estrogen/progestin Replacement Study (HERS) have added some critical data on the effect of hormone replacement therapy for secondary prevention in women with coronary artery disease. The study, however, is affected by several important methodological and statistical problems, which make its interpretation difficult and its conclusions useless for clinical practice. The results of the study should be evaluated with caution by physicians who give advice on hormone replacement therapy, and no woman should be taken off hormone replacement therapy because of HERS. Of importance, the results of HERS should not be used to suggest alternative forms of treatment, especially the selective estrogen receptor modulators (SERMs), for cardiovascular protection in postmenopausal women. *Int J Fertil* 46(5):248–256, 2001

KEY WORDS: HRT, progestins, androgenic, non-androgenic, adjunctive use, side effects

INTRODUCTION

POSTMENOPAUSAL HORMONE replacement therapy is an important component of preventive health care for menopausal women, and protection against coronary artery disease is a major benefit of this therapy. A sound rationale of the cardioprotective effect of hormone replacement therapy is the link between cardiovascular disease and sex hormones [1–3]. Indeed, women are protected until menopause from the development of coronary artery disease and lag behind men in the incidence of myocardial infarction and sudden death by 20 years. The reasons for this protection are largely unclear, but ovarian hormones are implicated in this protective effect, since castrated women not taking hormone replacement have an incidence of coronary artery disease similar to that of men of similar age.

A large body of evidence has accumulated to suggest that hormone replacement therapy is associated with a significant reduction in cardiovascular mortality and morbidity [1]. The majority of case–control and cohort studies, which have shown that estrogen replacement therapy in postmenopausal women is associated with a 35–50% reduction in cardiovascular mortality and morbidity, have been conducted using unopposed estrogen replacement therapy [4,5]. Progestins, which are now prescribed in hormone replacement therapy schemes in order to prevent the development of uterine malignancies, may affect vascular functions. Therefore, it is of pivotal importance to assess the effect of these hormones upon cardiovascular functions.

Progesterone receptors are present in the arterial wall, and there is evidence that the arterial effects of progestins are mediated through progesterone receptors as well as through down-regulation of estradiol receptors. Progestin therapy can stabilize arteries that were in a state of vasomotor instability, but may also induce vasoconstriction of estrogenized vessels [2]. At present, little is known regarding the effects of progestins upon the cardiovascular system and if these hormones influence the cardioprotective effects of estrogens.

PROGESTINS AND LIPID PROFILE

Ovarian hormones have an important effect on lipid metabolism. Unopposed estrogen replacement therapy lowers total serum cholesterol and LDL cholesterol increases HDL-cholesterol, especially the HDL_2 subfraction, and has an effect upon plasma triglycerides that is dependent upon route of administration. Estrogen replacement therapy also stimulates the removal of cholesterol from the systemic circulation, resulting in an increased reverse cholesterol transport.

Similarly to estrogens, progestins also affect the lipid profile, but, in contrast to estrogens, they induce hepatic lipase activity, increasing the degradation of HDL cholesterol. Although this effect seems to be related to the dose and to androgenic potency of the progestin, the addition of a progestin to estrogens tends to attenuate the increase in serum HDL cholesterol and the decrease in LDL cholesterol obtained with estrogen replacement therapy [6]. The effect of progestins upon lipid profile is strictly related to their biochemical structure, dose and regimen. Progestins with pure progestogenic effects do not alter lipid metabolism, 19-nortestosterone derivatives decrease HDL-cholesterol, and 17-alpha-hydroxyprogesterone derivatives have little effect upon the beneficial changes in plasma lipids induced by estrogens [6].

