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Risks of estrogens and progestogens

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Contrary to widespread irrational belief, estrogen replacement therapy (ERT) bears very little risk and, on the contrary, exerts a protective effect against atherosclerosis and cardiovascular disease. This protection most likely results from one or both of the following mechanisms: (1) a drive of the lipidic metabolism towards a "favorable" profile (decrease of total- and LDL-cholesterol and increase in HDL-cholesterol levels); (2) a favorable prostacycline/thromboxane balance towards vasodilatation and anti-aggregation. This is the case when natural estrogens are used, since synthetic estrogens (namely ethinylestradiol) overstimulate the hepatic production of proteins, such as renin substrate and angiotensinogen, with an increased risk of hypertension, vasoconstriction and platelet aggregation. Conjugated equine estrogens are not truly physiologic for human use and some of their estrogenic components can also predispose to hypertension and accumulate. Non-orally administered natural estrogens have less — almost no — metabolic impact and this could hypothetically result in an impaired protective effect against cardiovascular disease; the presently available estrogen implants are not satisfactory and their use frequently leads to estrogen accumulation. Hypertension and diabetes are no longer considered to be contra-indications to ERT: natural estrogens can even improve hypertension as well as glucose tolerance. Estrogen use, at least by the oral route, slightly increases the incidence of gallstones.

The sole other well-documented risk of unopposed (i.e., without administration of any progestogen) ERT resides in a 2×—3× greater risk of developing a carcinoma of the endometrium, the effect being dose- and duration-dependent. A progestogen challenge test is mandatory before initiating ERT and the addition of a progestogen must be considered in case of long-term ERT. Furthermore, patients having received ERT remain at increased risk for endometrial carcinoma development for many years and thus require careful post-treatment surveillance.

As far as breast cancer is concerned, and despite the clear involvement of exogenous estrogens in its etiology, the bulk of the data offers reassurance that low-dose exogenous estrogens will not dramatically increase its incidence. However, it remains controversial whether or not high doses and long duration could still, however, slightly increase the risk. Therefore, regular breast screening (X-ray) is mandatory and it is recommended to use the lowest estrogen dose possible that can treat menopausal complaints and/or prevent osteoporosis. In this respect, estrogen doses could perhaps still be reduced (to the equivalent of 0.3 mg conjugated equine estrogens), provided additional measures such as calcium supplementation and physical exercise are taken.

Synthetic progestogens can impair carbohydrate metabolism but this is seldom clinically relevant. On the contrary, in relation to their degree of androgenicity and to the dose used, they induce a potentially harmful lipidic profile towards promotion of atherosclerosis and increased risk of arterial vascular disease. When added sequentially or continuously to ERT, androgenic progestogens do counteract the supposedly favorable lipidic profile resulting from ERT and the net result depends on the doses of both steroids, on their route of administration, as well as on the nature of the progestogen. In this respect, it might be recommended to preferentially use progestogens with little or no androgen-

icity, such as micronized progesterone, dydrogesterone and possibly medrogestone; low doses of cyproterone acetate can be considered and the marketing of progestogens of the "third" generation (such as desogestrel, that does not counteract estrogens as far as the lipidic profile is concerned) is awaited. It should be kept in mind that synthetic progestogens could also facilitate the development of hypertension (while natural progesterone has been reported to exhibit hypotensive effects) and hypothetically disturb the prostacyclin/thromboxane balance towards an increased cardiovascular risk. However, the demonstration that addition of a progestogen might partially suppress the cardioprotective effect of ERT awaits epidemiological evidence.

The addition of a progestogen to ERT is thus justified only in non-hysterectomized women. Their solely demonstrated indication is indeed the prevention of the development of endometrial carcinoma. This requires a 10—12-day duration of administration of an adequate progestogen at a sufficient dose each "cycle" or month. Progestogen addition will, unfortunately, induce more or less tolerable side-effects and result in bleeding, that may or may not be accepted by the patient. Continuous combined estro-progestative treatment represents an interesting regimen for 60% of the patients who, fortunately, become and remain amenorrheic, exhibiting an atrophic endometrium.

(Key words: Estrogen replacement therapy, Risk)

Estrogens

One of the major reasons given by doctors or by patients against hormonal replacement therapy is the fear of inducing or aggravating hypertension and thrombosis. Women on high dose oral contraceptives, particularly those who are obese, hypertensive, have varicose veins or who smoke cigarettes, are known to be at increased risk of thromboembolism. It is because of these known risk factors that many medical practitioners have argued and still argue against the use of estrogens for post-menopausal women. The present state-of-the-art knowledge emphasizes, however, that these risks are almost totally restricted to the use of the synthetic estrogens (namely ethinylestradiol) contained in oral contraceptives.

Liver and gall bladder

The liver is intimately involved with the metabolism of sex steroids. As far as estrogens are concerned, they are conjugated within the liver (in preparation for their subsequent excretion by the kidney) but also directly excreted within the bile. Furthermore, estrogens increase the biliary cholesterol concentration, with possible formation of insoluble cholesterol crystals. It is indeed admitted that oral contraceptives, as well as post-menopausal estrogen replacement therapy, are associated with an increased risk of gallstones. In a case-control study, Kakar et al. [1] found that the risk of gallstone disease having required surgery was very small: 1.18 (95% confidence limits 0.65—2.13). In a prospective cohort study, Petitti et al. [2] found, on the contrary, a relative risk of 2.1 (confidence limits: 1.5—3.0) of cholecystectomy in women having ever used estrogen; the relative risk for past users decreased to 1.1, while that for current users increased to 3.9. This confirms, as previously consistently observed, that women receiving supplemental estrogen, are indeed at higher risk for gallbladder disease, at least when estrogen is given by the oral route.

Liver function

Recent studies [3,4] confirm the overall admitted lack of liver damage of orally administered "natural" estrogens (estradiol valerate or conjugated estrogens) regimens used in the postmenopause. Some of these regimens included sequential administration of noresthisterone (0.75 to 1.5 mg/day) or cyclical administration of norgestrel (0.15 to 0.5 mg/day). Both studies showed, as previously reported, decreased albumin levels. They also point out that some other changes (e.g., in liver enzymes) that do occur initially disappear after 12 months, suggesting a gradual adaptation to the hormonal stimulus and explaining some conflicting reports from cross-sectional studies.

"Estrogen-inducible" proteins

When given by the oral route, estrogens induce the overproduction of many proteins such as : sex-hormone binding globulin (with a subsequent effect on the bioavailability of estrogen itself in the circulation), cortisol-binding globulin, transferrin, thyroxine-binding globulin, ceruloplasmin and pregnancy-zone protein. This is especially the case for the synthetic ethinylestradiol, found to be already quite active in increasing these syntheses at a daily dose of 5 μg [5]. Although this effect had been attributed to a so-called "first-pass" effect through the liver, it has been demonstrated that, in the case of ethinylestradiol, its hepatic impact was quite similar when given by the vaginal route [6].

In this respect, the liver appeared to be less sensitive to equine conjugated estrogens, which are required in daily doses of at least 0.15—0.625 mg (depending of which protein was considered as the end point) to significantly increase the circulating levels of these estrogen-inducible proteins [7].

Conjugated equine estrogens were clearly found to be still more potent than piperazine estrone sulfate as well as micronized estradiol [8] and this can be attributed to the presence, in the former preparation, of more potent estrogens of equine origin (such as equilin). Truly natural estrogens were thus found to exhibit no major effect on the induction of globulins, although estradiol valerate exhibits still some stimulatory effect on the levels of sex-hormone binding globulin, the most sensitive marker for this estrogenic effect [9].

