ELSEVIER SCIENTIFIC PUBLISHERS IRELAND

Maturitas 18 (1993) 21–46

MATURITAS

Long-term hormone replacement treatment in menopause: new choices, old apprehensions, recent findings

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(Received 11 February 1993; revision received 19 April 1993; accepted 20 April 1993)

Abstract

In recent years there has been an increase in the use of parenteral oestradiol as an alternative to the conventional oral preparations used in hormone replacement treatment (HRT) in menopause, such as conjugated equine oestrogens (CEE). The latter have been subject in the past to apprehensions, partly due to misunderstanding and oversimplification but also in relation to problems that have arisen during the history of HRT, for example the increase in endometrial cancer risk deriving from the use of non-progestogen-opposed treatment. However, confidence in long-term HRT comes from the epidemiological findings, which refer mainly to the use of oral CEE unopposed by progestogen: a reduced risk of osteoporotic fractures and of cardiovascular disease, and a very limited risk of breast cancer. Oral oestrogens produce marked hepatocellular effects. These effects are, on the whole, favourable from the point of view of cardiovascular risk. In addition, it cannot be excluded that some hepatocellular effects of oral oestrogen, for example increased sex hormone binding globulin levels and reduced circulating insulin-like growth factor I activity, offer protection to the breast. As progestogen supplementation is needed in non-hysterectomized women, priority should be given to preparations, such as progesterone or dydrogesterone, that feature good endometrial activity without opposing oestrogen hepatocellular effects.

Key words: Menopause; Oestrogen replacement treatment; Progestogens; Hepatocellular effects; Sex hormone binding globulin; Insulin-like growth factor I

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SSDI 0378-5122(93)00765-B

1. Introduction

Long-term hormone replacement treatment (HRT) is being used not only for relief of immediate disturbances that arise during menopause but also, and more importantly, for the prevention of serious problems that may follow, such as osteoporosis and cardiovascular diseases.

Areas of doubt still exist, however, not only because of frequent misunderstanding and oversimplification but also, to some extent, in relation to problems that have arisen during the history of this type of treatment.

2. History

Long-term oestrogen therapy over the last 30 years has been subject to many changes of attitude (Table 1).

2.1. 1960s and early 1970s: enthusiasm

The theories supporting replacement therapy, not only for relief of subjective climacteric symptoms but also, and more importantly, for the prevention of bone and cardiovascular diseases consequent to oestrogen deficiency already existed before the 1960s. But it is only since the mid-1960s and following publications by Wilson [1] that replacement therapy has become widely popular, particularly in the United States.

2.2. Late 1970s and early 1980s: apprehension

Evidence was already available in the 1960s to suggest that oestrogen therapy should be opposed, as regards endometrial stimulation, by a progestogen supplement, following a sequential plan, and the same view was expressed by Wilson [2]. Nevertheless, particularly in the United States, in order to avoid menstruation-like bleeding, which was considered 'anachronistic' in subjects of a certain age, the practice of cyclical treatment with oestrogen alone, using the so-called 'sub-bleeding doses' [3], was widely followed. Preparations and doses were used — usually conjugated equine oestrogens (CEE) 1.25–0.625 mg/day orally — that could lead to endometrial proliferation. The consequences became known in 1975, when two case control studies were published simultaneously [4,5] and later confirmed by several other epidemiological investigations [6–8]: increased risk of endometrial cancer, albeit at low degrees of malignancy. This data obviously caused great concern, even in Europe, where oestrogen therapy was used less commonly and with a more correct

Table 1
Changes of attitude towards long-term oestrogen therapy

1960s and early 1970s: enthusiasm
Late 1970s and early 1980s: apprehension
Mid-1980s: recovery (prevention of osteoporosis)
End of the 1980s: renewed, motivated enthusiasm (cardiovascular protection)

methodology, i.e. with adequate progestogen compensation, which was known to be capable of preventing chronic proliferation and hyperplasia of the endometrium [9–12], increasing the risk of neoplastic degeneration.

Concern and mistrust were increased in the second half of the 1970s by new data concerning cardiovascular diseases (thrombo-embolism, myocardial infarction, cerebrovascular pathology) from oestro-progestogen oral contraceptives affecting younger women, who were, as such, less 'at risk' [13–15]. Even at that time there were sufficient elements to distinguish, for the risk of thrombo-embolism for example, the biological changes and clinical consequences caused on the one hand by oral contraceptives, usually containing high doses of synthetic oestrogen, and on the other hand by low-dose non-synthetic oestrogen replacement treatment regimens in menopause [16]. Nevertheless, caution and uncertainty prevailed in the face of the somewhat paradoxical doubt that oestrogen treatment, contrary to expectations supported by biological evidencs, could in fact increase, rather than reduce, cardiovascular risk. This doubt was fuelled not only by the extrapolation of data regarding the consequences of oral contraceptives (which at the time seemed to be incorrect, and later proved to be so) but also by some data regarding the use of non-synthetic oestrogens. One example of the latter was the unfortunate study of high-dosage CEE in males with myocardial infarction, which resulted in increased mortality [17], while another example was a number of studies regarding use of the same preparation in women of postmenopausal age [18].

All these reservations meant that the second half of the 1970s and the early 1980s saw a marked reluctance to use long-term oestrogen replacement therapy. The trend was rather towards short-term treatment aimed at minimising subjective disturbances. Even this application was mistrusted by the majority of internal medicine specialists and general practitioners. Oestrogen treatment was considered a potentially dangerous option for people who did not need true medical assistance but were seeking the obviously vain goal of eternal youth, mainly for cosmetic reasons. At the same time, however, a marked reserve, especially regarding cardiovascular risk, was expressed by experts such as those at the University of California Los Angeles Conference in 1983 [19].

Not enough was then known either about the importance of the postmenopausal osteoporosis problem, or, especially, about the fact that long-term oestrogen therapy might provide a real chance of preventing osteoporotic fractures.

