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M. L'Hermite

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REVIEW

Bioidentical menopausal hormone therapy: registered hormones (non-oral estradiol ± progesterone) are optimal

M. L'Hermite

Service de Gynécologie-Obstétrique, CHU Brugmann, Université Libre de Bruxelles, Bruxelles, Belgium

ABSTRACT

The many advantages of registered bioidentical sex hormones over registered, conventional, non-bioidentical menopausal hormone therapy (MHT) are considered. The transdermal route of estrogen administration avoids excess venous thromboembolic and ischemic stroke events. There is some indication that conjugated equine estrogens are more thrombogenic and most likely induce some hypertensive responses; estradiol might also be superior to conjugated equine estrogens (CEE) in terms of global cardiovascular health. The most valid evidence presently suggests that CEE-only treatment does not increase the risk of breast cancer and even may reduce it. But its combination with a synthetic progestogen (mainly medroxyprogesterone acetate) is a critical issue since it seems to be primarily associated with an increased incidence of breast cancer, however similar to or lower than that associated with some common lifestyle factors. Though not yet proven in a randomized, controlled trial, MHT continuously combining oral micronized progesterone with transdermal estradiol can presently be considered as the optimal MHT. It is not only safer than custom-compounded bioidentical hormones but also than oral conventional MHT and has the best breast profile; registered products for such optimal MHT are available around the world and must be preferred.

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Introduction

Lead Women's Health Initiative (WHI) investigators presently claim 'that MHT [menopausal hormone therapy] can safely be used for treatment of vasomotor symptoms by healthy women at low baseline risk for CVD [cardiovascular disease] and breast cancer'[1,2]. As far as cardiovascular risks are concerned, the WHI studies suggested that MHT initiation before 60 years of age (or less than 10 years after menopause) may be beneficial, especially without addition of medroxyprogesterone acetate (MPA) to conjugated equine estrogens (CEE)[3]. In the WHI CEE-only study, after a median 7.2 years of use and a total cumulative follow-up of 13 years, the decreased breast cancer risk observed during treatment[4] persisted[1]. On the other hand, in the WHI CEE + MPA study, after a median 5.6 years of use, the increased invasive breast cancer incidence observed during treatment[5] persisted after a total cumulative follow-up of 13 years[1]. All these data from randomized controlled trials (RCTs) exclusively concerned oral use of CEE with or without MPA, but many other observational studies have strongly suggested the superiority of an optimized MHT combining micronized progesterone and transdermal estradiol, as previously reviewed[6,7]. Misinterpretation and abusive generalizations of the initial WHI CEE + MPA results[8] led to MHT demonization by the lay press and the public, as well as by many physicians. Together with restrictive recommendations by regulatory authorities and very cautious guidelines by scientific societies, it led to unjustified use of custom-compounded bioidentical hormones. In the first part of the present invited review, the potential unspecific harms of custom compounding were described, as well as the more specific potential harm of increased endometrial cancer risk due to improper estrogen/progestogen balance in custom-compounded MHT[9]. In the present follow-up paper, we review the many advantages of using a non-oral (e.g. transdermal) route of estrogen administration, as well as using bioidentical ('natural', though chemically produced from vegetable raw material in monitored facilities) sex hormones (e.g. estradiol and progesterone). Let us already emphasize that, in most countries, registered products are available for the purpose of such optimal MHT, although until now almost never in a single product combining both estradiol and progesterone.

Advantages of bioidentical over other sex hormones

Estradiol

CEE are derived from the urine of pregnant mares; it is a complex mixture of mostly estradiol (sulfate), estrone and also of potent equine estrogens, androgens and progestogens that evidently are not natural to humans[10]. Though CEE manufacturing is closely monitored, slight variations in composition may occur, whether of any clinical relevance

CONTACT Professor M. L'Hermite marc.lhermite@chu-brugmann.be Service de Gynécologie-Obstétrique, CHU Brugmann, Place Van Gehuchten 4, B-1020 Bruxelles, Belgium

or not. Oral estradiol is mostly converted into estrone after digestive absorption. Thus oral CEE, already rich in estrone, will lead to disproportionate higher blood levels of estrone, which has roughly half the biological activity of estradiol. It can, however, exhibit discrepant effects (such as being more thrombogenic), leading to additional problems, especially in pathological conditions.