Coagulation

Most of the proteins essential for the normal blood clotting process, as well as most of the elements of the fibrinolytic system, are synthesized in the liver and are also "estrogen-inducible". This is clearly the case with the synthetic ethinylestradiol used in almost all oral contraceptives, even if its induction of an overproduction of clotting factors becomes clinically harmful in only a very limited number of cases (now that the daily doses have been reduced to and below 50 μg), when some precipitating factor initiates either the intrinsic or the extrinsic clotting system. This is so probably since estrogens also activate the fibrinolytic system [10].

Conjugated equine estrogens can also, to a minor extent however, increase clotting factors [11] but there is no epidemiologic evidence that they increased the risk of idiopathic venous thromboembolism in women aged 45—69 years [12].

As far as the true natural estrogens are concerned, estrone sulfate and estradiol (valerate) have been reported not to have any adverse effect on clotting factors [13,14] nor on antithrombin III [15], whose decrease is induced by synthetic estrogens and has been ascribed to an increased risk of thromboembolism. In the latter studies, estrogens were in some groups associated to cyclical administration of progestogens (norethisterone, norgestrel or dydrogesterone). The absence of any deleterious effect on coagulation from replacement with natural estrogens (plus progestogens) has also been confirmed by Notelovitz et al. [16]. It is perhaps worth mentioning here that surgical and natural menopause are associated with a shift towards fibrinolysis, as shown by significant elevations in antithrombin III, α_2 antitrypsin and plasminogen activity [17].

Blood pressure and hypertension

Oral estrogens have been shown to increase plasma renin substrate concentration, plasma renin activity and excretion of aldosterone [18—20]. An increased renin substrate does not automatically, however, mean a clinical increase in blood pressure, although it might increase the risk of developing hypertension. This is probably the case in some women taking oral contraceptives, whose use has been known for many years to bear a risk of inducing hypertension. It is similarly known since 1971 [19] that some post-menopausal women develop severe hypertension from the administration of conjugated equine estrogens: it was found to be the result of a derangement of their renin-angiotensin system and it reversed after therapy withdrawal.

The group of Judd has reported a stepwise increase in circulating levels of renin substrate after oral estrogens and found that as little as 0.3 mg of conjugated equine estrogens [7] or 5 μg of ethinylestradiol [5] were active on this hepatic synthesis. This is apparently relatively specific for these two kinds of estrogens:

— the synthetic ethinylestradiol, very potent and almost not metabolized, which exhibits enhanced hepatic effects;
— the equine conjugated estrogens derived from pregnant mare urine, comprise not only estrogens that are natural for the woman but also equine estrogens (equilin, equilenin and others) that are not physiologic for the woman; their overstimulatory effect on the liver is probably due to the presence of equilin (sulfate), found to potently increase angiotensinogen [21] and reported to exhibit a prolonged presence in the blood [22]. Serum angiotensinogen was indeed 3.5—5 times more influenced by conjugated equine estrogens than by respectively, piperazine estrone sulfate or micronized estradiol [8].

As reviewed recently by Wren [23], the incidence of hypertension among post-

menopausal women using "natural" estrogens is only slightly increased, while there even occurred a fall in blood pressure in some [24]. Lobo [25] considers that hypertension induced by natural estrogens (mostly with conjugated equine estrogens), that affects only 5—7% of treated post-menopausal women, is an unexplained idiosyncratic blood reaction; this reaction is, however, hypothetically explained by Wren [23] as resulting from an imbalance of prostacycline to thromboxane at the level of the vessel wall, leading to an increased peripheral vascular resistance.

Except in these women, natural estrogen replacement therapy has been actually shown to even lower blood pressure. This has been quite clearly shown by Luotola [26] in a crossover study versus placebo, in which 2 mg and 4 mg estradiol lowered blood pressure in normotensive and even in hypertensive subjects.

Non-oral estrogens and liver proteins

In contradistinction with the marked effect of ethinylestradiol given intravaginally on the induction of liver proteins, daily intravaginal administration of 250 μg micronized estradiol resulted only in a very slight (10%) but significant increase in sex-hormone binding globulin levels after 14 days [27].

During the first 6 months after subdermal implantation of a 25 mg estradiol pellet, inserted immediately after hysterectomy and oophorectomy, Lobo et al. [28] failed to observe any change in the levels of sex-hormone binding globulin.

More recently, estradiol has been administered percutaneously, either as a gel applied daily on the skin or as a TTS (transdermal therapeutic system) applied constantly upon the skin. Several authors reported that such administration of estrogens, at least at the doses used, failed usually to elicit any of the previously described stimulatory effects upon hepatic synthesis of proteins, including sex-hormone binding globulin and renin substrate [29—31]. In two studies [32,33], the levels of renin substrate and of sex-hormone binding globulin were even lower in patients treated through TTS than in the groups of those orally treated with 2 mg of either estradiol valerate or micronized estradiol; in the latter patients, these authors reported also decreased activity and/or levels of antithrombin III, that were unchanged in the TTS groups.

Vessel walls

Several lines of evidence indicate that estrogen exerts direct physiologic effects on vessel walls, inducing an increase in blood flow. As reviewed by Wren [23], all estrogens apparently increase the local production of prostacycline, resulting in vasodilatation and prevention of platelet aggregation, in opposition to the effects of thromboxane produced by the platelets. Then, depending on their various abilities to induce the hepatic synthesis of renin substrate and angiotensinogen (leading to the activation of platelet thromboxane), the various estrogens will differently influence the local prostacycline/thromboxane balance:

(1) synthetic estrogens will activate both prostaglandins and might thus in cer-

tain circumstances lead to vasospasm and platelet aggregation, with resulting clinically significant pathological events;

(2) since conjugated equine estrogens can also to some extent exhibit the same stimulatory hepatic effects, their use might also, but more exceptionally,