The PEPI trial has compared the long-term effect of different estrogen–progestin hormone replacement therapy regimens upon blood pressure and metabolic parameters in healthy women. This 3-year, multicenter, randomized trial compared the effects of placebo, conjugated equine estrogens (0.625 mg/day), conjugated equine estrogens plus cyclic medroxyprogesterone acetate (10 mg/day for 10 days/month); conjugated equine estrogens plus continuous medroxyprogesterone (2.5 mg/day); conjugated equine estrogens plus cyclic micronized medroxyprogesterone (200 mg/day for 12 days/month) on lipid profiles in healthy postmenopausal women [7]. The study included 875 postmenopausal women, and the primary study objective was to assess the differences between placebo and treatments on selected heart disease risk factors. At baseline, the women had a normal lipid profile with mean high-density lipoprotein cholesterol (HDL-C) value of 63 mg/dL and a low-density lipoprotein cholesterol (LDL-C) value of 140 mg/dL. Triglycerides and total cholesterol for the group averaged 104 and 244 mg/dL, respectively. Changes in HDL-C levels appeared to differ slightly among the treatment groups, but were all significantly greater than placebo. Conjugated equine estrogens alone produced the greatest increase in HDL-C while the adjunct of progestins somewhat reduced the positive increase in HDL-C. However, the adjunctive clinical impact of the different progestogens on the beneficial effect of conjugated equine estrogens is trivial.

The change observed between the progestogen regimens in the PEPI study is within 2 mg/dL, which, although significantly different between treatments, has no clinical importance. Furthermore, it has never been proved that in normocholesterolemic women with normal HDL-C and low LDL-C, like those included in the PEPI trial, an increase in HDL-C reduces cardiovascular mortality or morbidity.

Regarding the effect of progestins on LDL-C, in the PEPI study conjugated equine estrogens alone and each of the conjugated equine estrogens plus progestogen treatment regimens similarly decreased LDL-C as compared with placebo. Finally, triglyceride levels were similarly elevated in each of the four treatment groups, ranging from 11.4 to 13.7 mg/dL as compared with placebo. As mentioned for the changes in HDL-C, the clinical relevance of the changes between different treatments found in the PEPI trial is of trivial clinical importance. Statistically significant differences in metabolic parameters do not necessarily reflect a clinical effect. For example, decreasing total cholesterol levels in low-risk normocholesterolemic patients without cardiovascular disease has never been shown to reduce cardiovascular risk, while the effect on LDL-C may be of relevance. A 12 mg/dL increase in triglyceride in women with normal triglyceride levels does not cause hypertriglyceridemia or significant changes in coagulation profiles. Although small differences between treatments may be detected, the overall metabolic impact of clinical relevance of the different progestogens tested in the PEPI study has to be considered similar.

Because of its hepatic first-pass metabolism, micronized progesterone has the metabolic impact of nonandrogenic progestins, such as medroxyprogesterone acetate and cyproterone acetate [6]. Transvaginal administration of progesterone does not affect the metabolic changes induced by estrogen replacement therapy and must, therefore, be considered the only metabolically neutral form of progestin administration. Androgenic progestins such as norethisterone acetate have more detrimental effects upon plasma lipids. In recent years attention has been given to the association of lipid-lowering therapy and oral hormone replacement therapy for the treatment of hyperlipidemia in menopausal women. The combination of the two therapies seems to be more effective than either of them separately in reducing cholesterol and triglycerides in dyslipidemic women. Several studies have evaluated the effect of oral estrogen–progestin replacement therapy and statins in hypercholesterolemic women. Darling et al [8] and Sbarouni et al [9] compared the effect of simvastatin and hormone replacement therapy with conjugated equine estrogens (0.625 mg daily) and medroxyprogesterone acetate (2.5 mg daily) in hypercholesterolemic menopausal women and found that while simvastatin was more effective in reducing total cholesterol and LDL-C, it had no effect on Lp(a), which was reduced nearly 30% by hormone replacement therapy.

Davidson et al [10] compared the effect of estrogen replacement therapy with conjugated equine estrogens (0.625 mg daily), pravastatin (20 mg daily) and estrogen plus statin therapy in hypercholesterolemic postmenopausal women and found that while estrogen replacement therapy was as effective as pravastatin in increasing HDL-C it was less effective than pravastatin in reducing LDL-C. Of interest, the association of estrogen replacement therapy with conjugated equine estrogens and pravastatin was more effective than pravastatin alone in reducing total cholesterol, LDL-C and triglycerides. This latter effect is of particular importance since, as mentioned, oral estrogens alone may induce a slight increase in total triglycerides. Herrington et al [11] have evaluated the effect of pravastatin, oral hormone replacement therapy with conjugated equine estrogens, and medroxyprogesterone acetate on plasma lipids and endothelial function in hypercholesterolemic women. They found that pravastatin alone was more effective in reducing total cholesterol and LDL-C, that hormone replacement therapy was more effective in restoring endothelial function, but that combination therapy was more effective than the two therapies alone in lowering plasma cholesterol and LDL-C, in increasing HDL-C, and in improving endothelial function. Our group has recently reported that the association of Atorvastatin with conjugated equine estrogens and medroxyprogesterone acetate is more effective than Atorvastatin alone or in combination with estradiol and norethisterone acetate in lowering Lp(a) and total and LDL-C in menopausal women with severe hypercholesterolemia.

