PERGAMON

Journal of Steroid Biochemistry and Molecular Biology 69 (1999) 185–193

The Journal of Steroid Biochemistry & Molecular Biology

Progestins in the menopause ☆

Régine Sitruk-Ware*

Department of Endocrinology, St Antoine Hospital, Paris, France

Abstract

While the benefits of progestin use in hormone replacement therapy (HRT) are well recognised as far as endometrial protection is concerned, their risks and drawbacks have generated controversial articles. The data related to the progestin effect on breast tissue has been interpreted differently from country to country. However it has been admitted that, according to the type of progestin used, the dose and duration of its application, a predominant antiproliferative effect is observed in the human breast cells. As far as breast cancer risk is concerned, most epidemiological studies do not suggest any difference between the estrogens given alone or combined to progestins in HRT. When the cardiovascular risk factors are considered, some molecules with a higher androgenic potency than others, attenuate the beneficial effects of estrogens on the lipid profile and the vasomotion as well. On the other hand, other progestins devoid of androgenic properties do not exert these deleterious effects. The epidemiological data does not suggest any negative effect of the progestins administered together with estrogens on cardiovascular morbidity or mortality.

However, recent results suggest that in women with established coronary heart disease (CHD), HRT may not protect against further heart attacks, when the progestin selected possesses androgenic properties.

Complying with the classic contra indications of HRT and selecting molecules devoid of estrogenic, androgenic, or glucocorticoid effect should allow a larger use of the progestins without any major drawback.

1. Introduction

The main benefit well recognised for progestin use in hormonal replacement therapy (HRT) is the protection of the endometrium by opposing the proliferative effect of estrogens. On the other hand several risks are attributed to progestins as a class-effect although the molecules used in HRT vary and do not induce the same side-effects according to their pharmacological properties.

Among the alleged risks of progestins in HRT, cardiovascular risk and breast cancer risks have been the most debated issues. This article will address both risks and benefits of progestins in HRT and analyse the available data which led to opposing views on these issues.

2. Progestins and the endometrium

It is well known that progesterone and progestins regulates the estradiol (E2) action on the endometrial cells and prevent endometrial hyperplasia [1].

After a priming effect of estrogens, all progestins have been shown to mimic the action of progesterone and inhibit cell proliferation, decrease the estrogen and progesterone receptors (ER & PR), stimulate the effect of the 17 beta Estradiol dehydrogenase (E2DH) which converts E2 into Estrone (E1) a less active metabolite.

In the field of hormonal replacement therapy (HRT) it is now well accepted that estrogens should be opposed by the co-administration of a progestin at doses and duration able to inhibit the endometrial proliferation.

☆ Proceedings of the Xth International Congress on Hormonal Steroids, Quebec City, Quebec, Canada, 17–21 June 1998.

* Correspondence address: Exelgyn Labs, 6 rue Christophe Colomb, F-75008 Paris, France.

0960-0760/99/$ - see front matter
PII: S0960-0760(99)00053-9

Epidemiological studies have now clearly shown that combined HRT decrease not only the risk of endometrial hyperplasia but also the risk of endometrial cancer.

The effects of unopposed estrogen on the risk for endometrial cancer are now reasonably well defined. Risk increases with increasing duration of use, reaching a relative risk of about 10 after 10 or more years of use; the elevation in risk declines after cessation of use, but the risk is still significantly raised 5 or more years after last use [2].

With regards to progestin addition to estrogen, Key [3] reviewed the results of six epidemiological studies analysing the relationship of combined hormone replacement therapy and the risk of endometrial cancer. In all studies, use of estrogen with a progestin was associated with a lower relative risk than use of estrogen alone, but the risk was still higher than in untreated women. Both studies which presented results according to the duration of progestin use each month found that the relative risk was lower in women using progestins for 10 or more days per month than in women using progestins for less than 10 days per month.

As far as endometrial hyperplasia is concerned, it is undisputed that 12–14 days of progestins are required to decrease the risk below 1%. Most studies with sufficient numbers, using various steroids showed that unopposed estrogens induce hyperplasia in 20–42% of the cases, while the addition of a progestin (medroxy progesterone acetate, in either sequential or continuous combined regimens, nomegestrol acetate, trimegestone, norethisterone) would decrease that incidence to about 1%. [1,4]

The present regulations and guidelines about the evaluation of the efficacy of a progestational molecule to protect the endometrium, require one 12-month dose-ranging pivotal trial, comparing the selected unopposed estrogen dose and the same dose associated with several doses of the progestin to be assessed [5]. The primary efficacy analysis must show a clinically and statistically significant reduction in the 1-year incidence of endometrial hyperplasia, in at least one combination estrogen-progestin group compared with the equivalent dose level unopposed estrogen group. From a clinical perspective, the cut-off point should be around 1% in the combined group.

3. Progestins and the breast

The data is less clear-cut as regards the role of progestins on the breast tissue especially in postmenopausal women.

Although in vitro studies have shown that progestins induce similar decrease in ER and PR and increase in E2DH as they do in the endometrium, epidemiological studies have suggested that progestins do not revert the estrogen related increase in breast cancer risk in long-term use of HRT. Other studies suggested a protective effect of progestins [6].