2.3. Mid-1980s: recovery (prevention of osteoporosis)

At the end of the 1970s and the beginning of the 1980s the first data began to appear on the capacity of oestrogen therapy to retard postmenopausal loss of bone tissue [20–22], a biological action already attributed to replacement therapy in the 1960s [1] and even earlier by Albright [23]. By the first years of the 1980s an actual protection against fractures had been documented: a 55–80% reduction of wrist and hip fractures [24–27] and greater than 50% reduction in vertebral fractures [28]. At the same time the social importance of postmenopausal osteoporosis was highlighted. In the light of this data, together with the difficulty of identifying women at risk from osteoporosis, some experts in 1985 once again proposed long-term oestrogen therapy for all postmenopausal women showing no counterindica-

tions [29]. Even if this approach could not yet be widely accepted, the awareness of the osteoporosis problem that arose among practitioners paved the way for a substantial re-evaluation of the validity of oestrogen therapy: no longer just an optional extra for eccentrics trying to escape the inconvenience of no longer being young but a treatment capable of providing immediate benefits (towards subjective symptoms) and, more importantly, of preventing much more serious problems of a medical nature.

A certain unease remained about the difficulty of identifying women who were really at risk from osteoporosis and about a treatment useful for a minority (that 20–25% heading towards the clinical consequences of osteoporosis unless they received pharmacological preventive treatment) but that could involve the majority in unnecessary risks, not just in the form of tumours [6] but also cardiovascular illness, as was restated in a 1988 editorial in *Lancet* [30].

2.4. End of the 1980s: renewed, motivated enthusiasm (cardiovascular protection)

To offset the pessimism regarding cardiovascular risk, some studies had already appeared in the 1970s [31–33] that showed a reduction of coronary heart disease in women treated with oestrogen. During the 1980s, especially the first half, and the early 1990s the pessimism was overcome completely with the publication of the results of over twenty comprehensive and authoritative American epidemiological studies relating to the destinies of the many women who had used oestrogens. These were the same populations and, in many cases, the same study groups that had supplied the evidence in the late 1970s of the increased risk of endometrial cancer resulting from not using progestogen. With the exception only of the Framingham study [34] and a few minor papers, all the studies, regardless of type, showed a clearly reduced risk of coronary disease and myocardial infarction [35–39]. A reduced risk of stroke reported by one study [40] was important for preventive medicine, but another study failed to confirm this [37]. Overall, epidemiological data from the 1980s supports the assertion that CEE treatment, using dosages of 0.625 mg/day for 10 years after menopause, reduces mortality from myocardial infarction, and possibly also from stroke, by 50% [40].

The cardiovascular benefits from oestrogen therapy far outweigh the benefits for osteoporosis. For this reason many experts [41–44] feel that, regardless of the osteoporosis risk, this therapy should be made available to quite a wide range of women, including those at greater cardiovascular risk [44].

The optimism of the late 1980s and beginning of the 1990s has been boosted by epidemiological data concerning risk of tumours. Above all, it has been confirmed that sequential progestogen supplementation, for a period of 10–14 days per month, can not only minimize the risk of endometrial hyperplasia risk [9–11] but also negate any increase in the risk of endometrial adenocarcinoma [45–47] that had been identified as a result of non-opposed oestrogen therapy [4–8]. In addition, the potential risks for the breast have been clarified and proved to be, on the whole, rather limited. A meta-analysis was published recently of the sixteen most important epidemiological studies on the risk of breast cancer from the use of various therapeutic preparations and regimes [48]. Overall it revealed that there was no substantial increase in risk for treatment up to at least 5 years, and also a noticeably low risk

(except in women with a family history of breast cancer) for treatments lasting longer than 15 years (relative risk (RR) equal to 1.3 overall). This meta-analysis [48] draws attention to the fact that the cumulative increase in risk is largely due to the results of studies (mostly European) that included women treated in the pre-menopausal phase or who used oestradiol (with or without progestogen), in which there was a markedly increased relative risk (RR = 2.2) after 15 years' treatment. The proportional increase in risk per year of treatment on average was clearly lower in the studies using predominantly CEE unopposed by progestogens than in the studies using other preparations or treatment regimes: 0.010 for unopposed CEE versus 0.063 with other kinds of treatment [48]. Furthermore, the combined results from multiple studies provide strong evidence that treatment with 0.625 mg/day or less of CEE does not increase breast cancer risk [49,50].

Here it must be stressed that even the epidemiological findings regarding the benefits of long-term oestrogen therapy almost exclusively come from American studies and refer mainly to the use of unopposed CEE [51]. This is true for protection against osteoporosis [24–28] and for reduction in cardiovascular diseases, particularly myocardial infarction [35–40], recorded even in subjects with confirmed coronary stenosis [52] and/or cardiovascular risk factors [53].

Until new epidemiological evidence is available (which could take several years for equally reliable results) it is important to clarify whether and to what extent the substantial confidence (regarding risks) and great expectations (regarding benefits) generated by these studies can be *sic et simpliciter* attributed to other preparations and regimes.

3. The various oestrogen preparations

Table 2 gives a list of the oestrogen preparations currently used in post-menopausal long-term replacement therapy.

Those used for the longest time and most widely, especially in the United States, are the CEE, usually administered orally [51]. Other oral preparations are oestradiol valerate (E_2V), widely used in Europe [54], micronized oestradiol ($MicrE_2$), used in some countries, and, especially in order to improve vaginal trophism, oestriol (E_3), a weak oestrogen that may also be used topically [55]. Synthetic oestrogens, such as diethylstilbestrol and ethinyloestradiol [EE_2], are used less, because of their side-effects [56], although EE_2 at relatively low doses has been used to some extent.