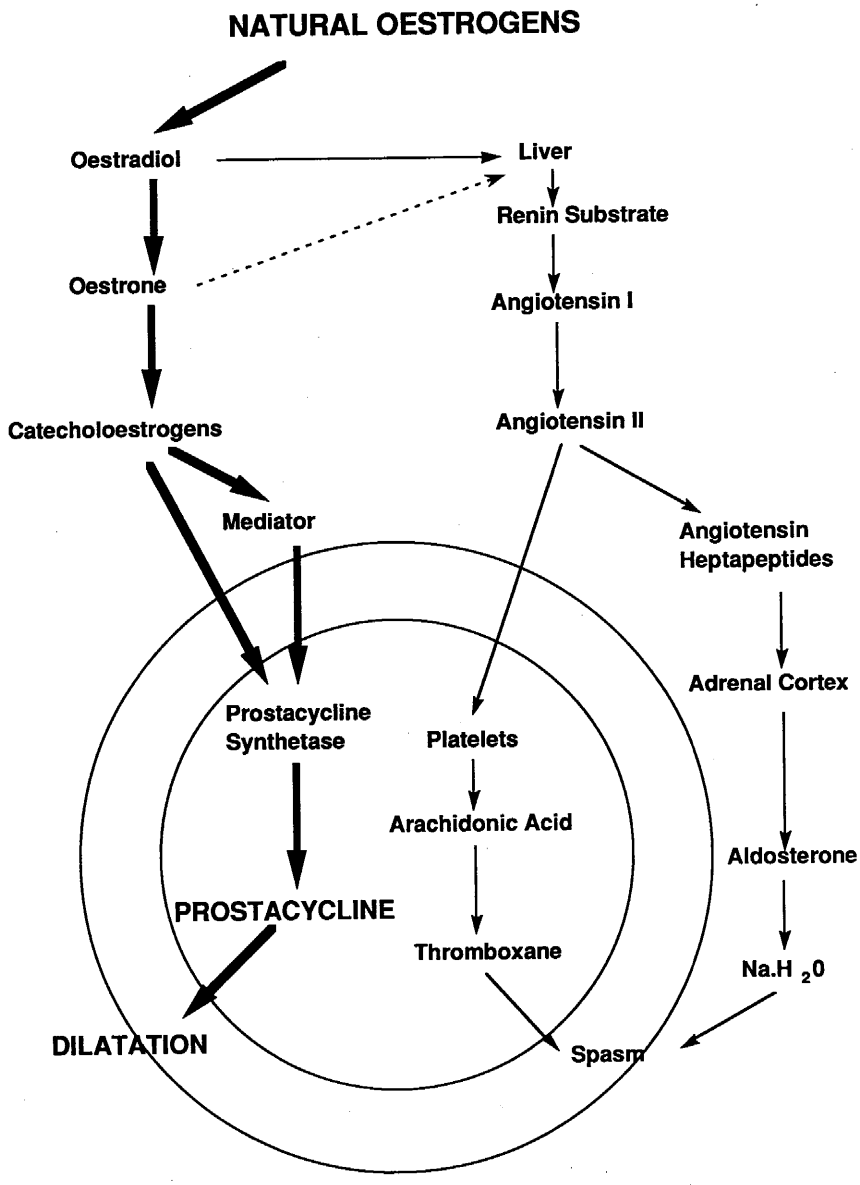

Fig. 1. Pathways describing how estrogens can influence the vessel wall prostacycline/thromboxane balance; natural estrogens that do not induce the overproduction of hepatic proteins (such as renin substrate) would lead preferentially to vasodilatation. Adapted, with permission from Wren [23].

lead to clinically relevant events, such as hypertension (thus viewed as the result of vasospasm, itself inducing increased peripheral vascular resistance);

(3) on the other hand, natural estrogens (Fig. 1) will only favor the pathway leading to vasodilatation and anti-aggregation as a result of increased local production of prostacyclin. At the present time, this mechanism is ascribed as being one of those likely involved in the cardioprotective effect of natural estrogens and even of ethinylestradiol [24].

Carbohydrate metabolism

Experience derived with oral contraceptives could lead to the conclusion that hormonal replacement therapy leads to deterioration of the carbohydrate tolerance; it has, however, been shown that it is the progestogen and not the estrogen that is responsible. Impaired glucose tolerance does not occur from hormone replacement therapy with conjugated equine estrogens or estradiol valerate [34,35] and it has even been recently suggested that use of estrogen alone may actually improve glucose tolerance by enhancement of insulin receptor binding [36]. Luotola et al. [37] have indeed reported even an improved glucose tolerance, in patients previously exhibiting an impairment of this tolerance, after 6 months of replacement therapy with 1—2 mg 17β-estradiol and despite the fact that it was cyclically associated to 1 mg norethisterone acetate.

Lipids and lipoproteins

Another hepatic effect of estrogens concerns lipoproteins and lipids. As far as triglycerides are concerned, it has been conclusively and repeatedly reported that the synthetic estrogens (particularly ethinylestradiol) increased their levels, even at the low daily dose of 10 μg [38]. On the contrary, conjugated equine estrogens, with the exception of a sporadic report [39] and natural estrogens were found to have little effect on triglycerides or even decrease their levels, as well as those of total cholesterol [40]: this effect is so clear that estradiol valerate has been proposed as a treatment for hypercholesterolemia and type-II (increased LDL) hyperlipoproteinemia, in which the estrogen-induced decrease in low-density lipoprotein-cholesterol (LDL-C) is directly related to its initial level [41,42].

It is also clear from the numerous studies published, as reviewed extensively in the last years by several authors [43,44] that all orally administered estrogens lead to increased high density lipoprotein-cholesterol (HDL-C) together with decreased LDL-cholesterol levels. The effects of 10 μg of ethinylestradiol upon the lipoproteins were 1.5—2.5 times greater than those of 2 mg estradiol valerate [9] and they are attributable to this synthetic steroid itself rather than to the first pass effect through the liver, since they similar after the intravaginal administration of ethinylestradiol [6]. In a study by Enk et al. [45] in castrated women treated with 2 or 4 mg estradiol valerate, a good positive correlation between the serum levels of total cholesterol, free cholesterol and phospholipids in the HDL fraction and the serum levels of apolipoprotein A_1 was found.

It was generally considered that natural estrogens, when given non-orally, fail to induce any significant change in lipids and lipoproteins. It had, however, been reported by Basdevant and Guy-Grand [46] that, in hypercholesterolemic and/or hypertriglyceridemic menopausal women, the percutaneous administration of estradiol (in a gel containing 1.5 mg per 24 h), significantly reduced within 4 weeks the levels of both cholesterol and triglycerides. More recently, it has been similarly reported that significant increase in HDL-C and decrease in total cholesterol and LDL-C occurred 12 weeks after subdermal insertion of 50 mg estradiol pellets, as well as at 24 weeks of use of the 0.1 mg estradiol TTS patch twice weekly [47].

Lipids and cardioprotection by estrogens

As emphasized by Lobo [25], LDL-C and intermediate-density lipoprotein-cholesterol are considered to be the major deleterious moieties, contributing, at the level of the vessel wall, to atherogenesis through a complex series of events. On the other hand, HDL-C, that plays a major role in the "reverse" cholesterol transport (back to the liver for degradation), has been widely and universally considered in the last decade as a protective element, as reviewed by Castelli [48].

The impact, on the incidence of myocardial infarction, of decreasing total cholesterol (for every 1% decrease, there is a 2% decrease in risk) or LDL-cholesterol (for every 11% decrease, there is a 19% decrease in risk), is well established [49,50]. On the contrary, it is undemonstrated, at least in women, that raising the HDL-C concentrations pharmacologically will reduce the risk of coronary heart disease. From a recent prospective study in men, Pocock et al. [51] confirmed, however, that after adjustment for total cholesterol and other risk factors, men in the highest fifth of HDL-C had 2 times less risk than men in the lowest fifth; triglycerides had no predictive importance once other risk factors had been taken into account. Within HDL-C, it is the HDL_2 fraction that has been most consistently linked with protection from cardiovascular disease [52]. In men and women in the seventh decade of life, these levels are inversely correlated with truncal fat, plasma insulin levels and the presence of glucose intolerance: Ostlund et al. [53] concluded that HDL_2 levels are thus not independently associated with sex or total body fat.

Epidemiologic evidence from the Framingham study [54] clearly showed a marked increase in the incidence of cardiovascular disease after menopause. Colditz et al. [55] more recently confirmed the previous reports that it is mostly surgical menopause that is associated with an increased risk, while there was no appreciably increased risk within the first several years after natural menopause.