On the other hand it is well established that high doses of progestins are successfully used in the treatment of advanced breast cancer as a second line endocrine therapy.

The two main progestins used in clinical practice, as treatment of advanced breast cancer, are medroxyprogesterone acetate (MPA) and megestrol acetate (MA). When used at high doses, these compounds exert an antigonadotropic effect which has been observed both in pre and post menopausal women. Another important effect of progestins is related to their ability to decrease the amount of estrone sulfate (E1 S) in breast tissue. Pasqualini et al. [7] have demonstrated that several progestins can block the conversion of E1 S to E2 very significantly in hormone-dependent breast cells.

The dual effect of progesterone and progestins on the cell cycle has been demonstrated suggesting that according to the duration of application the same steroid can drive the cells into the phase of multiplication or place them in a resting state [8].

Also progestins exert different effects according to the steroid from which they derive e.g. pregnanes, estranes or gonanes. Some of the estrane derivatives are able to stimulate breast cell multiplication in vitro through an ER mediated pathway. Most of the pregnanes do not exert such effect [9]. Also some of the pregnane derivatives stimulate the apoptotic process leading to cell death [10].

Striking differences are observed in the progestin use in Europe or in the USA. In France, where the rate of progestin consumption per woman is higher than in the USA, the breast cancer rate has not increased as sharply as observed in North America [6].

In a large French cohort study of premenopausal women with benign breast disease receiving high doses of progestins, Plu-Bureau et al. [11] have shown a decreased risk in breast cancer in the group of women receiving 19-nor testosterone derivatives for at least 15 days per cycle. The other progestins did not decrease the risk significantly.

A consensus paper of the 'European Progestin Club' [12] addressed the various controversies between countries and suggested new prospective studies to be done with newer types of progestins available in Europe. However, they conclude from the presently available data, that progestins with a pharmacological profile compared to that of the natural progesterone would be preferred.

Although cancer genesis is multifactorial, it may be concluded that progestins do protect endometrial tissue against the estrogen proliferative action and if they do

not protect breast tissue and decrease the risk of breast cancer, at least they do not increase it.

4. Progestins and cardiovascular disease

It is now well-established that cardiovascular disease (CVD) represents the major cause of death in women just as in men but at a later age.

In women the incidence of CVD increases after the menopause and it has been shown that the risk of atherosclerosis increases by 3–4-fold after a natural menopause [13].

A number of epidemiological studies performed since the early 1980s indicate around a 50% reduction in cardiovascular morbidity and mortality in women using estrogens after the menopause [14,15]. However, the controversy is ongoing as regards a possible selection bias in the studies; healthier women receiving estrogens for long-term use more often than women at risk [15].

This hypothesis has been reinforced by the recent results from the Heart and Estrogen/progestin Replacement Study (HERS) research group, indicating that in postmenopausal women with established CHD, an HRT regimen with conjugated estrogens (CEE) and medroxyprogesterone acetate (MPA), does not protect from further heart attacks [16].

These findings were disappointing but not unexpected in the light of previous animal experiments.

Indeed a better understanding of the mechanisms underlying the protective effect of sex steroids was provided by animal studies using the monkey model [17] as well as studies of postmenopausal women, using surrogate markers of cardiovascular risk [18,19]. There is now evidence that estrogens will improve the endothelial function and hence the vascular tone, as well as improve the lipid profile [20], the carbohydrate metabolism [21] and hemostatic parameters [22].

The controversy was raised again regarding the role of progestins, prescribed together with estrogens to protect the endometrium, and shown for some of the most prescribed molecules to oppose partially the beneficial effect of estrogens [23]. Unfortunately that concern was directed towards progestins as a class-effect, although several categories of progestins are often prescribed, and striking differences exist according to the type of molecules which have been tested [24–26]. Obviously, natural progesterone and some of its derivatives such as the 19-norprogesterone molecules do not exert any androgenic effect [24,26] and hence no negative effect on the lipids while the 19-nortestosterone derivatives and even some 17-hydroxyprogesterone molecules exert a partial androgenic effect [24,27] explaining some of the negative effects observed on cardiovascular risk factors or surrogate markers of risk.

Given these class differences it would appear inappropriate to claim that progestins in general compromise the cardioprotective effects of estrogens without specifying which of these progestins reverse the estrogen effects and those which do not as indicated by the existing data.

4.1. Results from observational and prospective studies

Grodstein et al. [28] reported the relationship between cardiovascular disease and HRT in 59,337 women followed for up to 16 years. Compared with the risk of major coronary heart disease for women who did not use hormones, the relative risk was 0.6 for women using estrogens alone and even lower at 0.39 for those using combined hormones.

The authors found no association between stroke and use of combined hormones. For this study, conducted in the United States, the progestin used was most likely medroxyprogesterone acetate.

Although this large observational study confirms the previous results of Falkeborn et al. [29] in Sweden and Psaty et al. [30] in the United States, the possibility of a selection bias is raised again. Women who stay on long-term HRT are usually healthier on average than those who do not, with lower blood pressure, lower weight and they exercise more often. Grodstein et al. [28] have adjusted for these confounding factors as did the other researchers. However only the long-term randomised controlled trial, of the Women's Health Initiative will bring a definite conclusion.