Table 2
Main oestrogen preparations used in long-term replacement treatment, also offering protection against bone and cardiovascular problems

Oral administration	Parenteral administration
Conjugated equine oestrogens (CEE), 0.625 or, more rarely, 1.250 mg/day	Oestradiol by percutaneous gel, 1.5–3 mg/day
Oestradiol valerate (E_2V), 1–2 mg/day	Oestradiol by patches, 0.050 or, more rarely, 0.100 mg/day
Micronized oestradiol ($MicrE_2$), 2 mg/day	

Parenteral administration (apart from the relatively uncommon vaginal prescription of CEE and E_3) was used infrequently in the form of oestradiol (E_2) injections or pellets until some years ago. But since preparations of E_2 have become available in percutaneous gel or transdermal patches, parenteral administration is becoming more and more frequent [57].

CEE preparations contain sulphate esters of oestrone (E_1) and E_2 and of the ring B unsaturated equine oestrogens (also active in humans) equilin, equilenin and dihydroequilins or dihydroequilenins. The major components are E_1 sulphate (E_1S) (45%) and equilin sulphate (25%) [58]. After oral administration, E_1S reaches the peripheral circulation and is subsequently converted in part to E_1 and E_2 [59]. The currently used dosages of CEE (0.625–1.250 mg/day) bring plasma levels of E_2 up to those of the early follicular phase of the menstrual cycle and levels of E_1 notably higher, from two to five times that of E_2 [60–62]. High levels of equilin are also obtained [60]. Oral administration of E_2V and $MicrE_2$ at the currently used dosage of 1–2 mg results in plasmatic E_2 values higher than those obtained with CEE and similar to those of the intermediate to late follicular phase of the menstrual cycle [62,63]. In addition, oral E_2V and $MicrE_2$, like CEE, bring plasma E_1 to levels considerably higher than those of E_2 [57,62–64] and also produce high plasma levels of E_1S [65]. On the other hand, parenteral administration of E_2, e.g. by percutaneous gel or transdermal patches, gives plasma levels of E_1 that are equal to or lower than those of E_2 [61,63–66]. It should be considered that the excess of E_1 and E_1S in patients on oral treatment does not noticeably contribute to the increase of oestrogenic activity, e.g. on pituitary function [65]. In fact E_1 (with the possible exception of hepatocellular action — see below) has one-tenth of the potency of E_2 [67] and probably acts, like E_1S, mainly as a reservoir for E_2 [65].

The actions of oestrogen can be set out as follows:

(a) direct actions on target organs (hypothalamic-hypophyseal system, breast, uterus, and vagina; probably also bone tissue, collagen, and vessel walls);
(b) actions via other organs (several actions affecting bone metabolism);
(c) hepatocellular effects.

3.1. Hepatocellular effects

The intensity of the hepatocellular effects, which takes the form of an influence on protein hepatic synthesis, varies noticeably from one preparation or administration route to another (Fig. 1). For example, the hepatocellular action of orally administered CEE proves to be more than double that of $MicrE_2$, at similarly effective dosages on pituitary function [68]. The synthetic product EE_2 appears to be even stronger, with an action two to five times more than that of CEE [68]. Probably because of their structure, the synthetic oestrogens are more resistant to intracellular processes of metabolism and degradation, so their activity can be prolonged. The same applies to the equine oestrogens, equilin and dihydroequilin, which comprise approximately 35% of CEE [68]. This could explain the fact that both synthetics and CEE also act on hepatic function when parenterally administered [69]. In the case of CEE, high circulating levels of E_1S and E_1 could also contribute to the hepatocellular effects. Uptake of these steroids by the liver is easier and, at least for E_1S, much greater than uptake by the uterus or brain [69]. Moreover, E_1 binds preferen-

		Circulating hormone levels				First pass hepatic effect	Hepatocellular potency
		EE_2[(a)]	Equine estrogens[(b)]	E_1[(c)]	E_2[(d)]		
Ethinylestradiol	oral	↑				yes	++++
	non oral	↑				no	++
Conjugated equine estrogen	oral		↑	↑	↑	yes	++
	non oral		↑	↑	↑	no	+
Estradiol	oral			↑	↑	yes	+
	non oral			↑	↑	no	-

a) ethinylestradiol; b) equilin dihydroequilin, etc; c) estrone; d) estradiol.

Fig. 1. Hepatocellular strength of different oestrogen preparations and administration routes.

tially to the liver receptor sites and seems to be twice as active as E_2 in hepatocellular effects [57]. It should be remembered that high E_1S and E_1 levels are also characteristics of orally administered E_2V and $MicrE_2$ [63–65], which could help to explain their strong hepatic effect [57,63,68], although this is relatively reduced in comparison with that of oral CEE [68].

More generally, great importance is given to the fact that with oral administration the high levels of oestrogens reaching the portal vein make the liver a preferential target [57], the so-called first-pass hepatic effect [67,70]. Parenteral administration of E_2, which features neither first-pass hepatic effect nor elevated E_1 levels, has less or no influence on hepatic function [57,63,66,68].

Table 3 lists the main hepatocellular effects of oestrogen administration. The changes that have attracted greatest attention up to now are in the area of lipopro-

	Abdominal obesity	Oral estrogen treatment	Non oral E2[(1)] treatment
Estrogen activity	↑	↑	↑
SHBG [(2)] levels	↓	↑	↔
Androgen activity	↑	↓	↔
FFA [(3)] levels	↑		↓
Insulin levels	↑	↔	↔
Circulating IGF-I activity[(4)]	↑	↓	↔

(1) 17β-estradiol; (2) Sex Hormone Binding Globulin; (3) Free Fatty Acids;
(4) as expressed by Insulin-Like Growth Factor I (IGF-I) and/or IGF-binding protein 1 levels.

Fig. 2. Comparison of biological features possibly involved in breast cancer risk in different postmenopausal conditions [90].