From these studies it seems clear that combination therapy with oral estrogens (alone or in association with nonandrogenic progestins) and statins is the most effective therapy for the treatment of hypercholesterolemia in menopausal women.

PROGESTINS AND CORONARY ATHEROSCLEROSIS

The vasodilatory and antiatherogenic effects of estrogens on normal and diseased arteries are well

known. Estrogens reduce the progression of coronary atherosclerosis both in animals and in humans and, administered either acutely or chronically, can reverse acetylcholine-induced vasoconstriction in animals and humans. When administered in combination with estrogens, progestins may interfere with the effect of estrogens.

Adams et al [12], who evaluated the effect of estrogen replacement therapy with and without adjunctive progestins in ovariectomized monkeys fed an atherogenetic diet, found that estradiol-17β significantly reduces (by half) the degree of coronary atherosclerosis and that the addition of progesterone did not reduce the antiatherogenic effect of estradiol. In another study, the same group evaluated, in the same animal model, the effect of conjugated equine estrogens together with medroxyprogesterone acetate. Conjugated equine estrogens reduced by 70% the degree of coronary atherosclerosis, while the addition of medroxyprogesterone resulted in a nonsignificant decrease of coronary atherosclerosis [12]. It is important to point out, however, that the effect of progestins upon the arteries of non-human primates may be affected by metabolic pathways in the animals different from those present in human arteries. Therefore, the effects of progestins upon atherosclerosis and vascular function cannot be fully extrapolated from animals to humans.

Recently, Herrington et al [13] compared in a placebo-controlled study the effect of hormone replacement therapy with conjugated equine estrogens alone or in combination with medroxyprogesterone acetate upon the progression of coronary atherosclerosis in normocholesterolemic women with proven coronary artery disease (ERA Study). After a 3.2-year follow-up, no significant difference in mean coronary artery stenosis was found between women allocated to active therapy or placebo. This was an elegant study; it showed that neither hormone replacement therapy nor statins (which were largely used in the placebo group) reduced the progression of coronary artery disease in menopausal women when the coronary atherosclerotic plaque is well formed and has already produced significant narrowing of coronary vessels.

From a preventive point of view, it is more fruitful to seek to prevent plaque formation, and progression of small plaques, rather than expecting a reduction in size of small atherosclerotic plaques. The evaluation of intima–media thickening may help to identify initial stages of atherosclerosis. Several studies have shown that long-term hormone replacement therapy reduces the intima–media thickness in hormone users compared with non-users, suggesting that an exact role for hormone replacement therapy in preventing progression of atherosclerosis in menopausal women has not yet been established, and the results of ERA cannot be used to draw any conclusion on the effect of hormone replacement therapy on prevention of coronary artery disease in the setting of either primary or secondary intervention.

As for the ERA study, most studies evaluating the effect of estrogen–progestin therapy upon intima–media thickness have been conducted using medroxyprogesterone acetate. Therefore, data on the anti-atherogenic effect of progestins other than medroxyprogesterone acetate are lacking at present.

PROGESTINS AND VASCULAR REACTIVITY

Progesterone and progestins have vasoactive properties which are in part mediated by the progesterone receptors. Since progesterone receptor expression on the cellular surface is induced by estrogen exposure, it becomes clear that estrogen exposure may affect the response of the vascular tree to progestins.

Several studies have evaluated the effect of progesterone and progestins on coronary arteries in vitro and have demonstrated an endothelium-independent relaxation to progestins with minimal differences between the different substances. Miller et al [14] assessed coronary artery relaxation in coronary artery strips from ovariectomized dogs treated with estrogen, progesterone or estrogen plus progesterone. The relaxation response was similar in the coronary arteries of those animals receiving estrogen and in those receiving progesterone, while it was minimally reduced in the group receiving the combination therapy. Therefore, it seems that, in vitro, there is little or no detrimental effect of progesterone and progestins upon vascular functions.