Several ongoing prospective trials focus on primary or secondary prevention of CHD [16,31]. From all the large ongoing studies, HERS has just published the first results in the JAMA of August the 19th, 1998. The other trials will be completed just after the turn of the century.

The Women's Health Initiative in the United States and the Medical Research Council-HRT study, in Europe are designed as long-term primary prevention trials and would enroll postmenopausal women without coronary disease. The long-term follow-up under treatment or placebo will help to answer the questions of the presumed protective effects of HRT to prevent the occurrence of CVD and CHD.

In women with documented CHD, it was not clear, whether estrogen would improve survival or not until the results of HERS appeared [16].

The study was designed to determine whether estrogen (conjugated equine estrogen) plus continuous progestogen (medroxyprogesterone acetate) is better than placebo in preventing recurrent events in women with documented coronary disease.

In this randomised, double-blind, placebo-controlled

trial, 2763 women have been followed-up for 4.1 years on average. The main objective of the study was to determine whether HRT would reduce the morbidity and mortality of cardiovascular disease in this high-risk group and the primary outcome was the occurrence of non-fatal myocardial infarction (MI) or CHD death.

After 4 years of follow-up the same number of events were recorded in both the active and the placebo groups indicating that the combined HRT regimen selected did not reduce the overall rate of coronary events in postmenopausal women with previous CHD.

Their relative hazard (RH) for a further event was of 0.99 (95% Confidence Interval; CI 0.8–1.2). Also, there was no significant difference between groups in any of the secondary outcomes despite a net decrease in LDL and an increase in HDL cholesterol levels in the hormone group.

A more detailed analysis is ongoing in order to explain why the therapy did not bring the expected protective effect of HRT. Nevertheless, the authors concluded that although they do not recommend starting HRT for the secondary prevention of CHD, they would find it appropriate for women receiving it to continue, given the favorable pattern of CHD events after several years of treatment.

It is obvious that different molecules may bring along different results, unfortunately, most of the large ongoing trials have selected the same HRT regimen for their study design and we shall not have an answer about a possible beneficial effect of other treatment regimens.

5. Risk factors for cardiovascular disease and role of progestins

Among the main cardiovascular risk factors recognised for both men and women, cigarette smoking, high cholesterol levels, hypertension, diabetes mellitus and obesity may be preventable causes of coronary heart disease. In women, the estrogen deprivation following the menopause may affect several of these risk factors and it is now well accepted that estrogen replacement therapy (ERT) will improve cholesterol levels, diastolic blood pressure, insulin sensitivity and some of the clotting factors [20–22,24]. The existence of atherosclerosis in the vessels tree definitely increases the risk of cardiovascular disease.

The beneficial effects of estrogens on the vasodilating endothelial factors, hence on vasomotion [32] would definitely play a major role in the primary prevention of coronary heart disease in women.

5.1. Effects of the progestins on lipids and lipoproteins

Most of the studies evaluating the effect of estrogens on the lipoproteins indicated a reduction of LDL-C levels and an increase of HDL-C levels by 10–15% [33]. The addition of a progestin to ERT may affect the lipid formula, however the effects differ according to the type of the progestogen. Progestogens with androgenic properties reverse partially the HDL-raising effect of estrogen [24,34] while natural progesterone and some 19 nor-progesterone derivatives such as nomegestrol acetate do not affect the HDL levels [24,35].

In the postmenopausal Estrogen/Progestin Intervention trial [24], (the PEPI trial), 875 postmenopausal women were followed for 3 years in a randomised double-blind, placebo controlled trial. The three combined regimens of estrogen and progestin induced an increase in HDL levels and a decrease in LDL levels. However, the increase in HDL-C was partially reversed in the groups where medroxyprogesterone acetate (MPA) was added to oral estrogens while oral micronised progesterone did not modify the estrogen-induced rise. The results observed for LDL under estrogen were not modified by the addition of a progestin either MPA or progesterone.

In the study from Crook et al. [34] where 19-nortestosterone derivatives were evaluated in a 6-month randomised comparative study, levonorgestrel given orally reversed significantly the HDL-raising effect of estrogen. Norethisterone Acetate (NETA) given transdermally in doses as low as 250 μg per day also reversed the estrogen effect although to a lesser extent than observed with levonorgestrel.

In another randomised comparative double-blind trial comparing the effects of nomegestrol acetate (NOM Ac) to NETA both given orally at the dose of 5 mg per day, the increase in HDL-C observed under estradiol valerate was partially reversed by NETA but not by NOM Ac, a 19-norprogesterone derivative [35].

Moreover, in a 3-month randomised prospective study comparing the effect of a placebo and two oral estradiol + NOM Ac combinations, the progestin being given at doses of 2.5 and 3.75 mg daily for 14 days per cycle, NOM Ac did not reverse the effects of oral E2 on LDL-C and apolipoprotein A1. It also induced a significant decrease in lipoprotein (a) as previously observed with MPA [36].

These results indicate that it is not the dose or route of administration which is the most important factor to consider for progestins effect on HDL but rather the molecule from which they derive. Those progestogens derived from progesterone and devoid of androgenic properties, do not impede the beneficial estrogen effects.

The relevance of these lipid changes has to be questioned.