Table 3
Main hepatocellular effects of oestrogen administration

1. HDL cholesterol, VLDL and triglyceride increase
2. Renin substrate increase
3. Coagulation factor changes
4. Bile lithogenicity increase
5. Sex hormone binding globulin (SHBG) increase
6. Insulin-like growth factor I (IGF-I) decrease; IGF binding protein 1 (IGFBP-1) increase

teins, particularly concerning the very low-density lipoproteins (VLDLs) and the high-density lipoproteins (HDLs). As a result of oral oestrogen therapy there is an increase of VLDL hepatic secretion [71]; this leads to an increase in triglyceride levels [71–75]. This increase seems to be dose-dependent: for example, CEE produce a 24% triglyceride increase at a dose of 0.625 mg/day but a 38% increase at a dose of 1.250 mg/day [73]. On the other hand, doses of 0.625 and 1.250 mg/day produce similar increases (about 16%) in HDL-cholesterol levels [73]. This HDL increase seems to be due to an increased ApoA secretion [71] and, probably more consistently, to a reduced hepatic lipase activity [71,73,76,77].

Increased synthesis of renin substrate is another hepatocellular effect of oral oestrogen treatment [68,78]. This is also dose-dependent, being more evident, for example, with 1.250 mg/day than with 0.625 mg/day of CEE [68].

Oestrogen therapies tend to influence coagulation equilibrium in various ways. However, potentially thrombophilic changes, such as higher fibrinogen and reduced antithrombin III levels, when present, are compensated by increased fibrinolytic factors [7,79,80].

One of the hepatocellular functions that is more sensitive to oestrogen administration is sex hormone binding globulin (SHBG) synthesis [68]. Oral administration of both CEE and E_2, at the dosage currently used in HRT, leads to a clearcut increase in sex hormone binding globulin values [63,81–83]. SHBG binds specifically the most active androgens (testosterone, dihydrotestosterone), as well as E_2, although with less stability, and E_1, with even less affinity [81,84]. SHBG also binds the equine oestrogens equilin and 17-beta-dihydroequilin, with affinity similar to that of E_1 and E_2, respectively [58]. The biological role of SHBG has not yet been fully determined [81]. Specific cellular uptake of steroid binding proteins, including SHBG, has recently been demonstrated, and a role for these proteins in intracellular action has been suggested [81]. However, the most prevalent interpretation is that the main action of SHBG is that of reducing the quota of sex hormones (SH), either free or blandly bound to albumin, which can pass easily through the vessel walls and act at tissue level [81,85]. The main consequence of increased levels of SHBG would therefore be a lower rate of SH, both oestrogens and androgens, which are free and thus active [81,84,85].

Several studies show that in postmenopausal women oral EE_2 at the relatively low dose of 0.01–0.02 mg/day causes a reduction in circulating insulin-like growth

Table 4
Sex hormone binding globulin (SHBG), insulin-growth factor I ((IGF-I), growth hormone (GH) and insulin levels before and at the sixth month of treatment wih conjugated equine oestrogens 0.625 mg/day (24 days per month) [91]

	n	Basal	Sixth month	*P*
SHBG (nmol/ml)	18	55.72 ± 26.08	142.80 ± 53.08	< 0.001
IGF-I (ng/ml)	13	179.80 ± 48.02	113.30 ± 33.73	< 0.002
GH (ng/ml)	13	3.47 ± 3.52	8.59 ± 7.32	< 0.02
Insulin (microU/ml)	14	7.97 ± 1.18	6.26 ± 1.41	< 0.01

factor I (IGF-I) and an even more pronounced increase in growth hormone (GH) levels [86]. Since circulating IGF-I is mainly of hepatic derivation, its suppression is probably a hepatocellular effect of oral EE_2, while GH increase seems to be a consequence of the feedback mechanism due to the IGF-I reduction [86]. In fact transdermal administration of E_2 does not produce significant modifications of GH levels; it produces, on the other hand, an increase or no variation of serum IGF-I [86,87]. A further reduction in circulating IGF-I activity could be caused by the increased hepatic production of IGF binding globulin 1 (IGFBP-1), as has been shown with higher doses of EE_2 [88]. There is no literature data on the effect of CEE on IGF-I level. Several studies published in the 1970s failed to show any influence on GH [89]. Therefore it could be hypothesized that CEE, even though exerting a hepatocellular effect, causes a reduction in IGF-I level less than EE_2 [90]. Some of our results, on the contrary, indicate a strong action of oral CEE on IGF-I and GH serum levels (Table 4). Consequently, it can be held that CEE, even at the 0.625 mg/day dose, exerts action on the IGF-I/GH axis that cannot be further increased by the use of oestrogen preparations (such as EE_2) with higher hepatocellular strength. Changes in the IGF-I/GH equilibrium brought about by oral oestrogen do not seem to constitute a negative influence as far as resistance to insulin is concerned [92]. For example, administration of high-dose EE_2 to acromegalics, which causes a fall in IGF-I levels but no change in GH levels, results in improved carbohydrate tolerance and reduced insulin responses to glucose [92]. Oral CEE do not seem to interfere unfavourably with insulin levels [93–95]. In a large-scale study it was found that treated postmenopausal women had lower basal and stimulated insulin levels than postmenopausal women who were not taking CEE [94].

Many of the hepatocellular effects (Table III) have, or could have, clinical implications, and the consequences of using one type of oestrogen therapy or another could vary according to their hepatocellular strength (Fig. 1). Working from this, we will now consider the various clinical areas potentially affected by the different oestrogen therapies.

3.2. Cholelithiasis

Increased lithogenicity of the bile is undoubtedly a risk factor for colelithiasis. This risk has been documented for oral oestrogens [7,96], while there is probably little or no risk with parenteral oestrogens.

Table 5
Oestrogen treatment: clinical relevant effects on cardiovascular risk factors

	Potential influence on risk	Oral EE_2[a]	Oral natural oestrogens	Parenteral oestradiol
1. Lipoprotein modifications	Decrease	+	+	+
2. Action on vessel walls	Decrease	+	+	+
3. Renin substrate increase	Increase	+	(+)	–
4. Coagulation factor changes	Increase	+	(+)	

[a]Ethinyloestradiol, especially for dosages > 0.030 mg/day.