In vivo studies have suggested that synthetic progestins may antagonize the vasodilatory effect of estrogens in experimental animals. Adams et al [15] have evaluated the separate and combined effects of conjugated equine estrogens and medroxyprogesterone acetate on coronary reactivity of atherosclerotic monkeys. Estrogen exposure increased coronary dilator responses and blood flow reserve, while co-administration of medroxyprogesterone acetate resulted in a 50% reduction of the dilator response. The effect of synthetic progestins cannot be fully translated to humans because of the different metabolic pathways in animals and humans, as mentioned above.

In humans, different progestins and different therapeutic regimens may have different effects upon vascular reactivity. Since estrogen use induces production of progesterone receptors, progestins given in a cyclical regimen should, theoretically, have more pronounced unfavorable vascular effects, while continuous combined regimens should reduce the potential detrimental effects of progestins. Androgenic progestins have been reported to reduce the beneficial effect of estrogens upon pulsatility index more than progesterone and less androgenic progestins, such as medroxyprogesterone acetate and cyproterone acetate. Similar findings have been reported from studies of carotid artery stiffness [16].

Our group has recently reported the effect of the addition of cyproterone acetate to estradiol valerate upon endothelial function in 20 postmenopausal women at increased cardiovascular risk. Estradiol valerate significantly increased flow-mediated dilatation of the brachial artery as compared to baseline, and this effect was not influenced by cyproterone acetate, suggesting that cyproterone acetate does not reduce the beneficial vascular effect of estrogens. Similar findings have been obtained using conjugated equine estrogens and continuous combined medroxyprogesterone acetate.

We have also evaluated the effect of two different regimens of hormone replacement therapy upon endothelial function and forearm vascular resistance in menopausal women with grade 1 hypertension whose blood pressure values were well controlled by therapy with diuretics. Patients entered a double-blind, single cross-over study evaluating the effect of continuous combined hormone replacement therapy with either conjugated equine estrogens plus medroxyprogesterone acetate or estradiol-17β plus norethisterone acetate. Compared with baseline, conjugated equine estrogens plus medroxyprogesterone acetate caused a marginal reduction of blood pressure, while the association of estradiol-17β plus norethisterone acetate increased blood pressure values (Figure 1). A significant difference in systolic blood pressure was noted between the two treatment phases. Endothelial function was improved by conjugated equine estrogens plus medroxyprogesterone acetate, while it was negatively affected by estradiol-17β plus norethisterone acetate. The changes in blood pressure observed during hormone therapy were mainly attributable to the effect of the two hormone regimens upon forearm vascular resistances. Indeed, while conjugated equine estrogens plus medroxyprogesterone acetate reduced