First of all, the role of HDL changes in the alleged cardiovascular protective effects of estrogens accounts for 30 to a maximum of 50% of these effects [37]. Also, in an epidemiological study analysing the relative risk of myocardial infarction of estrogen-progestin users versus non-users, a 'protective' effect appeared for all therapies as compared to no treatment, even in the group using levonorgestrel the most androgenic of the progestins used so far in hormonal replacement therapy (HRT) [29].

Moreover, the recent results of HERS indicate no secondary prevention benefit in patients with CHD, despite a net decrease in LDL and an increase in HDL cholesterol levels in the hormone group [16].

As a pratical recommendation, one should conclude that, overall, the effects of most HRT on lipids and lipoproteins would seem to be on balance beneficial [20], but the selection of the least androgenic progestins should be recommended for long-term therapy.

5.2. Effects of progestins on the carbohydrate metabolism

Glucose intolerance and hyperinsulinemia are well-known risk factors for cardiovascular disease. Postmenopausal women have an age-related deterioration of glucose metabolism [38] and have been shown to have a reduced number of peripheral insulin receptors compared with premenopausal women in the early follicular phase [39].

Insulin is a potent stimulus to endothelial cell growth and also regulates LDL receptor activity [40–41]. Therefore a reduction in fasting insulin levels may be important in controlling one of the mechanisms of CVD.

De Cleyn et al. [42] conducted an 8-month study where 20 women received 0.625 mg conjugated equine estrogens per day given alone for 2 months, then with the addition of dydrogesterone 20 mg/day for 12 days per month for the following 6 months. Oral glucose tolerance tests (OGTT) performed before and after each treatment regimen showed a decrease in the area under the glycemia curve with both treatments. A slight increase in insulinemia was found in the combined treatment group but was not statistically significant.

Later, Godsland et al. [21] in an open, randomised comparative study of 61 postmenopausal women, evaluated the effect of oral equine estrogens with sequential oral levonorgestrel (0.075 mg/d, 12 d/month) or transdermal estradiol with sequential transdermal NETA (0.250 mg/d, 14 d/month). Using intravenous glucose tolerance tests they found that oral therapy caused a deterioration of glucose tolerance and an overall increase in plasma insulin most likely due to the androgenic properties of norgestrel. On the other hand, no change in insulin response or in glucose occurred with the transdermal therapy although the progestin used also exhibited some androgenic properties on lipids [34] but obviously did not affect carbohydrate metabolism when given transdermally.

The 19-norprogesterone derivatives appear to be neutral towards the carbohydrate metabolism as shown by Dorangeon et al. [43] studying the nomegestrol acetate effect in premenopausal women. In these women who did not receive exogenous estrogens, the administration of NOM Ac at doses of 5 mg/d over 20 days per cycle for 6 months did not affect the response in plasma glucose and plasma insulin to the OGTT.

5.3. Progestins effects on the hemostatic risk factors for cardiovascular disease

The suggested preventive effect of sex steroids on the development of atherosclerosis might be counteracted by their possible thrombogenic effect indicated by recent studies among oral contraceptive users. Obviously ethinyl estradiol contained in the contraceptive pill is no longer used in ERT and the so-called third generation progestins are not yet widely used for HRT.

In the large cohort studies and essentially the Nurses Health Study [28] no significant association has ever been found between stroke and hormones. In recent observational studies current users of HRT have been found at an increased risk of venous thromboembolism [16,44,45]. Three papers published in the Lancet on 12 October 1996, led to a published statement from the Committee on Safety of Medicines of the MCA in the UK [45]. The articles express concern as all studies showed an increased risk of deep venous thrombosis and/or pulmonary embolism in women currently taking HRT. The relative risks were of 2.1–3.5 according to the study.

The fact that the risk appears to be concentrated in the first year would suggest that some women, more sensitive or with predisposing factors would develop thrombotic events with any HRT and then stop therapy, while the other women who tolerate it better remain in the longer-term users group.

The recent results of the Heart and Estrogen/Progestin replacement Study (HERS) indicate that combined treatment with conjugated equine estrogens (CEE) and MPA did increase the rate of thromboembolic events in women with previous CHD, as compared with placebo [16] (RH 2.89; 95% CI 1.5–5.6). This double-blind randomised placebo-controlled study confirm the results of the observational studies above-described. The role of the progestin in this apparently negative effect has to be evaluated.

Therefore it is of the utmost importance to investigate the effects of the various sex steroids on the

hemostatic parameters in order to select for therapy those devoid of unwanted effects.

In the large 3-year PEPI trial already mentioned, the combined regimen of equine estrogens plus MPA or plus progesterone lowered fibrinogen levels [24] one of the markers considered to be an independent risk factor for myocardial infarction and stroke [22].

The plasma fibrinogen concentrations increase with age especially during the menopausal transition. In a recent 2-year open prospective study, 42 post menopausal women received estradiol given transdermally (50 μg/d) and MPA (5 mg/d, 12 days every second month). The hemostatic risk factors were measured at baseline, at 3 months and after 2 years of treatment and compared to the results observed in an untreated control group of 18 postmenopausal women as well as a reference group of 20 premenopausal women. Fibrinogen levels significantly decreased under HRT while it slightly increased in the untreated women. Similarly, FVII antigen and PAI-1 antigen decreased after 2 years of treatment but slightly increased in the control group. There were no changes in AT III or protein C values in any group. Therefore a beneficial effect of the sex steroids used in the study was demonstrated on the hemostatic parameters involved as a defense system against thrombosis [22].