3.3. *Cardiovascular diseases*

The genesis of cardiovascular pathology is typically multifactorial. Two of the more important factors, which can be influenced by oestrogen therapy, are the plasma lipids and the blood pressure: in the simplest terms, risk is directly proportional to the values of the ratio of total cholesterol to HDL-cholesterol and to the values of blood pressure [97]. Another area potentially susceptible to the influence of some kinds of oestrogen therapy is the delicate and complex coagulation equilibrium: oscillations in this could have special clinical relevance where there is an irregularity in or damage to the inner vessel stratum, e.g. as a result of atheromas [79,97].

Table 5 summarizes the main consequences of oestrogen therapy with potential repercussions on cardiovascular risk.

(i) Relevant modifications to the *lipoprotein* system arise from hepatocellular effects affecting VLDLs and HDLs. The consequent increase in triglyceridemia as observed during oral oestrogen treatment [71–75] is subject to a certain amount of controversy about its clinical consequences [52,72,75,98]. Also, HDL-cholesterol level increase, because of the action mechanism that probably prevails (inhibition of hepatic lipase) [71,76,77], might not be as favourable as has been thought up to now [77]. On the other hand, the most favourable lipoprotein modification is held to be the reduction of LDLs, with lower LDL-cholesterol levels [72,73,75]; this is due to greater receptor activity towards the LDLs [71,73], valid both for oral and parenteral oestrogens [7,71,75]. The latter also reduce triglyceride levels [7,75] and, in long-term treatment, tend to increase slightly HDL-cholesterol levels [7,18]. In general it is possible to say that from the point of view of cardiovascular risk the lipoprotein system is favourably affected by all types of oestrogen therapy.

(ii) Action on *vessel walls* is also of a favourable nature, and it can be assumed that there are no noticeable differences between different administration routes. Oestrogens directly affect the vessel wall, stimulating blood flow in peripheral organs, including the heart and brain [7,75,99–102]. This constitutes an important protection factor against vascular disease, representing, among other things, a mechanism to prevent hypertension. Furthermore, the oestrogens probably intervene in the

mechanisms that cause atherogenesis [75,103], either by direct action or as a result of hepatocellular action [104]. In this respect, some importance could be given to reduced circulating IGF-I activity, which has been revealed with EE_2 by several studies [86] and recorded by us also with CEE at the current dose of 0.625 mg/day (Table 4). In fact, emphasis is given nowadays to the action of various growth factors in the genesis of atheroma [105], and since the IGF-I is a potent smooth muscle cell mitogen, it is possible that it contributes to the atherogenic process even by an endocrine mechanism [106].

(iii) Increased synthesis of *renin substrate* is a potential cause of hypertension. This is a hepatocellular action and therefore particularly marked with oral synthetics, less markedly present with oral CEE, even less with oral E_2 in dosages used in HRT, and absent in parenteral E_2 administration [68].

(iv) Oestrogen therapies can affect *coagulation* in many ways: increased platelet adhesion, reduced antithrombin III, and increased levels of coagulation factors [79]. A large part of these are hepatocellular actions and so are more intense with oral synthetic oestrogens [68] and weak or absent with parenterals [107]. These potentially thrombophilic actions are counterbalanced by simultaneous increase in fibrinolytic factors [7,79,80].

Overall (Table 5), with the oral synthetic oestrogens, unfavourable consequences tend to predominate; this can be interpreted, especially in cases of high dosages and in association with 'androgenic' progestogens such as in the 'old' contraceptive pills, as constituting a cardiovascular risk [13–15]. Conversely, with oral non-synthetic oestrogens favourable actions predominate, which has been confirmed by numerous epidemiological data cited above [35–40], referring especially to CEE, as previously pointed out. About one-third of the protective effect can be attributed to action on the lipo-proteins [36,75], while great importance is now given to actions on the vessel walls and particularly to increased blood flow [7,75,99–102]. These seem to prevail over the consequences of increased renin substrate, as far as arterial pressure is concerned; in fact, contrary to previous fears, numerous data show that natural oestrogen therapy, in general, does not lead to hypertension [7,75,97]. A (reversible) rise in blood pressure can be detected only in a small number of patients, who are probably hypersensitive to renin substrate increase [7,97]. With natural oestrogens, in dosages currently used in HRT, changes in the coagulation equilibrium do not seem to have clinical relevance, even in situations leading to damage to the vessel walls. In fact oral CEE treatment has brought about a reduction in cardiovascular mortality, even in women with risk factors — such as vascular pathology, hypertension, obesity, or sedentary life-style [53,108,109] — or with confirmed coronary stenosis [52]. Nevertheless, apart from the already documented higher mortality among infarcted males after treatment with high dosages of oestrogens [17], some data referring to subgroups, such as women who started treatment at an advanced age or those who smoke [109,110], seems to call for a certain amount of caution. These findings could relate to the use of really excessive CEE dosages, in excess of 1.250 mg/day, which is not uncommon in American series going back to the 1960s and 1970s [51]. Such high dosages have recently been recognized as less helpful as to biological modifications, and perhaps counterproductive as to cardiovascular risk [35]; their more frequent use could explain the results of older studies [18] as well as the Framingham study [34].

3.4. Bone metabolism

According to a recent hypothesis [111], favourable oestrogenic action on bone metabolism could depend partly on a hepatocellular effect, i.e. lowering of hepatic synthesis of IGF-I and consequent increase in GH, as was revealed with EE_2 by several studies [86] and recorded by us with CEE (Table IV). Nevertheless, the predominant opinion is that oestrogens act on bone metabolism mainly by stimulating, without hepatic mediation, the activation of vitamin D and, perhaps, also the synthesis of calcitonin [112–114]; furthermore, they can have a direct effect on the bone tissue via specific receptors [114]. In fact data is already available showing that E_2 administration by transdermal patches is capable of slowing postmenopausal bone loss, exactly the same as oral oestrogens [115–117].

3.5. Breast cancer

Breast tissue is well known to be a target organ for direct action of oestrogens. However, it must not be overlooked that the mechanisms favouring development of breast cancer are very complex [7].