There occurs some changes in lipids during the menopause: no major change in HDL-C (but a slight decline) and an overall marked increase in both total-and LDL-cholesterol, thus an apparently unfavorable effect on lipid metabolism [56]. From a study of X-rays for calcified deposits in the abdominal aorta, Witteman et al. [57] concluded that, after adjustment for age and other risk factors, women with a natural menopause had a 3.4 times (5.5 times for women who had bilat-

eral oophorectomy) greater risk of atherosclerosis than premenopausal women. The hypothesis is that these changes in lipids that occur during and after menopause might be related to the loss of the apparent protection from cardiovascular disease, of pre-menopausal women (as compared to men). There is presently some doubt, however, that the apparently protective action of endogenous estrogen before menopause is mediated by the plasma lipoprotein system. Nevertheless, it is presently well admitted that post-menopausal estrogen use reduces the incidence of and the mortality from coronary heart disease by 40—70%, as reviewed by Sitruk-Ware and Ibarra de Palacios in 1989 [58]: Table I lists the results of the cohort studies published between 1983 and 1989. With the exception of a single study [59] that has been much criticized [60], all these studies point to a definite protective effect of estrogen upon cardiovascular disease. It should, however, be noted that earlier studies showed either no or even an increased risk and that this clear difference has been attributed to changes in prescribing habits in the early 1980s (with a reduction of the estrogen doses and exclusion of patients with risk factors).

Moreover, when the occlusion of the coronary arteries was studied by selective coronography, three groups [61—63] reported significantly reduced relative risks of 0.37, 0.44 and 0.5 for post-menopausal estrogen users. It now appears well established that post-menopausal use of oral estrogens (without added progestogens) exerts a protective role on cardiovascular disease, but it has not been dem-

TABLE I

COHORT STUDIES (1983—1989) ON THE RELATIONSHIP BETWEEN POST-MENOPAUSAL ESTROGEN REPLACEMENT THERAPY AND CARDIOVASCULAR (CV) RISK (ADAPTED WITH PERMISSION FROM SITRUK-WARE AND IBARRA DE PALACIOS [58])

Authors	Impact studied	RR of users
Wilson et al. [59]	Coronary heart disease	1.9*
	Stroke	2.3*
	Death from CV disease	1.9
Bush et al. [64]	Death (excluding cancer)	0.4*
Stampfer et al. [65]	MI and death from CHD	0.5*
Henderson et al. [66]	Death from MI	0.5*
Petiti et al. [67]	Death from MI	0.3*
Colditz et al. [55]	Coronary heart disease after:	
	natural menopause	0.8*
	oophorectomy	0.7*
Bush et al. [68]	Death from CV disease	0.37*
Paganini-Hill et al. [69]	Death from stroke	0.53*
Criqui et al. [70]	Death from CV disease	0.81
Henderson et al. [71]	Death from MI	0.59*
Beard et al. [72]	Coronary heart disease	0.6*
Hunt et al. [73]	Death from CHD	0.5*

CHD: coronary heart disease; MI: myocardial infarction; RR: relative risk.
*Statistical significance at $P < 0.05$.

onstrated that this protective effect is mediated by changes in lipids (although this mechanism is widely assumed); other mechanisms (such as locally on the prostacycline/thromboxane balance) could contribute or be responsible.

Estrogens and breast cancer

As reviewed by Miller and Anderson [74], there is considerable epidemiological evidence for the involvement of endogenous estrogens in the etiology of breast cancer, such as: the increased risk with a prolonged reproductive life (early menarche, late menopause) and with overweight (possibly because of increased peripheral production of estrogens by the adipose tissue); the protection associated with early or surgical menopause. Insofar the role of endogenous estrogens in carcinogenesis is viewed to be likely promotional, by expanding the pool of cells either susceptible to or already partially transformed by carcinogens, or by stimulating the growth of malignant cells, with a progression from occult disease to clinically-apparent tumors.

In contradistinction to this obvious role of endogenous estrogens in breast carcinogenesis, evidence whether exogeneously administered estrogens might increase the risk of breast cancer has been surprisingly difficult to obtain and this expected association has not yet been conclusively demonstrated, despite more than 7 cohort and 19 case-control studies on this topic. As reviewed by Pejovic-Lenfant [75]:

— only 8 of these studies reported a significantly increased relative risk (between 1.3 and 3.4);
— in 2 studies, the use of synthetic estrogens (diethylstilbestrol or ethinylestradiol) was shown to increase the risk;
— 3 out of the 10 studies that have investigated the influence of the estrogen dose, have shown a significantly increased risk for daily doses higher than 1.25 mg (or implants and depot formulations);
— 2 out of the 17 studies that have looked after an effect of the duration of estrogen use, reported relative risks enhanced to 2.7 to 3.0 after 10—15 years of treatment.

Based on 23 studies that provided adequate data, Armstrong [76] performed a meta-analysis, whose results are summarized in Table II. These results are unequivocal, that ever use of estrogen does not alter the risk of breast cancer by any measurable amount. However, this analysis also provided weak positive results from the two following subsets of data:

(1) patients treated with high doses of exogenous estrogens;
(2) women with a family history of breast cancer.

In this respect, it should be considered to avoid estrogens implants that are renewed much too early (at the recurrence of vasomotor instability), leading to estrogen accumulation over time [77,78].

TABLE II

SUMMARY RELATIVE RISKS OF BREAST CANCER IN RELATION TO ESTROGEN USE, AS DERIVED FROM A META-ANALYSIS (ADAPTED WITH PERMISSION FROM ARMSTRONG [76])

Type of study (no. of studies)	Relative risk (95% confidence limits)
All studies (23)	1.01 (0.95—1.08)
with adjustment[a] (12)	1.05 (0.97—1.14)
Studies of postmenopausal women (12)	0.96 (0.89—1.05)
with adjustment[a] (7)	0.99 (0.90—1.08)
Highest dose category in each study	1.28 (1.06—1.54)
Women with a family history	1.25 (0.83—1.88)

[a]Adjustment for type (natural or surgical) of menopause, age at menopause or both.

The bulk of the presently available data offers thus reassurance that the prescription of low-dose estrogens as replacement therapy will not dramatically increase the incidence of breast cancer. Caution is still mandatory and treated women must, at least for medico-legal protection, be submitted to the screening programs that are now widely recommended in any woman. This is especially true since long-term treatment (for example up to 75 years of age at least, as proposed by Lufkin et al. [79]) could still bear some increased risk [80,81]. Thus, Bergkvist et al. [82], in a cohort study of long-term perimenopausal treatment, found an overall relative risk of 1.1, which was significantly increased to 1.7 (95% confidence limits: 1.1—2.7) after 9 years of estrogen treatment. The latter study has been, however, the subject of many criticisms [83,84]; other studies [85,86] failed to demonstrate any appreciable increase in the risk of breast cancer with treatment duration or latency, even of 20 years or longer. Nevertheless, the issue of a possible slight effect of long-term estrogen use on the incidence of breast cancer warrants further evaluations.

Benign breast disease, at least when epithelial proliferation is present (but this is usually not known in the absence of a biopsy), has been considered as a risk factor for the development of breast cancer; some consider it even as a contraindication to estrogen replacement therapy. This concept should perhaps be revised at the light of a report by Dupont et al. [87], who followed, for up to 17 years, 84% of the patients from more than 10 000 consecutive breast biopsy specimens of benign lesions. Exogenous estrogens were found to lower significantly the observed breast cancer risk (relative risk of 0.98, instead of 1.8 for nonusers), mostly in patients with proliferative disease without atypia (relative risk of 0.92 versus 1.9). It should be noted that this protective effect was restricted to patients who took estrogens after their entry biopsy, while patients biopsied when they were taking estrogens, were at increased risk: the latter result was considered by the authors as due to a cohort effect, presumably due to a dose effect (since women who took estrogens before 1956 were at 2.3 times the risk of other estrogen users).