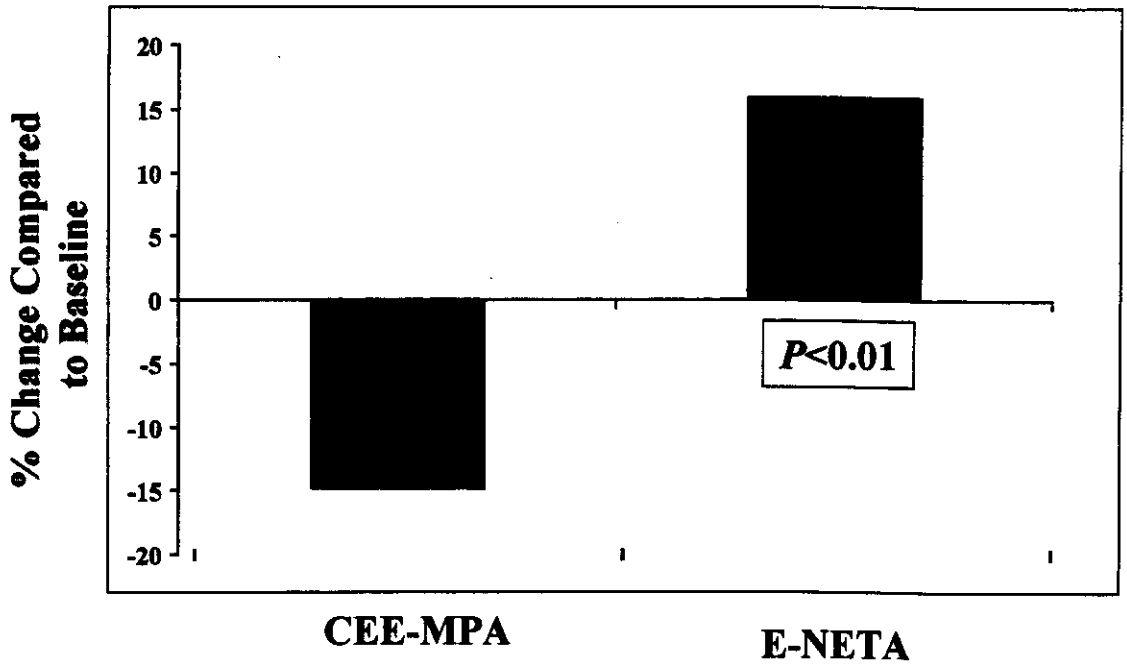

FIG. 1. Effect of estrogen–progestin treatments on brachial artery resistance. Peripheral vascular resistance is reduced by medroxyprogesterone acetate, increased by norethisterone acetate. CEE-MPA-conjugated equine estrogens/medroxyprogesterone acetate; E-NETA=17β-estradiol/norethisterone acetate. From Rosano et al, in Paoletti et al (eds): *Women's Health and Menopause*, 1997.

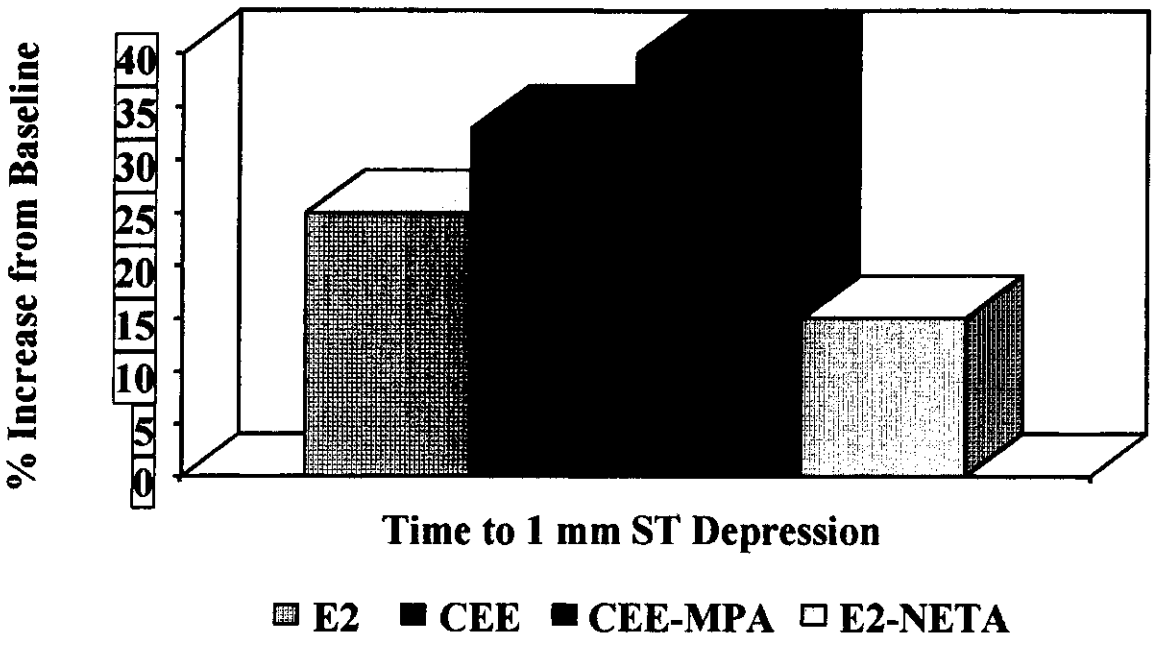

FIG. 2. Effect of estrogens and progestins upon exercise-induced myocardial ischemia (From: Rosano et al: *Lancet* 342:133–136, 1993; *J Am Coll Cardiol* 33(2) (abstract); Haines C et al: NAMS Meeting 1999). E2 = 17β estradiol; CEE = conjugated equine estrogens; CEE-MPA = CEE/medroxyprogesterone acetate; E2-NETA = E2/northisterone acetate.

brachial artery resistances, these were increased by estradiol-17β norethisterone acetate [6].