Oral oestrogens cause a series of hepato-mediated biological changes with potential implications for breast cancer risk. Apart from the increased oestrogenic activity itself, these changes are the opposite to those resulting from abdominal obesity (Fig. 2), for which there is epidemiological evidence of an increased breast cancer risk in postmenopause [118–120]. Particularly important could be the induction of high levels of SHBG, which reduces both oestrogenic and, especially, androgenic activity; the low levels of the latter probably represent an important difference between women under oral oestrogen treatment and those with abdominal obesity [90]. Another potentially important difference derives from reduced circulating IGF-I activity because of interference in its hepatic synthesis and in the synthesis of one of its binding proteins, IGFBP-1. In fact some breast cancer cell lines, particularly if oestrogen-receptor-positive, express IGF-I receptors, and IGF-I is mitogenic for them; as a consequence, IGF-I is a potential paracrine or endocrine stimulator of breast cancer cell growth [121]. Moreover, IGF-I and oestradiol have synergistic effects on human breast cancer oestrogen-responsive cell lines [121]. The possibility does exist that the increase of GH serum level, reactive to the IGF-I decrease [86], contrasts the potential favourable action of the latter. In fact the GH could have a stimulating action on breast tissue, for example by determining a greater production of IGF-I by part of the stroma, thus increasing its paracrine action. However, it must be considered that while the stroma of normal breast tissue readily expresses IGF-I, the cancer stroma loses this capacity in favour of the expression of the insulin-like growth factor II [121], which is probably less sensitive or not sensitive to the GH stimulating action. It follows that the circulating IGF-I decrease, together with SHBG increase, induced by oral oestrogens could be protective to the breast.

These biological consequences do not arise with E_2 treatment using the parenteral route. This is because hepatocellular effects are non-existent or much reduced in this form of therapy, as is the influence on synthesis of SHBG [57,61,63,66,83], IGF-I [86,87] and, probably, of IGFBP-1 [88]. It should be pointed out that at the level of single tissues, the significance of changes in SHBG [81] and, especially, IGFBP-1 [88] is not yet clear. Moreover, one study suggests that there

may be increased risk to the breast when using oral EE_2, the synthetic oestrogen with the most marked hepatocellular effect [122]. Nevertheless it is worth considering the possibility that the other more widely used oral oestrogens, particularly the CEE (the only ones for which sound epidemiological data concerning breast cancer risk is available [48–50]), feature a favourable balance between oestrogenic stimulation and biological changes offering protection to the breast [90]. Treatment with parenteral E_2 also produces a possible protective action, through its capacity for reducing free fatty acid levels [123]. However, it seems premature to extend to this type of therapy the information on the relationship between CEE and breast risk, which is largely reassuring, especially for dosages not in excess of 0.625 mg/day [49,50].

3.6. Endometrial cancer

Endometrial stimulation is a typical direct action of oestrogens; it is therefore present with all preparations, except oestriol [55], irrespective of administration route. Consequently, in non-hysterectomized women, progestogen use is essential [124] (see below) in order to prevent endometrial pathology.

4. The progestogen problem

Table 6 lists the main progestogens used in HRT in postmenopause. The most commonly used, in Europe and especially in the United States, is medroxyprogesterone acetate (MPA) [51]. Dydrogesterone (DYDR) is also widely used in Europe and, less commonly, other pregnane derivatives, such as medrogestone, cyproterone acetate, and 19-norprogesterone derivatives. 19-nortestosterone derivatives have been used above all in northern European countries; in the United States they accounted for 11% of prescriptions, compared with 89% for MPA [51], while in Sweden their use is much more widespread [125]. Oral micronized progesterone is used in some European countries. Parenteral routes (transdermal for norethisterone acetate [126] and vaginal for progesterone [127]) might be interesting alternatives for the future.

4.1. Hepatocellular effects

Progestogens, especially when taken orally, can oppose the hepatocellular effects of oestrogen with an intensity that is proportional to their residual androgenic action

Table 6
Main progestogens used in postmenopause hormone replacement treatment

Oral	Parenteral
Medroxyprogesterone acetate (MPA)	Norethisterone acetate, transdermal
19-Nortestosterone derivatives	Progesterone, vaginal
Dydrogesterone (DYDR)	
Medrogestone	
Cyproterone acetate	
Micronized progesterone	

Table 7
Oral progestogens in increasing order of hepatocellular strength

Micronized progesterone
Dydrogesterone (DYDR); medrogestone; cyproterone acetate; 19-norprogesterone derivatives
Medroxyprogesterone acetate
19-Nortestosterone derivatives (excluding the more modern desogestrel and gestodene)

[7,71]. Literature data, especially regarding action on the lipids, is abundant but not always consistent, even taking into consideration different experimental approaches. Nonetheless a scale can be drawn up for hepatocellular strength of oral progestogens (Table 7). The scale goes in increasing order from natural progesterone (minimum hepatocellular strength) to derivatives of 19-nortestosterone (maximum hepatocellular strength, at least in the older formulations such as norethisterone and norgestrel, thus excluding the more modern preparations such as desogoestrel [128,129] and gestodene [128], not yet currently employed in replacement therapy).

As far as the lipids are concerned, the most typical oestrogenic hepatocellular action, namely the rise in triglycerides and HDLs, is distinctly opposed by the old derivatives of 19-nortestosterone [7,71,130–134]. An action of this kind, albeit more limited, is also present with MPA [7,71,130–135]. On the contrary, micronized progesterone does not cause substantial interference with oestrogen action [7,71,74,132,135,136]; DYDR, medrogestone and cyproterone behave similarly [7,71,132,137,138]. Initial data seems to indicate that derivatives of 19-nortestosterone (for example norethisterone acetate), when administered transdermally, thus avoiding the first-pass hepatic effect, are substantially free of actions on the lipids [126].