That relatively low (thus comparable to physiology) doses of exogenous estro-

gens given as replacement therapy, apparently do not run a major risk of inducing breast cancer seems to us quite logical at the light of recent results of fundamental research, suggesting paracrine and autocrine feedback loops within the breast, in which the tumoral growth would be regulated by estrogen produced locally in the surrounding adipose tissue, production itself regulated by growth factors produced by the tumor in response to estrogens produced also locally by the tumorous cells:

- tissue levels of estradiol are higher in malignant than in normal or benign breast tissues and no change was observed with menopausal status [88];
- mammary tissue levels of estrogens are higher than in the plasma; this can partly be the result of local production of estradiol through the activities of aromatase (transforming androgens to estrogens), estrogen sulfatase and hydroxysteroid dehydrogenase [89,90];
- as Lippman and Dickson [91] reviewed the work of their research group, mammary cancer cells produce a number of growth factors (GH) (such as transforming GF_α, epidermal GF, insulin-like GF) that appear to regulate, in an autocrine loop, their own growth;
- the aromatase activity of human adipose cells is regulated by the same growth factors [92];
- aromatisation (and thus biosynthesis of estrogen) in breast fat is significantly higher in patients with breast cancer than with benign disease; furthermore, within the breasts of women with cancer, this biosynthesis is enhanced in the quadrants bearing the tumor [93].

It is thus quite conceivable that local production of estradiol is much more important than addition of exogenously administered estrogens, at least at low, replacement, dosages. In this respect, one should consider to even more reduce the daily dose of estrogens (for example at the equivalent of 0.3 mg of conjugated equine estrogens) in the long-term treatment for osteoporosis prevention: as shown by Ettinger et al. [94], this might be quite effective, provided additional measures are taken, such as calcium supplementation and perhaps exercise.

Unopposed estrogens increase the risk of endometrial carcinoma

In a WHO Scientific Report [95], 17 out of 22 studies published since 1975 were considered to support a strong association between endometrial cancer and estrogen replacement therapy. These case-control (retrospective) studies reported relative risks of between 5 and 15, that were dependent on both the dose and the duration of estrogen use. Many of these papers had been criticized in one way or another but a causal relationship between estrogen use and increased risk of endometrial carcinoma is presently widely accepted. Since this subject has been many times reviewed extensively (such as for example in 75, 96—98), we will focus our attention only on some specific, prominent or new points.

Although most studies reported a latency of about 2 years, Cramer and Knapp

[96] emphasized a very brief period (6 months) of estrogen exposure in some studies, more consistent with the detection of a previously undetected ("occult") carcinoma, which became symptomatic (= bleeding) due to the hormonal administration. Horwitz and Feinstein [99] had indeed shown that detection bias (arising from the increased diagnostic attention received by women with uterine bleeding during estrogen exposure) could lead to a great overestimation of the risk: when alternatively utilizing a set of cases and controls consisting of patients having all received dilatation and curettage or hysterectomy because of uterine bleeding, the odds ratio fell indeed from 11.98 to 1.7. As pointed out by Ettinger et al. [100], this method can, however, also introduce another bia and lead to an artificially reduced risk of estrogen-associated endometrial carcinoma: estrogen use might indeed be more prevalent in bleeding women without cancer than in the general population, since estrogen can also lead to bleeding, for example from other, non-cancerous, organic pathologies. The latter authors confirmed a greater prevalence of endometrial carcinoma (9.9% versus 1.4%) and reported higher incidences of abnormal vaginal bleeding, curettage and hysterectomy (ratios of 7.8, 4.9 and 6.6, respectively) in unopposed estrogen users than in non-users; the prevalence of hysterectomy reached 28.2% of users, compared with 5.3% in non-users. They reported, in women evaluated for post-menopausal bleeding, a relatively weak (relative risk : 1.4) association between estrogen use and endometrial carcinoma. Their data also do not support the widely admitted notion of a better pronostic for endometrial carcinoma in a woman taking estrogens.

Recent studies particularly highlighted that the increased risk for endometrial carcinoma development remained so for 6—10 and perhaps up to 14 years after discontinuing therapy [101—103], emphasizing the requirement for post-treatment surveillance and thus not only before and during estrogen administration.

It seems worth to mention that Rubin et al. [103] reported, in their women up to 55 years, that prior use of oral contraceptives for more than 1 year, may reduce the risk of endometrial cancer associated with estrogen replacement therapy and that this effect apparently persists for more than 15 years after last oral contraceptive use.

The most recent studies seem to confirm that the risk had been initially somewhat overestimated, although this can also be the result of a change in prescription habits towards lower doses of estrogens. Rubin et al. [103], in their population-based case-control study, reported thus only a 2—3-fold increase in the risk. At present, we are aware of only a single cohort follow-up study, published by Persson et al. [104]: they reported an overall 1.8 (95% confidence limits : 1.1 to 3.2) relative risk of endometrial carcinoma after exposure to any unopposed estrogen for more than 6 years; the relative risks were 2.2 for more than 3 years exposure to conjugated estrogens and 2.7 if estradiol was used.

Ovarian epithelial cancer

It had been thought that the occurrence and/or the progression of epithelial

ovarian cancer might be partially related to the elevated gonadotropins, hence the hypothesis that hormonal replacement therapy might be protective. A 40% decreased risk was indeed reported by Hartge et al. [105] but could not be confirmed more recently by Kaufman et al. [106]. The latter authors found even elevated relative risks for some categories of use, especially nulliparous women. Nevertheless, they concluded that their data do not support the hypothesis that estrogens use would increase the risk of epithelial ovarian cancer (and especially not of endometrioid ovarian cancer).

Estriol

Estriol (E_3) has long been considered as a so-called "impeded" or "weak" or "short-acting" estrogen, because of the discrepancy between its nice estrogenic effect on the human vaginal epithelium and its minimal estrogenic effect upon proliferation of the endometrium, although it can be used with some, mitigated, effect for the relief of vasomotor complaints [107]. Estriol does bind to the specific estrogen receptors (ER) and induces all early (0—3 hrs) uterotrophic responses but fails to simulate true uterine growth, unless repetitively administered, what allows then probably a sufficiently long retention of the ER—E_3 complex within the nucleus [108]. Given usually in low and undivided daily doses, estriol appeared to be quite inert in stimulating the hepatic "estrogen-inducible" proteins [109], plasma renin activity [110], coagulation factors [111,112], as well as in modifying total cholesterol, HDL-cholesterol and triglycerides [111].

As far as the endometrium is concerned, there occurred almost never hyperplasia and curettage for bleeding (in 0.6—4%) revealed usually an atrophic endometrium [113,114]. Although E_3 is quite capable to stimulate in vitro DNA synthesis in normal human mammary epithelial cells [115], Bergkvist et al. [82], in their prospective study, found no increased risk of breast cancer after classical use of estriol. Unfortunately, this estrogen, that is quite useful in some clinical circumstances, has been found by Lindsay et al. [116] to be unable to satisfactorily prevent bone loss, although patients receiving 12 mg daily (given in divided doses for up to 2 years) exhibited significantly less (1.9%/year, instead of 3.6%/year) bone loss and significantly reduced urinary excretions of calcium and hydroxyproline.