These data show that different estrogen–progestin treatments have different effects upon blood pressure and vascular reactivity. The adjunctive use of more androgenic progestins with estrogens seems to deleteriously affect peripheral vascular resistance. It may be possible that some of the effect observed is dose dependent and that lower doses of androgenic progestins may have an almost neutral vascular effect.

A careful selection of the dose and type of progestin to add to estrogens seems to be crucial in order to preserve, and possibly enhance, the beneficial vascular effects of estrogens. These effects may be of clinical relevance for those patients with cardiovascular disease, or those with increased vascular reactivity, as found in Raynaud's phenomenon, migraine, vasospastic angina, and syndrome X.

EFFECT OF PROGESTINS UPON CHEST PAIN AND MYOCARDIAL ISCHEMIA

In recent years, it has become evident that estrogens do have anti-ischemic and anti-anginal properties. We have demonstrated that acute and chronic administration of estradiol-17β improves exercise-induced myocardial ischemia in menopausal patients with coronary artery disease, and improves chest pain in female patients with angina and normal coronary arteriograms. The question arises as to whether the use of progestins may influence these beneficial estrogens.

We have also shown that norethisterone acetate reverses the anti-anginal properties of estradiol-17β in female patients with syndrome X and may even worsen symptoms in these patients [17] (See Figure 2). Recently, we have reported that adjunctive therapy using vaginal progesterone (45 mg/daily) or medroxyprogesterone acetate (10 mg/daily) with estradiol-17β did not worsen exercise-induced myocardial ischemia in 18 postmenopausal women with coronary artery disease. No difference was found between baseline and estradiol-17β plus medroxyprogesterone in either time to 1 mm ST depression or exercise time, while vaginal progesterone further improved both.

The present study demonstrated that in menopausal patients with coronary artery disease, the addition of cyclical natural progesterone to estrogen replacement therapy enhances the benefi-

cial effects of estrogen therapy upon exercise-induced myocardial ischemia, while cyclical medroxyprogesterone acetate dose not have such a beneficial effect. More recently we have shown that in patients receiving equine estrogens the use of continuous combined medroxyprogesterone acetate improves exercise performance more than the cyclical regimen [6].

Therefore, it seems that in patients with proven cardiovascular disease, and in those at increased cardiovascular risk, less androgenic progestins administered in a continuous combined scheme are preferable. Although some studies have shown that vaginal progesterone administration enhances the beneficial effects of estrogens, these data cannot be translated to micronized progesterone given orally, because the latter undergoes an important first-pass effect.

EFFECT OF ESTROGEN AND PROGESTIN USE ON THE RISK OF CARDIOVASCULAR DISEASE

There is a large body of evidence suggesting that estrogen replacement therapy after menopause can provide protection against heart disease and, possibly, stroke. The most substantial benefit, a 35–50% reduction in cardiovascular mortality and morbidity, is conferred on current estrogen users. Few epidemiological studies have investigated the effect of addition of a progestogen to estrogen therapy upon cardiovascular mortality and morbidity. Nachtigall et al [18] reported a 68% reduction in the risk of myocardial infarction in women given estrogen and cyclic progestin compared with women receiving placebo. Falkeborn et al [19] found that women prescribed an estrogen–progestin combination had a reduction in the risk of myocardial infarction of 50% when compared with women in the general population, while the risk reduction in women receiving estrogen alone was 26%. Similarly, Psaty et al [20] reported a reduction in the risk of myocardial infarction in women receiving estrogen alone (relative risk 0.69) or estrogen–progestin combination (risk reduction 0.68) versus non-users. The report of a 16-year follow up of 59,337 women included in the Nurse's Health Study suggested that those currently taking estrogen with progestins (most commonly medroxyprogesterone acetate) had a significant reduction in their risk of heart disease [5]. In this study, it was found that women who took estrogen with progestin had a 61% reduction in the risk of a major coronary event as compared with women who never use hormone replacement therapy. Despite this protective effect upon cardiac events, estrogen therapy alone or in combination with progestins did not show any protective effect upon stroke. Based on these results, it seems conceivable that the risk of major coronary events is substantially reduced by combined hormone replacement therapy and that progestins do not decrease the cardioprotective effect of estrogens. All these studies have been conducted in healthy women and, therefore, the effect of the addition of a progestin to estrogens in patients at risk for cardiovascular disease may be different because of the effect of progestins upon lipid profile and vascular functions.