Generally, the more potent equine estrogens present in CEE result in greater stimulation than estradiol, of hepatic synthesis of estrogen-inducible products, with resulting favorable and mostly unfavorable effects. For example, increases in sex hormone binding globulin, a good indicator of hepatic stimulation, were more than double in users of CEE (0.625 mg/day) than in users of estradiol (1 mg/day)[11].

In vitro, in human breast tumor cell line MCF7, metabolites of equilin (about 22% of the total content of CEE) exhibited cytotoxic properties with carcinogenic potential[12]. In animals, only estradiol increased platelet RNA and secretion of the vasodilator nitric oxide[13].

Because of all these data, it would seem more appropriate preferentially to use estradiol, the 'natural' bioidentical estrogen, rather than a complex mixture of more than 200 steroids, of which some are specific to horses, not physiologically present in humans and can have unknown properties.

Gallbladder disease and cholecystectomy

In the Million Women Study (MWS) cohort[14], the risk of gallbladder disease was somewhat greater (heterogeneity $p \leq 0.001$) in users of CEE (relative risk (RR) 1.79; 95% confidence interval (CI) 1.72–1.87) than of estradiol (RR 1.62; 95% CI 1.54–1.70). In the Etude épidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort[15], on the contrary, the sensitivity analysis (restricted to women exposed to only one type of MHT) showed similar risks of cholecystectomy in users of unopposed oral estradiol (adjusted hazard ratio (HR) 1.83; 95% CI 1.18–2.86) and in users of unopposed oral CEE (adjusted HR 1.90; 95% CI 1.17–2.11). But, in the latter study, the risk was significantly greater ($p = 0.01$) in unopposed oral CEE than in oral CEE + progestogen users, while such a possible protective effect of the added progestogen was not observed compared to unopposed oral estradiol ($p = 0.2$); conversely, the cholecystectomy risk of combined estrogen/progestogen (E/P) users appeared similar to that of never-MHT users, regardless of the many types of comparison and of adjustment performed[15].

Estrogens, blood pressure and stroke

Though MHT effects upon blood pressure remain somewhat controversial, it is admitted that more than 5% of CEE users exhibit a hypertensive response considered 'idiosyncratic', while most studies have shown a trend towards reduced blood pressure with estradiol[16], especially for transdermal estradiol[17]; however. it can vary with respect to age[18]. High blood pressure has a critical impact on stroke risk (a five-fold increase for blood pressure values $\geq$160/100 mmHg). In patients pharmacologically treated for hypertension, more than 90% of strokes occurred in those with uncontrolled blood pressure[19]. Similarly, an increased stroke risk was evidenced in hypertensive (but not in normotensive) women under MHT (almost exclusively oral estradiol combined with norethisterone acetate (NETA), only 0.4% being CEE users)[20]. Furthermore, in the observational WHI study, it appeared that oral estradiol might be associated with a lower stroke risk (HR 0.64; 95% CI 0.4–1.02) than oral CEE[21].

Estrogens and hemostasis

The prothrombotic global hemostatic profile was greater in women treated with CEE than with estradiol, independently of estrogen dose as well as of MPA use (in 27%)[22]. Since a significant correlation between estrone levels and peak thrombin generation (a global marker of hypercoagulability) had been evidenced[23], this greater thrombotic risk from CEE might be due to its considerable content of estrone, in spite of some conversion of oral estradiol into estrone. There are also scarce but convincing data suggesting that some combined E/P associations may be more thrombogenic than estrogens alone, and CEE more than estradiol. Thus significantly greater venous thromboembolic (VTE) risks (RR 2.08; 95% CI 1.02–4.2; $p = 0.045$) and possibly myocardial infarction risks were observed in CEE than in estradiol users[24]. Furthermore, combining reliable Finnish Registers (the nationwide Prescription Register and the National Causes of Death Register), it has been evidenced that estradiol-based MHT was accompanied by reduced coronary heart disease (CHD) mortality rates, whatever the time of MHT initiation (even after age 70 years, but the earlier the initiation the greater the risk reduction), as well as the addition of a progestogen (48% used NETA and 35% MPA)[25].