Also with another progestin than MPA, Basdevant et al. [46] showed no effect of nomegestrol acetate on plasminogen, fibrinogen, protein C and S. The only change observed was a significant increase in antithrombin III which indeed may not be considered as a negative effect.

5.4. Effects of progestins on blood pressure

Menopause by itself has no influence on high blood pressure (BP) according to longitudinal studies [47]. Whether normotensive or hypertensive women would be at higher risk of increased BP under treatment has been questioned.

Foidart [48] has evaluated the effect of transdermal estradiol (50 μg/day) and sequential use of MPA (10 mg/d for 12 days/month) on the blood pressure of hypertensive women whose condition was therapeutically controlled. Only one patient out of 92 experienced an increase in diastolic blood pressure; no effect of treatment was detected on either the systolic or diastolic blood pressure of the remaining 91 patients.

In another study, long-term treatment with a combined regimen of transdermal estradiol and medroxyprogesterone acetate in normotensive postmenopausal women was reported by Pang et al. [49]. In this case, treatment was associated with a reduction in mean systolic and diastolic blood pressures.

In both studies, combined HRT with MPA did not appear to negatively affect blood pressure.

5.5. Effects of progestins on the vessels

Much attention has been directed towards the effects of sex steroids on the vessels and although estrogens have been shown to exert beneficial effects on the vascular wall, it has been suggested that some progestins may reverse that benefit.

The most recent studies regarding the mechanisms by which estrogens may afford cardioprotective effects have examined their effect on the endothelial function. The presence of estrogen binding sites in endothelial cells has been documented in animal and human arteries [50]. A direct role of estrogens on the endothelium has been suggested and may be related to binding of the steroids to their receptors.

The endothelium is actively involved in regulating vascular tone through the production of endothelial factors with vasodilating or vasoconstricting properties. Hayashi et al. [51] have found evidence of a greater production of nitric oxide in female, rather than the male rabbit aorta, suggesting that estrogens might affect the release of this endothelial vasodilating factor.

In postmenopausal women, the levels of vasodilatory factors, nitric oxyde and prostacyclin, as well as vasoconstrictive factors, endothelin-1 and thromboxane-A2, vary under therapy. Ylikorkala et al. [52] have recently shown that especially women who smoke have high levels of endothelin-1. In these women, transdermal combined therapy with estradiol and norethisterone acetate were able to significantly decrease the levels.

Other recent studies performed in vitro, on vascular smooth muscle cells (VSCM) indicated that sex steroids, both E2 and P, inhibit their proliferation [53]. Progesterone at physiologic levels inhibited DNA synthesis and proliferation in these cells in a dose-dependent manner [54].

In the cynomolgus monkey [17,32], it was shown that 17beta-estradiol modulated the responses of the coronary arteries of the animals to acetylcholine (ACC). Estrogen deprived atherosclerotic monkeys were compared to animals receiving estrogen replacement therapy. The degree of coronary artery constriction following an infusion of acetyl choline was measured in both groups of animals. Paradoxical vasoconstriction occurred following ACC in the untreated animals while estradiol therapy restored the normal endothelium dependent vasodilation. The process occurred rapidly, vasomotion being restored to normal within 20 mn of an intravenous injection of estrogens. Progesterone did not reverse the effects of estrogens.

Similar regulation of the vasomotion was found in women with coronary disease, those receiving ERT exhibiting a dose-dependent vasodilation in response to ACC, in contrast with the untreated women who

exhibited a vasoconstriction [55]. The changes observed in the vasomotion of the postmenopausal women appear to be as prompt as observed in monkeys [56]. Collins et al. [57] showed that intracoronary estradiol decreased the ACC-induced vasoconstriction in nine postmenopausal women, but not in seven men of similar age.

It has been suggested that progestins would partially reverse the estrogenic effects based on the assumption that these molecules exert an anti-estrogenic effect at several target levels.

Sullivan et al. [23] studied the effects of conjugated equine estrogen given alone during 21 days and with added progestin, MPA 10 mg for 10 days on forearm vascular resistance in postmenopausal women. They found that resting vascular resistance and resistance after cold pressor stimulation rose significantly and at a higher level during combined treatment than after estrogen alone.

In the monkey model, as above-described the addition of cyclic or continuous MPA to estrogens inhibited ACC responses by 50% [58]. Miyagawa et al. [59] comparing the effects of progesterone and MPA on the same model, from the standpoint of coronary artery vasospasm, showed that progesterone plus estradiol protected, but MPA plus estradiol failed to protect, allowing vasospasm. On the opposite, the studies from Williams and Adams [60] and from Williams et al. [61] indicated that a nonandrogenic progestin, nomegestrol acetate, does not diminish the beneficial effects of estrogen on the coronary dilator response in monkeys.

Therefore not all progestins behave the same way on the vascular wall and nonandrogenic molecules would appear to be safer on that respect.