High doses of estriol, especially when given in divided daily doses, can indeed exert more classic estrogenic effects, including endometrial stimulation and even hyperplasia [117], as well as increased HDL-cholesterol levels [118].

It should be mentioned that, after its vaginal administration, the proportion of unconjugated E_3 (the only biologically active) in serum is much greater than after oral administration: 0.5—1.0 mg E_3 intravaginally can thus roughly be estimated equivalent to 8—12 mg E_3 orally [119—121]. There is thus a theoretical possibility that daily intravaginal E_3 administration might result in more classical estrogenic effects, although only a minimal endometrial response (mid-proliferative in 2 cases) was reported after 3 months of such administration of 0.5 mg E_3 pessaries [122].

Progestogens

Progestogens alone can be used as a challenge test after the menopause in order to detect gynecological pathologies, mainly of the endometrium [123] and this should thus be recommended as a mandatory test before initiating post-menopausal hormonal replacement therapy [124].

Except when estrogens were considered to be contra-indicated and/or progestogens prescribed for treatment of breast or endometrium carcinoma, progestogens alone have been only seldom used as hormonal replacement therapy. In these cases, progestogens of the "old" generations and at relatively high or very high doses were utilized. As far as climacteric syndromes are concerned, a daily dose of 80 mg megestrol acetate was required for almost complete abolishment of hot flushes [125]; oral 2 × 100 mg/day of medroxyprogesterone acetate improved significantly better hot flushes and sweating than placebo [126]; norethisterone 5 mg daily was much less effective than 15 μg ethinylestradiol [127].

There are scarce data indicating that such high doses of some progestogens do also protect against bone loss: this effect was reported by Dequeker et al. [128] in women uninterruptedly treated for 3 to 13 years with 5 mg daily of lynestrenol, as well as by Abdalla et al. [129] over two years of continuous administration of 2 × 5 mg daily of norethisterone.

Such high doses of these progestogens should, however, probably be avoided because of the epidemiological evidence that they may be predisposing to an increased risk of cerebrovascular accident [130]. A significantly increased incidence of arterial disease has been indeed recently reported by Huovinen et al. [131], at autopsy of mentally retarded women, in 86 who had been treated continuously for an average of 81 months with lynestrenol (at daily doses varying from 2.5 to 15 mg), as compared to a group of 84 non-treated patients.

The hazards of vascular arterial disease under progestogens have been attributed to the ability of the "androgenic" progestogens (mostly those derived of 19-nortestosterone, such as norgestrel and norethisterone) to modify lipid metabolism: no change, or perhaps a slow increase with time, of LDL-cholesterol [132] but a significant reduction in HDL-cholesterol, mostly due to a reduction in the HDL_2 subfraction [133]; the concomitant decrease of triglycerides from 19-nortestosterone derivatives [132] can only be, on the other hand, slightly beneficial.

This enhanced plasma hepatic lipase activity, leading to lowered HDL-C and HDL_2-C levels under treatment with "androgenic" progestogens, does apparently not occur with the C-21 progestogens derived from 17-hydroxyprogesterone, such as medroxyprogesterone acetate (MPA) and cyproterone acetate, as reviewed by Tikkanen et al. [134].

The effect of depo-MPA (150 mg intramuscularly every three months) appears, however, somewhat controversial: Barnes et al. [135] found no change in HDL-C, while Deslypere et al. [136] reported lower HDL-C; the latter was confirmed, under daily oral 100 mg MPA treatment, by Lehtonen et al. [137].

In the postmenopause, desogestrel, despite its structural relation to norgestrel, was found to be devoid of any androgenic-like activity, inducing by itself no change in HDL-C and HDL_2-C, although still reducing triglycerides at the daily dose of 125 μg [138].

Progestogens and blood pressure

Progesterone can counteract the vasodilating effect of estradiol [139] and thus lead to increased blood pressure but, on the other hand, it is also able to compete with aldosterone to increase natriuresis, thus inducing a decrease in blood pressure [140]. Practically, oral micronized progesterone has been conclusively found, in a double-blind, placebo-controlled crossover study performed in hypertensive men and in hypertensive post-menopausal women, to significantly decrease blood pressure in a dose-dependent manner [141].

An anti-aldosterone effect has not been found for any other synthetic progestogen, except gestodene which has been recently introduced in oral contraception. On the contrary, as reviewed by Carr [142], there are scarce data in oral contraceptive users, that significant increases in blood pressure do occur with increasing doses of levonorgestrel or of norethindrone acetate, combined to the same dose of ethinylestradiol.

Carbohydrate metabolism

Menopausal women are at higher risk for altered carbohydrate metabolism, with age-related increased glucose intolerance and insulin resistance, thus increasing their cardiovascular risk. From the data obtained from oral contraceptive use, it is now agreed that it is the progestogen component which is mainly responsible for the impaired glucose tolerance under oral contraceptives. As discussed by Gaspard [143], all progestogens alter glucose tolerance and insulin effectiveness in this increasing order: progesterone, dydrogesterone [144], 17-acetoxyprogesterone derivatives and 19-nortestosterone derivatives; use of low dosages of all progestins minimizes their impact on carbohydrate metabolism so that it can become clinically almost not relevant. Diabetic subjects receiving oral diabetic treatment, experienced thus no deterioration of their glucose tolerance within 6 months of a cyclic substitution therapy with 17β-estradiol (1—2 mg daily) and norethisterone acetate (1 mg daily for 7 days per cycle) [37].

Coagulation

As stated by Notelovitz [145], there is almost no data about the effect of progestins on the coagulation system and most information can only be deducted by oral contraceptive data, suggesting little effect of progestins.

Estrogens and progestogens

Prevention of endometrial carcinoma

As periodically reviewed [98,146,147], the administration of progestogens can

prevent the occurrence of endometrial hyperplasia (whether cystic, adenomatous or atypical) and the development of endometrial carcinoma, depending on the dose and the type of progestogen and on its duration of administration. There is presently a consensus [148] that only those patients with their uterus intact, require to be given progestogens, in addition to their estrogen replacement therapy.

The daily doses supposedly required for proper secretory transformation of the previously estrogenized post-menopausal endometrium have been defined according to biochemical and histological criteria: 150 μg *dl*-norgestrel or 1 mg norethindrone [149], 300 mg micronized progesterone [150], 10 mg dydrogesterone [151]; at the daily dose of 10 mg, medroxyprogesterone acetate was considered by Lane et al. [152] to produce a suboptimal response, while Gibbons et al. [153] reported a satisfactory, homogeneous, secretory pattern. These minimal doses were determined on the basis of a relatively short (6 days) administration and it is thus not impossible that they could perhaps be somewhat reduced when a longer duration is applied. There appears now to be an international consensus [154] that the duration of progestin administration is an important factor for endometrial safety and that increasing its administration beyond 7—10 days of use has further beneficial suppressive effect on the endometrium. However, there are also data indicating that a 12-day progestogen course every 4—6 cycles will likely eliminate also any hyperplasia that might have developed [155]: this regimen should thus be considered attractive and carefully evaluated.