The results of the Heart and Estrogen/progestin Replacement Study (HERS) have added some critical data on the effect of hormone replacement therapy for secondary prevention in women with coronary artery disease [21]. The aim of the study was to evaluate whether daily treatments with conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) would reduce coronary events in women with established coronary artery disease. The study, which included 2,763 postmenopausal women with a mean age of 66.7 years, did not show any protective effect of hormone replacement therapy on cardiovascular end points in elderly women with coronary artery disease, and suggested a possible increase in the occurrence of acute coronary events during the first year of hormone therapy. Overall, there were 172 myocardial infarctions in the hormone-treated group and 176 in the placebo group, with an increased incidence (post hoc analysis) in events in the hormone group during the first year and a clear trend toward a reduction of cardiac events with the treatment after 2 years. The study confirmed the increased incidence of deep venous thrombosis with the use of hormone replacement therapy, but no difference in the number of thromboembolic events was noted. The authors concluded that combined estrogen–progestin therapy does not reduce the risk of coronary events in postmenopausal women with pre-existing coronary artery disease, but that the continuation of use in women already taking this therapy may prove beneficial.

The study, however, is affected by several important methodological and statistical problems that make its interpretation difficult—and its conclusions useless for clinical practice. The first problem with the study is the relatively old age of the study population (67.5 years). Women at this age are rarely considered for initiation of hormone replacement therapy. The major concern with the study is that, although conducted in a fairly large patient population, it does not have enough statistical power to

detect significant differences between patients allocated to hormone replacement therapy or placebo. The size of the trial was determined by power calculations based upon assumptions which were not met. Indeed, the sample size of the study was calculated on the basis of a yearly event rate of 5% in the placebo group, while the observed event rate in this group was 3.3%, which makes the statistical estimates insufficient. With such an event rate, the sample size should have been at least twice that of the placebo group. Another important problem is the short duration of the study. The "per protocol" estimated duration of the study should have been 4.75 years, but the study was interrupted without a clear explanation at 4.1 years, when there was a significant trend toward a reduction in cardiac events in the hormone treated group. If the study had been continued to its planned duration, it would probably have shown a significant reduction in the occurrence of coronary events in the hormone-treated patients. The reported increase in cardiovascular events during the first year in the hormone-treated group has no relevance, since it was a post hoc analysis and the study was not sized to detect that effect. Furthermore, this increased incidence of cardiovascular events during the first year seems to be attributable more to a low event rate in the placebo group than to an increased incidence in the hormone-treated group.

Further studies are warranted to evaluate the effect of hormone replacement therapy on cardiovascular prognosis. Fortunately, other randomized studies will evaluate the effect of estrogen and estrogen–progestin replacement therapy upon cardiovascular events in menopausal women. Until completion of these studies, hormone replacement therapy should be seen by cardiologists with no enthusiasm, but also with no fear.

CONCLUSION

The data available at present on the cardiovascular effect of progestins suggest that the adjunctive use of progestins with estrogen replacement therapy may have different effects depending on type, dosage and route of administration of progestins. Some progestins may antagonize the favorable cardiovascular effect of estrogens. Furthermore, the scheme of administration (continuous or sequential) may influence the cardiovascular effects of the hormones, and it is, therefore, possible that similar hormones may have different effects according to their scheme of administration.

While in menopausal women not at risk for coronary events any progestin can be administered safely, in menopausal patients at risk for coronary artery disease less androgenic progestins (or natural progesterone) seem to be the progestational agents of choice as they avoid the unwanted detrimental effects of androgenic progestins.

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