Data regarding any oral progestogen interference with other hepatocellular effects of oestrogen is rather limited. MPA would appear to reduce, although not significantly, the CEE-induced rise in renin substrate [139]. No particular interference on coagulation equilibrium is recorded, except a tendency to a further increase in fibrinolytic activity [140].

SHBG increase, one of the more perceptible consequences of oestrogen hepatocellular action, is clearly opposed by derivatives of 19-nortestosterone, such as norgestrel, at a dose of 0.150–0.250 mg/day [131,133,141]. The action of MPA seems rather less important, if not virtually non-existent [131,133]. Some data of ours suggest absence of interference by DYDR with the CEE-induced rise in SHBG levels [91].

There is no literature data on possible progestogen interference on the reduction of circulating IGF-I level caused by oral oestrogens. Preliminary data of ours seem to suggest absence of interference on the part of DYDR [91], and, on the contrary, a reverse effect of norethisterone acetate on the CEE-induced decrease of IGF-I serum level (unpublished observations).

Progestogens might alter tolerance to glucose, causing resistance to insulin. This happens in accordance with a scale corresponding exactly to that of hepatocellular strengths (Table VII) [7,142]. Minimum action on carbohydrate metabolism is ex-

erted by progesterone and by DYDR [7,142,143]. Progestogens with similar metabolic activity probably behave similarly. MPA activity seems more intense [142], but it did not reveal significant influence on glycemia or insulinemia in a wide cross-sectional study [94]. The strongest action in respect of carbohydrate metabolism comes from derivatives of 19-nortestosterone with residual androgenic action [7,142].

On the basis of the above summarized biological effects we can examine the consequences of progestogen addition on various clinical areas already taken into consideration as regards oestrogen therapy.

4.2. Cholelithiasis

There is insufficient data concerning possible progestogen interference on oral oestrogen-induced lithogenicity of the bile, which, as already stated, increases risk of cholelithiasis [7,96].

4.3. Cardiovascular diseases

Progestogen use, partly as a hepatocellular effect and partly as a direct effect, might oppose the benefits of oestrogens on cardiovascular risk [7,40]. It should not be forgotten that practically all data confirming this favourable action refers to women treated with CEE unopposed by progestogen. However, the small amount of epidemiological data available at present, from a small prospective study on MPA use [33] and two retrospective studies on use of 19-nortestosterone derivatives [122,144], appears to contradict apprehension [75]. Similar reassurance comes from cross-sectional data concerning the lipoprotein system, arterial pressure and carbohydrate metabolism in women treated with oestrogen (mainly oral CEE) alone or with progestogen supplement (mainly MPA) [94,145]. These data refer, of course, to cyclical use of progestogen, following the sequential scheme. Moreover, even if overall the data is enough to reduce the reservations advanced just a few years ago, it should not prevent choice of progestogens that both act satisfactorily on the endometrium and are free of potentially counterproductive biological effects.

Table 8 sets out the possible repercussions of oral progestogens on cardiovascular risk. The hepatocellular changes in the lipoprotein system and the alterations in carbohydrate metabolism, both potentially unfavourable, are described above; least effects are caused by progesterone and DYDR [7,142,143] and can probably also be expected from other preparations with similar metabolic activity. Another unfavourable action could work directly on the vessel walls and counteract the increased blood flow caused by the oestrogens; this type of action may be typical of all preparations, including natural progesterone [7,99,102]. The latter, however, seems to be capable of intervening favourably on the water-salt metabolism to counteract the tendency to increased blood pressure [146,147].

Until micronized progesterone (per os or by other administration routes) is available, the best preparations in terms of repercussions on cardiovascular risk appear to be those (DYDR etc.) closest to progesterone for metabolic consequences.

4.4. Bone metabolism

The progestogens, like progesterone, could act directly on bone tissue to produce

Table 8
Oral progestogens: clinical relevant effects on cardiovascular risk factors

	Potential influence on risk	19-nortesterone derivatives[a]	MPA[b]	DYDR[c] and others[d]	Micronized progesterone
Lipoprotein modifications	Increase	+	(+)	–	–
Influence on carbohydrate metabolism	Increase	++	+	(+)	(+)
Reduced blood flow	Increase	Possible	Possible	Possible	Possible
Influence on water-salt metabolism	Decrease		–		+

[a]With residual androgenic action.
[b]Medroxyprogesterone acetate.
[c]Dydrogesterone.
[d]Medrogestone, cyproterone acetate, 19-norprogesterone derivatives.

favourable effects, which could be synergic with those of oestrogens [114,148]. Nevertheless, it is felt that progestogen supplement can add little to the benefits for bone metabolism offered by oestrogens [124,149].

4.5. Breast cancer

Even if the available epidemiological data is inconclusive [150], some studies suggest that the addition of progestogens to oestrogen replacement treatment may increase breast cancer risk above that associated with exposure to oestrogens alone [150,151]. A directly stimulating action of progestogen on breast tissue is possible [150,152,153], but still debatable [150,153,154]. As mentioned, some progestogens with greater hepatocellular strength (especially the old derivatives of 19-nortestosterone at relatively high doses) oppose the oral oestrogen actions potentially protective to the breast, i.e. the SHBG serum level increase and, probably, the circulating IGF-I activity reduction. As a consequence, those progestogens could indirectly produce an unfavourable action for the breast [91,155]. The greater or lesser frequency of use of those progestogens in different series could explain the difference in results from one epidemiological study to another [91]. For example, the study that produced the most discomforting data in relation to progestogen addition [156,157] was conducted in Sweden, where, as already mentioned, the most frequently used progestogens are derivatives of 19-nortestosterone such as norgestrel [125].

4.6. Endometrial cancer

Prevention of endometrial pathology, which may be induced by unopposed oestrogen stimulation, is the only reason for suggesting progestogen addition. The remaining reservations concerning reduction of oestrogen benefits for cardiovas-

cular risk and the uncertainty of a possibly increased risk to the breast suggest avoiding the use of progestogens in patients with hysterectomy; this was the recommendation made in 1988 by a Consensus Conference [124]. For non-hysterectomy subjects the Conference recommended, as a rule, to follow the sequential scheme, administering progestogen for 10–12 days per month.