More recently, in an attempt to find out which is the minimal daily dose of progestin to be administered for 12 days (in addition to conjugated equine estrogens), Fraser et al. [156] reported a wide inter-patient variation in response: none of the 9 progestogen dose regimens (0.1 mg norethisterone acetate; 0.35, 0.7, 1.0, 2.5 and 5.0 mg norethisterone; 75, 150 and 300 μg *dl*-norgestrel) succeeded to induce secretory change in every patient. On the other hand, Padwick et al. [157] have observed that patients with proliferative endometrium start to bleed earlier than those with secretory transformation (in the case of sequential therapy). When day 1 is defined as the first day of progestogen addition and day 12 as the last, women with uniform secretory change were found not to start bleeding before day 11. They concluded that the pattern of onset of bleeding can thus be a useful predictor of endometrial status; furthermore, it may then help the clinician to tailor the dose and duration of progestogen administration to every patient, according to the undesired complaints (such as edema, abdominal bloating, weight gain, drowsiness, premenstrual irritability, lower abdominal cramps, breast tenderness, depressive symptoms) she may present from the added progestogen. A consensus was even reached that, "in some women with a uterus who are totally progestogen intolerant, it was deemed reasonable to prescribe estrogen therapy without the addition of progestogen provided that appropriate monitoring is performed and that the patient is made aware that this mode of treatment is a departure from standard practice".

Recent data confirm that sequential progestogen administration protects against estrogen-related endometrial cancer but apparently perhaps not to the extent that was initially thought. In their report of the preliminary results of a

cohort study [73], 8 of the 14 cases of endometrial cancer had received therapy which was predominantly or entirely opposed; only one case, however, had received an opposed regimen that could be admitted as sufficiently protective (12 days per month of an adequate progestogen at adequate daily doses); furthermore, only 2 women had not previously been treated with an unopposed estrogen regimen. In their prospective cohort follow-up study, Persson et al. [104] found an unchanged risk (relative risk: 0.9 with 95% confidence limits at 0.4—2.0) of endometrial carcinoma when progestogens were cyclically added for the entire period of estrogen treatment; there was, however, no reduced risk to below that in an untreated population, as earlier reported [98] and the authors concluded that progestogens either remove or delay the increased risk from the estrogen. Nevertheless, Persson et al. [104] found also an increased risk (2.4) for women who took estradiol for more than three years but received progestogen for only part of this time. However, no details as to dose, type and duration of progestogen administration were available.

Blood pressure

In post-menopausal women, there is evidence that combining synthetic progestogens with "natural" estrogens, does not induce any significant change in blood pressure (142,158), although a chronic increase in catecholamines, as reported by Blum et al. [159], might predispose to future increases in blood pressure. Thus the possibility exists that a small percentage of susceptible women, especially in an older population already prone to hypertension development, will experience increased blood pressure from the administration of synthetic progestins together with estrogens [160].

Coagulation and vascular risk

In menopausal women receiving conjugated equine estrogens for 3 weeks and 10 mg medroxyprogesterone acetate (for 7 days), Notelovitz [145] reported a greater plasminogen activity (thus a marked fibrinolytic effect) than in a previously studied group of castrated women receiving only estrogens [161]. There was no effect on prothrombin and thrombin times nor any evidence of intravascular coagulation.

A matter of potential concern resides, however, in the possible effects of progestogens on the vessel wall balance of thromboxane to prostacycline. Animal experiments show that progesterone itself or norethisterone alone (162,163) would not affect or even increase prostacycline production. On the contrary, based on the serum levels of stable metabolites, Ylikorkala et al. [164] reported an increase in the concentration of the vasoconstrictory thromboxane in climacteric women with vascular instabilities treated with natural estrogens combined cyclically with levonorgestrel (250 μg/day) or norethisterone acetate. Similarly, progesterone, even at low concentration, has been found to abolish the stimulating effect of estradiol on prostacycline formation [165], at least in umbilical vessels.

Thus the possibility exists that progestogens, by counteracting to some extent the estrogenic stimulation of the vasodilatory prostacycline, would also predispose to an increased risk of vascular accidents by this mechanism.

Bleeding under estro-progestogens

Sequential addition of progestogens to the estrogen replacement therapy will usually result in a regular pattern of withdrawal bleeding. Although some view it as a medical benefit that can reduce, if not obviate, the need for endometrial biopsy [147], most women resent it as tiresome when it has to be continued for many years and/or when it means reappearance of menses (should the hormonal replacement therapy be instituted at some time after menopause).

This subject has been thoughtfully studied and the reader can be refered to a review by Fraser [166] on the influence of the progestogen regimen on bleeding patterns. Let us emphasize that irregular, breakthrough bleedings can occur in about 14% of the patients [167]; that the occurrence of regular bleeding depends on the dose of estrogen [168] as well as on that of the progestogen; that the frequency of withdrawal bleeding gradually declines with age, with only 60% of the women at age 65 continuing to bleed regularly; that perimenopausal women clearly are more prone to irregular, even uncontrollable bleeding [169]; that withdrawal bleeding occurs apparently less often when using oral micronized progesterone [170].

Lipidic profile under estro-progestogens

Numerous reports appeared, describing the changes in lipids and lipoproteins that do occur under sequential, cyclic estro-progestogen replacement therapy [43]. As stressed by Whitehead et al. [147], lipid and lipoprotein studies can be hazardous to interprete when care had not been taken of many parameters that can interfere: diet, alcohol intake, season, exercise, caffeine and tobacco; strict overnight fasting; standardization of laboratory measurements. Furthermore, a possible carry-over effect by previous hormonal treatment in at least the last 3 months must be excluded; a sufficiently long (at least 12 months) period of study and an untreated reference group are also required.

As reviewed by Crona et al. [171], the qualitative net result is only partly dependent on the sum of the effects induced by the estrogen and the progestogen, respectively: a third property of the progestogen, namely its "anti-estrogen" effect, will also interfere. Preparations in which the estrogen dominates will produce essentially estrogenic changes (i.e., increased triglycerides and HDL-C), while the use of a strongly androgenic progestogen (such as a 19-nortestosterone derivative) will induce androgenic effects (reduced triglycerides and HDL-C) [172]. In this respect, it is worth to stress that the vaginal route of administration of levonorgestrel did not alter the "androgenic" lipid modifications induced by this progestogen, although one might argue that the estrogenic influence was less than expected, due to the simultaneous administration of estradiol through the vaginal ring pessary [173].

Nevertheless, it seems established that, in order to obtain a "favorable" lipidic profile, one has to restrict the use of progestogens to 17α-hydroxyprogesterone derivatives, dydrogesterone [174], cyproterone acetate [175], micronized progesterone [176] or medrogestone [177], at least when used at the usually recommended, effective and available daily doses. The metabolic impact of the added progestogen is also a matter of dose [178]: the supposedly inert cyproterone acetate, when given daily at 50 mg, will also induce a decrease in HDL-C and apoprotein A_1 [179]; on the other hand, the continuous addition of only 1 mg/day of norethisterone acetate still resulted in a favorable lipidic profile, though less favorable than on estrogen alone therapy but not significantly so [180].

One would look forward to the availability, for post-menopausal use, of the progestogens of the "new", third, generation: gestodene and norgestimate with their (very) low androgenicity, and desogestrel; the latter progestogen is quite remarkable since, despite its higher intrinsic androgenic activity than norethisterone, desogestrel has been found not to counteract the favorable lipid changes induced by estrogen and thus not to inhibit the rise in HDL-C levels [138,181], but it still reduced triglycerides levels.