6. Conclusion

While the benefits of progestins are undisputed as far as the endometrial protection is concerned, the controversies related to the potential risks have to be reassessed according to the type of progestins considered. Progesterone itself and natural derivatives of the molecules would not display androgenic or estrogenic properties and hence behave differently at the end organ, both on the breast tissue and on the vascular wall. Further epidemiological data are needed considering separately the different types of steroid used in clinical practice which vary from country to country.

References

[1] The Writing Group for the PEPI Trial, Effects of hormone replacement therapy on endometrial histology in postmenopausal women, J. Am. Med. Ass. 275 (1996) 370–375.

[2] D. Grady, T. Gebretsadik, K. Kerlikowske, V. Ernster, D. Petitti, Hormone replacement therapy and endometrial cancer risk: a meta-analysis, Obstet. Gynecol. 85 (1995) 304–313.

[3] T.J. Key, Progestins in post menopausal women: epidemiological data on relationships with endometrial and breast cancer risk, in, R. Sitruk-Ware, D. Mishell, (Eds.), Progestins and Antiprogestins in clinical practice, M. Dekker Inc. publ., New York, 1999 (in press).

[4] J.D. Woodruff, J.H. Pickar, for the Menopause study group, Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone, Am. J. Obstet. Gynecol. 170 (1994) 1213–1223.

[5] FDA HRT Working Group, Guidance for clinical evaluation of combination estrogen/progestin-containing products used for hormone replacement therapy of post menopausal women, Menopause 2 (3) (1995) 131–136.

[6] R. Sitruk-Ware, G. Plu-Bureau, Progestogen use and breast cancer, in: B.G. Wren (Ed.), Progress in the Management of Menopause, Parthenon Publ, Carnforth UK, 1997, pp. 203–210.

[7] J.R. Pasqualini, G. Chetrite, B.L. Nguyen, C. Maloche, L. Delalonde, M. Talbi, M.C. Feinstein, C. Blacker, J. Botella, J. Paris, Estrone sulfate-sulfatase and 17beta-hydroxysteroid dehydrogenase activities; a hypothesis for their role in the evolution of human breast cancer from hormone-dependence to hormone independence, J. Steroid Biochem. Mol. Biol. 53 (16) (1995) 407–412.

[8] C.L. Clarcke, R.L. Sutherland, Progestin regulation of cellular proliferation, Endocr. Rev. 11 (1990) 266–301.

[9] W.H. Catherino, V.C. Jordan, Nomegestrol acetate, a clinically useful 19-norprogesterone derivative which lacks estrogenic activity, J. Steroid Biochem. Mol. Biol. 55 (2) (1995) 239–246.

[10] J. Desreux, A. Noël, J.L. Thomas, A.M. Bernard, J. Paris, R. Delansorne, J.R. Van Cauwenberge, H. Van Cauwenberge, D. Francart, V. Heinen, J.M. Foidart, Progestin induced apoptosis of normal human breast cells: an in vivo and in vitro study, in: Eighth International Congress on the Menopause, Sydney, Australia, November 1996, Abstract F173, 1996, p. 97.

[11] G. Plu-Bureau, M. Lê, R. Sitruk-Ware, J.C. Thalabard, P. Mauvais-Jarvis, Progestogen use and decreased risk of breast cancer in a cohort study of premenopausal women with benign breast disease, Br. J. Cancer 70 (1994) 270–277.

[12] A.E. Schindler, C. Campagnoli, R. Druckmann, J. Huber, J.R. Pasqualini, K.W. Schweppe, J.H.H. Thijssen, progestin Club European, Aspects of progestin activity on the breast, Maturitas 29 (1998) 61–65.

[13] J. Wittemen, D. Grobbee, F. Kof, A. Hofman, H. Valkenburg, Increased risk of atherosclerosis in women after the menopause, Br. Med. J. 298 (1989) 642–644.

[14] D. Grady, S.M. Rubin, D.B. Petitti, C.S. Fox, D. Black, B. Ettinger, V.L. Ernster, S.R. Cummings, Hormone therapy to prevent disease and prolong life in postmenopausal women, Ann. Intern. Med. 117 (1992) 1016–1037.

[15] T. Meade, A. Berra, Hormone replacement therapy and cardiovascular disease, Br. Med. Bull. 48/2 (1992) 276–308.

[16] S. Hulley, D. Grady, T. Bush, C. Furberg, O. Herrington, B. Riggs, E. Vittinghoff, Heart and estrogen/progestin replacement study (HERS) research group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women, JAMA 280 (1998) 605–613.

[17] T.B. Clarkson, M.S. Anthony, Klein K. Potvin, Hormone replacement therapy and coronary artery atherosclerosis: the monkey model, Br. J. Obstet. Gynecol. 103 (S13) (1996) 53–58.

[18] J.M. Sullivan, Hormone replacement therapy and cardiovascular disease: the human model, Br. J. Obstet. Gynecol. 103 (S13) (1996) 59–67.

[19] D.R. Holdright, A.K. Sullivan, C.A. Wright, J.L. Sparrow, D. Cunningham, K.M. Fox, Acute effect of estrogen replacement therapy on treadmill performance in postmenopausal women with coronary artery disease, Eur. Heart J. 16 (1995) 1566–1570.