As variations of this scheme, two contrasting lines of tendency have been suggested for several years, both of them, for the moment, to be followed only within a framework of controlled clinical studies.

The first line, consisting of continuous, combined administration of both oestrogen and progestogen leading to endometrial atrophy in order to minimize bleedings, has already been the subject of numerous publications [7,130,158–160]. It overlooks the reservations about the consequences of some progestogen for cardiovascular risk and for the breast. It should be noted that with suitable preparations and dosages, e.g. MPA 5 mg/day, no unfavourable influences on the lipoproteins have been shown [159], and better results could be obtained with other preparations, such as cyproterone acetate or DYDR [7]. Nevertheless the limited importance increasingly placed these days on the role of lipoprotein changes in explaining the mechanism of oestrogen cardiovascular protection [75], together with the relevance given to other, not yet fully explained action modes that could be opposed by progestogen, demand a certain caution. An approach that is similar to the 'continuous combined' regimen in desired results (endometrial atrophy and absence of bleeding), but without reservations, in as much as the progestogen action is mainly local, is that of oestrogen treatment opposed at the endometrial level with a progestogen intrauterine device [161,162].

The second line of tendency, which is to return to oestrogen therapy unopposed by progestogen, including non-hysterectomized women, arises from an overreaction to the apprehensions mentioned above and is prompted by the opinions of internists, lipidologists and epidemiologists on the basis of low mortality caused by endometrial adenocarcinoma [130]. This is obviously an unjustified line, and in fact the Consensus Conference on progestogen use [124] considers the approach of oestrogen alone in non-hysterectomized women only in exceptional circumstances, e.g. in the case of total intolerance to progestogens or in clinical prospective studies, providing adequate information to the patient and a careful follow-up, both during therapy and long after. Here it should be noted that the risk of developing endometrial cancer remains increased for more than 10 years after the completion of non-progestogen-opposed therapy, even if the treatment is relatively short-term (1–3 years) [7,130]. In addition, there are unacceptable rates of morbidity (irregular bleeding) and surgery (from diagnostic therapeutic curettages to hysterectomies) due to unopposed endometrial stimulation [163].

Of the progestogens that are substantially free of metabolic actions, cyclically administered MPA has been confirmed as capable of compensating oestrogen-induced risk of endometrial cancer [33,45,47]. However, thorough studies applying biochemical as well as histological tests (DNA synthesis, nuclear receptors for oestradiol, oestradiol-dehydrogenase) showed that action of MPA on the oestrogenized endometrium is less than optimal [164,165]. Micronized progesterone and DYDR have also been thoroughly evaluated by the above-mentioned tests [166,167].

Micronized progesterone 200 mg/day was found to induce significant biochemical and morphological effects on the oestrogenized endometrium [166]. DYDR 5 mg/day showed a less than optimal response, while 10 mg doses showed effects similar to those seen in the secretory phase of an ovulatory cycle [167]. The efficacy of DYDR, especially at a 20 mg/day dose but also at 10 mg/day, in opposing endometrial stimulation by oestrogen (CEE 1.250 mg/day) was reconfirmed recently by Whitehead's group [168]. Of the progestogens that are free of metabolic actions, DYDR has the best-documented endorsement as to endometrial action.

5. Conclusion

Certainty and trust in long-term oestrogen therapy come from the important American epidemiological studies, which refer mainly to the use of oral CEE unopposed by progestogen. This is true for the highly important findings on protection against fractures from osteoporosis [24–28] and against cardiovascular disease [35–40] and on the rather limited risk of carcinoma of the breast, which can be seen only after 10–15 years of therapy and/or with elevated doses [48,50].

Oral oestrogens, both because of the hepatic first pass due to their administration route and because of the biological characteristics of their constituents [68], produce marked hepatocellular effects. These include increase in renin substrate, HDL-cholesterol and triglycerides levels [68]. Despite a certain amount of continued debate about the role and clinical consequences of the last of these [52,72,75,98], there can be no doubt that the overall biological picture induced by oral oestrogen therapy is not counterproductive. This is emphasized by the fact that oral CEE significantly reduces the risk of cardiovascular disease even in the subjects most exposed, such as those with risk factors [53,108,109] or with proved coronary stenosis [52]. It should be mentioned that, nowadays, when looking at the benefits derived from oestrogen, there is a tendency to understate the aspect of lipid changes [75]. On the other hand, emphasis is placed on other effects, for example on blood flow in peripheral organs [7,75,99–102] (which, among other things, can oppose in most cases any tendency towards hypertension caused by increased renin substrate) or on the genesis of atherosclerosis [103,104] stemming from action on the vessel walls, probably largely direct [75,104], but perhaps also partly deriving from hepatocellular effects [104]. In addition it cannot be excluded that some hepatocellular actions of oral oestrogen, for example increased SHBG levels and reduced circulating IGF-I activity, can offer protection to the mammary gland and help limit risk to the breast [90,91].

Until epidemiological data becomes available on the consequences of parenteral oestrogen administration, it seems wise to promote the old oral preparations as a general policy, at least for long-term treatment (more than 2–3 years). Parenteral long-term administration would seem to be the option for women showing particular indications for replacement therapy (e.g. confirmed risk of osteoporosis) and at the same time contra-indications to oral oestrogen, such as pre-existence or appearance of disorders of the gastro-enteric system (cholelithiasis, gastric intolerance, etc.) or of hypertension or hypertriglyceridemia.

Progestogen should, as a rule, be administered sequentially in non-

hysterectomized women, giving priority to preparations, such as progesterone or DYDR, that feature good endometrial activity [166–168] together with absence of major metabolic actions that are either potentially harmful (e.g. on carbohydrate metabolism) and/or capable of opposing oestrogen hepatocellular effects [7,71,91,132,135–138,142,143].

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