Estro-progestogens and the breast

Gambrell [182] had reported a lower incidence of breast cancer is his estrogen-progestogen users, incidence that was even significantly lower than that of the untreated group; the validity of this study has been, however, heavily criticized. More recently, the results of one case-control [183] and of one cohort [82] studies, both large and population-based, were compatible (although not statistically significantly) with a possible increase in the risk of breast cancer when progestins had been administered sequentially during long-term estrogen replacement therapy: relative risks were, respectively, 1.36 (95% confidence limits: 0.98—1.87) and 4.4 (95% confidence limits: 0.9—22.4).

These results have to be put together with recent research data on the role of progesterone and progestogens on proliferation of the breast epithelium: as reviewed by Anderson [184], the breast certainly undergoes a response to the menstrual cycle; progesterone is interpreted as a permissive agent in causing breast stimulation and the breast and the endometrium can no longer be equated. This gives also support to the estrogen plus progestogen hypothesis of Pike [185] for development of breast cancer.

Continuous combined estrogen/progestogen treatment

Rather than adding progestogen when the endometrium has been prior estrogenized, it has been proposed to start together the administration of both the estrogen and the progestogen in order to prevent endometrial proliferation. Progestogens have indeed an antimitotic action and suppress DNA as well as estradiol and progesterone receptors synthesis. This regimen is further indefinitely continued with the hope to avoid any bleeding and to keep the endometrium atrophic.

This topic has been very recently reviewed in details by Whitehead et al. [147]. It is clear that these regimens are associated with a very high incidence of irregular bleedings, especially at the start of the therapy; that peri-menopausal women are much more susceptible than post-menopausal women to irregular bleeding; that progestogen doses have to be adapted (= increased) individually to minimize this problem. The high incidence of bleeding (and possibly progestogen-related side effects) finally leads to a high drop-out rate but patients remaining in the study are usually amenorrheic and remain so for very extended periods, with seldom any spotting (in 1.5 to 5% of the cases). When amenorrhea is indeed obtained, endometrium was always found to be atrophic or hypoplastic (as reviewed in 147); it should also be mentioned that, in a study by Staland [186], all patients with endometrial hyperplasia at the onset of therapy, exhibited an atrophic or hypoplastic endometrium at 12 months. Until now, there are no epidemiological data pertaining to the effective prevention for endometrial cancer development from such continuous combined estrogen/progestogen regimens but, to our knowledge, there has not yet been a single report of an endometrial carcinoma arising during such treatment in a patient in whom the pretreatment biopsy was negative.

Most of the studies have used, as progestogen, norethisterone (clearly, at the daily dose of 1 mg, it is the one whose use is associated with the least incidence of bleeding) or medroxyprogesterone acetate. More reliable work need to be done in order to determine the effects of such therapy on lipid and lipoprotein metabolism but it appears generally that it counteracts, to a more or less degree, the supposedly favorable lipidic profile that should result from estrogen administration. In this respect, cyproterone acetate [175] and possibly dydrogesterone [187] would probably represent better choices. Micronized progesterone would be perfect at the light of the report by Hargrove et al. [188]: continuous combined estradiol/progesterone resulted over 1 year in decreased total cholesterol but increased HDL-C levels from baseline. Unfortunately, oral micronized progesterone induces quite often sedative and hypnotic effects [189] that can constitute a benefit (in case of sleeping problems) but also a problem in some women.

Estrogen/progestogen treatment and cardiovascular risk

There are until now no epidemiological data on this subject and one can thus only speculate on the possible effect of added progestogens on the cardioprotective effect of estrogens, in favor of the firm existence of which there is now an international consensus [154]. Such speculations have been done by Henderson et al. [190], on the basis of the combination of a relatively low dose of estrogens (equivalent to 0.625 mg conjugated equine estrogens) combined to an adequate dose of progestogen for 10 days per month over 10 years.

A summary of the postulated changes in annual mortality induced by, respectively, unopposed and opposed estrogen replacement therapy, as estimated by Henderson et al. [190] is given in Table III. This evaluation can be pessimistic since it is based on a 36% (10 out of 28 days) reduction in the beneficial effect of

TABLE III

ESTIMATED CHANGES IN ANNUAL MORTALITY, AS INDUCED BY ESTROGEN REPLACEMENT THERAPY (USING 0.625 mg/day OF CONJUGATED EQUINE ESTROGENS), ACCORDING TO THE SEQUENTIAL ADDITION (OPPOSED) OR NOT (UNOPPOSED) OF A PROGESTOGEN FOR 10 DAYS PER CYCLE (ADAPTED FROM HENDERSON ET AL. [190] WITH THE PERMISSION OF THE AUTHOR AND OF THE PUBLISHER, THE AMERICAN FERTILITY SOCIETY

Condition	Unopposed		Opposed	
	RR	Mortality* change	RR	Mortality* change
Hip fracture	0.4	−33	0.28	−40
Endometrial cancer	6.0	+26	1.0	0
Breast cancer	1.6	+61	1.6	+61
Ischemic heart disease	0.52	−284	0.69	−184
Net change for:				
Non-hysterectomized		−230		−163
Hysterectomized		−256		−163

RR: relative risk, as estimated per 10 years of use.
*Per 100 000.

estrogen replacement therapy and it is thus only valid for progestogens with high androgenic effect on lipids, when given sequentially.

From these hypothetical figures, it is quite clear that hysterectomized women will not benefit at all from the addition of progestogens and that, in non-hysterectomized women, the benefit from endometrial cancer prevention (−26) is more than counterbalanced by the increase (+100) in mortality from ischemic heart disease. It should also be emphasized that a relative risk of endometrial cancer of 6.0 under unopposed estrogens might well be overestimated at the light of the most recent data [103,104] and that there might be also an increased risk of breast cancer from the progestogen. This hypothetical speculation would one lead either to choose unopposed estrogen replacement therapy (with a slightly increased risk for endometrial carcinoma, but that will be diagnosed early) or to choose progestogens not counteracting the favorable estrogen-induced lipidic profile, i.e., essentially micronized progesterone or possibly desogestrel.

However, the true validity of such recommendations awaits conclusive epidemiological data. It is indeed not proven at all that these pharmacologically-induced alterations in lipids will reflect themselves in the effective rates of cardiovascular accidents and death. Data obtained in monkeys by Adams et al. [191,192], using norgestrel and estrogen, orally or intravaginally (the estrogen being 17β-estradiol in that case), indicate indeed that there is not necessarily any worsening of atherosclerosis from a pharmacologic lowering of HDL-C: the extent of the coronary artery atherosclerotic plaque of animals fed a moderately atherogenic diet, was much smaller in animals treated with oral contraceptives than in nontreated animals, as well as in those receiving intravaginally estradiol + levonorgestrel. These authors postulated that ethinylestradiol (and/or oral

estrogens) might counteract locally, at the level of the arterial intima, the atherogenic influence of decreased HDL-C from the androgenic progestogen.

Alternatives to progestogen addition

Unopposed estrogen replacement therapy is quite conceivable provided careful and regular monitoring in order to detect and treat pre-malignant endometrial hyperplasia and thus avoid cancer:

— regular endometrial sampling, for example annually, has been recommended but is not always easy, accepted and unharmful, although new technical devices might improve compliance [193];
— preliminary results indicate that abdominal ultrasound could reliably exclude significant endometrial pathology [194] and that vaginal sonography could even be better since it enabled to detect most of the endometrial changes that occur in response to post-menopausal hormone replacement therapy [195].

Another promising approach resides in the combination of anti-estrogens such as clomiphene citrate [196—198] or tamoxifen [199] to the estrogen replacement therapy: the preliminary results seem interesting but more research is clearly required before widespread use.

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