[20] J.C. Stevenson, Are changes in lipoproteins during HRT important?, Br. J. Obstet. Gynecol. 103 (S13) (1996) 39–44.

[21] I.F. Godsland, K. Gangar, C. Walton, M.P. Cust, M.I. Whitehead, V. Wynn, J.C. Stevenson, Insulin resistance, secretion, and elimination in postmenopausal women receiving oral or transdermal hormone replacement therapy, Metabolism 42 (1993) 846–853.

[22] C. Lindoff, F. Peterson, I. Lecander, G. Martinsson, B. Astedt, Transdermal estrogen replacement therapy: beneficial effects on hemostatic risk factors for cardiovascular disease, Maturitas 24 (1996) 43–50.

[23] J.M. Sullivan, B.A. Shala, L.A. Miller, J.L. Lerner, J.D. McBrayer, Progestin enhances vasoconstrictor responses in postmenopausal women receiving estrogen replacement therapy, Menopause 2 (4) (1995) 193–199.

[24] The writing group for the PEPI trial, Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the postmenopausal estrogen/progestin interventions (PEPI) trial, JAMA 273 (1995) 199–208.

[25] M.R. Adams, J.R. Kaplan, S.B. Manuck, D.R. Koritnik, J.S. Parks, M.S. Wolfe, T.B. Clarkson, Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys: lack of an effect of added progesterone, Arteriosclerosis 10 (1990) 1051–1057.

[26] I. Duc, J. Botella, P. Bonnet, F. Fraboul, R. Delansorne, J. Paris, Antiandrogenic properties of nomegestrol acetate, Arzneim Forsch/Drug Res. 45 (1) (1995) 70–74.

[27] D.D. Bradley, J. Wingerd, D.B. Petitti, R.M. Krauss, S. Ramcharan, Serum high-density-lipoprotein cholesterol in women using oral contraceptives, estrogens and progestins, N. Engl. J. Med. 299 (1978) 17–20.

[28] F. Grodstein, M.J. Stampfer, J.E. Manson, G.A. Colditz, W.C. Willett, B. Rosner, F.E. Speizer, C.H. Hennekens, Postmenopausal estrogen and progestin use and the risk of cardiovascular disease, N. Engl. J. Med. 353 (1996) 453–461.

[29] M. Falkeborn, I. Persson, H.O. Adami, R. Bergstrom, E. Eaker, H. Lithell, R. Mohsen, T. Naessen, The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement, Br. J. Obstet. Gynaecol. 99 (1992) 821–828.

[30] B.M. Psaty, S.R. Heckbert, D. Atkins, R. Lemaître, T.D. Koepsell, P.W. Wahl, D.S. Siscovick, E.H. Wagner, The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women, Arch. Intern. Med. 154 (1994) 1333–1339.

[31] C.P. Spencer, A.J. Cooper, J.C. Stevenson, Clinical trials in progress with hormone replacement therapy, Exp. Opin. Invest. Drugs 5 (6) (1996) 739–749.

[32] J.K. Williams, M.R. Adams, H.S. Klopfenstein, Estrogen modulates responses of atherosclerotic coronary arteries, Circulation 81 (1990) 1680–1687.

[33] T.L. Bush, V.T. Miller, Effects of pharmacologic agents used during menopause: impact on lipids and lipoproteins, in: Mishell Jr (Ed.), Menopause Physiology and Pharmacology, Year Book Medical Publ. Inc, 1987, pp. 187–208.

[34] D. Crook, M.P. Cust, K.F. Gangar, M. Worthington, T.C. Hillard, J.C. Stevenson, M.I. Whitehead, V. Wynn, Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on serum lipids and lipoproteins, Am. J. Obstet. Gynecol. 166 (1992) 950–955.

[35] P. Dorangeon, J.L. Thomas, P. Gillery, M. Lumbroso, M.C. Hazard, Short term effects on lipids and lipoproteins of two progestogens used in postmenopausal replacement therapy, Eur. J. Clin. Res. 3 (1992) 187–193.

[36] J. Conard, A. Basdevant, J.L. Thomas, E. Ochsenbein, C. Denis, T.T. Guyene, H. Degrelle, Cardiovascular risk factors and combined estrogen-progestin replacement therapy: a placebo-controlled study with nomegestrol acetate and estradiol, Fertil. Steril. 64 (1995) 957–962.

[37] T.L. Bush, E. Barrett-Connor, L.D. Cowan, M.H. Criqui, R.B. Wallace, C.M. Suchindran, H.A. Tyroler, B.M. Rifkind, Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the lipid research clinics program follow-up study, Circulation 75 (1987) 1102–1109.

[38] R.A. Jackson, Mechanisms of age-related glucose intolerance, Diabetes Care 13 (S2) (1990) 9–19.

[39] R. De Pirro, A. Fusco, A. Bertoli, A.V. Greco, R. Lauro, Insulin receptors during the menstrual cycle in normal women, J. Clin. Endocrinol. Metab. 47 (1978) 1387–1389.

[40] R.W. Stout, E.L. Bierman, R. Ross, Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells, Circ. Res. 36 (1975) 319–327.

[41] A. Chait, E.L. Bierman, J.J. Albers, Low density lipoprotein receptor activity in cultured human skin fibroblasts: mechanisms of insulin-induced stimulation, J. Clin. Invest. 64 (1979) 1309–1319.

[42] K. De Cleyn, P. Buytaert, M. Coppens, Carbohydrate metabolism during hormonal substitution therapy, Maturitas 11 (1989) 235–242.

[43] P. Dorangeon, J.L. Thomas, M. Lumbroso, M.C. Hazard, S. Dorangeon, Effects of nomegestrol acetate on carbohydrate metabolism in premenopausal women, in: XIIIth World Congress of Gynecol and Obstet (FIGO), Singapore 1991, Abstract No. 0636, 1991.

[44] S. Perez-Gutthann, L.A. Garcia-Rodriguez, A. Duque-Oliart, A. Castelisague-Pique, HRT and the risk of venous thromboembolic event, Pharmacoepidem Drug Safety 4 (S1) (1995) 553 Abstract 118.

[45] Committee on Safety of Medicines, Risk of venous thromboembolism with hormone replacement therapy, Current Problems in Pharmacovigilance 22 (1996) 9–10.

[46] A. Basdevant, C. Pelissier, A. Conrad, H. Degrelle, T.T. Guyenne, J.L. Thomas, Effects of Nomegestrol Acetate (5 mgld) on hormonal, metabolic and hemostatic parameters in premenopausal women, Contraception 44 (1991) 599–605.

[47] E. Casiglia, D. d'Este, G. Ginocchio, G. Colangeli, C. Onesto, P. Tramontin, G.B. Ambrosio, A.C. Pessina, Lack of influence of menopause on blood pressure and cardiovascular risk profile: 16-year longitudinal study concerning a cohort of 568 women, J. Hypertension 14 (1996) 729–736.

[48] J.M. Foidart, The effects of estraderm TTS 50 + medroxyprogesterone acetate on blood pressure in hypertensive post-menopausal women, in: G. Samsioe (Ed.), Cardiovascular disease and HRT. New Perspectives, Parthenon publ. Carnforth, UK, 1991, pp. 41–44.

[49] S.C. Pang, Dale G.A. Green, M.I. Cedars, A.C. Cambone, K. Lozano, P. Eggena, H.L. Judd, Long term effects of transdermal estradiol with and without medroxyprogesterone acetate, Fertil. Steril. 59 (1993) 76–82.

[50] A. Bergquist, D. Bergquist, M. Ferno, Estrogen and receptors in vessels walls, Act. Obst. Gynecol. S. 72 (1993) 10–16.

[51] T. Hayashi, A.M. Fukoto, L.A. Ignarro, G. Chaudhuri, Basal release of nitric oxide from aortic rings is greater in female rabbits than in male rabbits implications for atherosclerosis, Proc. Natl. Acad. Sci. 59 (1992) 11,259–11,263.

[52] O. Ylikorkala, B. Cacciatore, I. Paakkari, M.J. Tikkanen, L. Viinikka, J. Toivonen, The long-term effects of oral and transdermal postmenopausal hormone replacement therapy on nitric

oxide, endothelin-1, prostacyclin, and thromboxane, Fertil. Steril. 69 (5) (1998) 883–888.
[53] A.J. Morey, A. Pedram, M. Razandi, B.A. Prins, R.M. Hu, E. Biesiada, E.R. Levin, Estrogen and progesterone inhibit vascular smooth muscle proliferation, Endocrinology 138 (8) (1997) 3330–3339.
[54] W.S. Lee, J.A. Harder, M. Yoshizumi, M.E. Lee, E. Haber, Progesterone inhibits arterial smooth muscle cell proliferation, Nature Medicine 3 (9) (1997) 1005–1008.
[55] D.M. Herrington, G.A. Braden, A.K. Williams, T.M. Morgan, Endothelial-dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy, Am. J. Cardiol. 73 (1994) 951–952.
[56] G.M.C. Rosano, P.M. Sarrel, P.A. Poole-Wilson, P. Collins, Beneficial effects of estrogen on exercise-induced myocardial ischaemia in women with coronary artery disease, Lancet 342 (1993) 133–136.
[57] P. Collins, G.M.C. Rosano, P.M. Sarrel, L. Ulrich, S. Adamopoulos, C.M. Beale, A.G. McNeil, P.A. Poole-Wilson, 17beta-estradiol attenuates acetylcholine induced coronary arterial constriction in women but not men with coronary heart disease, Circulation 92 (1995) 24–30.
[58] A.K. Williams, E.K. Honore, S.A. Washburn, T.B. Clarkson, Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys, J. Am. Coll. Cardiol. 24 (1994) 1757–1761.
[59] K. Miyagawa, J. Rösch, F. Stanczyk, K. Hermsmeyer, Medroxyprogesterone acetate interferes with ovarian steroid protection against coronary vasospasm, Nature Medicine 3 (3) (1997) 324–327.
[60] J.K. Williams, M.R. Adams, Estrogens, progestins and coronary artery reactivity, Nature Medicine 3 (3) (1997) 273–274.
[61] J.K. Williams, R. Delansorne, J. Paris, Estrogens, progestins and coronary artery reactivity in atherosclerotic monkeys, J. Steroid Biochem. Molec. Biol. 65 (16) (1998) 219–224.