Global cardiovascular health

Recent RCTs[26,27] have shown that, in women having initiated MHT soon after menopause, not only estradiol users gained global cardiovascular benefit (such as in the CEE-only WHI RCT) but also estradiol/progestogen users (contrary to CEE + MPA WHI users). It is noteworthy that these RCTs used estradiol and not CEE, although combined with another progestogen – oral NETA[26] or vaginal progesterone[27]. Indeed, such cardioprotection (and reduced overall mortality) was finally evidenced in the CEE-only arm of the WHI trial[3], while all-cause mortality remained unaffected in both arms[1]; in the combined WHI arm, MPA apparently concealed the favorable CHD effects, suggesting an impact of the type of progestogen used.

Progesterone

Let us first emphasize the many advantages of progesterone over most synthetic progestogens (especially MPA), as previously outlined[6]. For example, MPA (but not progesterone) counteracts almost all beneficial effects of estrogens on endothelial function, coronary and cardiovascular systems, lipidic profile, carbohydrate metabolism, insulin resistance and diabetes mellitus. Furthermore, progesterone exhibits a

specific anti-hypertensive activity[28] that also could contribute to its favorable cardiovascular activity.

Though progestogens are usually considered to be devoid *per se* of any thrombogenic activity, several reports strongly suggest that the type of progestogen is important since some of them apparently exacerbate the thrombogenic effects of oral estrogens on VTE risk[29] and probably even on stroke risk[30]. But it is not the case for micronized progesterone, although stratification according to the type of progestogen used in combination with estradiol has not been done separately for oral and transdermal estradiol users[30,31].

In the MWS cohort, addition of a progestogen (MPA, NETA or norgestrel) did not significantly modify the increased risks of gallbladder disease and cholecystectomy[14]. On the contrary, in the E3N cohort[15], opposed MHT (the majority used micronized progesterone) failed to modify cholecystectomy risk, whatever the route of estradiol administration (oral or transdermal).

Another clinical advantage for most women is that oral (but not vaginal) micronized progesterone is lightly sedative and thus improves falling asleep when given at bedtime; it may also restore disturbed sleep[32].

Breast cancer and the progestogen in MHT

It should be recalled that, in the WHI CEE + MPA arm, the claimed increased risk in breast cancer incidence[8] was not significant (adjusted 95% CI 0.83–1.92). On the contrary, in the CEE-only arm, there was a tendency for a reduced breast cancer risk, particularly in highly compliant women (i.e. having used more than 80% of their medication)[4]. Most observational studies, however, could not evidence such reduced breast cancer risk. Such possible protective effect could be related to a time gap effect, making estrogens apoptotic in prior estrogen-deprived women[33,34]. Seven scientific societies, USA and international, endorsed in 2016 the following revised global consensus statement: 'The risk of breast cancer in women over 50 years of age associated with MHT is a complex issue … [it] seems to be primarily, but not exclusively, associated with the use of a progestin … [and its] incidence of <1.0 [case] per 1000 women per year of use … is similar or lower than the increased risk associated with common factors such as sedentary lifestyle, obesity and alcohol consumption'[35]. As far as breast cancer incidence is concerned, at least two recent observational studies (in France and UK, respectively) similarly reported a lack of increased breast cancer risk from estrogen-only use[36,37]; in the E3N cohort, however, it was indeed the case for overweight and obese women (body mass index (BMI) $\geq 25\,kg/m^2$) but not for current long-term (>5 years) normal-weight (BMI $<25\,kg/m^2$) users (HR 1.33; 95% CI 1.02–1.72)[36]. Furthermore, in a Finnish nationwide comparative study, breast cancer mortality was reduced in all MHT users (almost exclusively estradiol, <1% being CEE users), the reduction tending to be larger in estrogen than in E/P users[38], the progestogen being primarily NETA or MPA.

Moreover, all progestogens appear not equal with respect to breast cancer risk; progesterone is quite neutral to the breast, as judged from accumulated experimental data that were previously reviewed[6,7] and from the E3N cohort. MPA specifically[39] and possibly most other synthetic progestogens (when associated with estrogen), can be mitogenic to the breast. For example, CEE + MPA (but not transdermal estradiol + micronized progesterone) significantly increased ($p = 0.003$) normal breast cell proliferation, as evidenced by Ki-67 positivity and mRNA levels[40].

The last report of the E3N cohort[36], specifically oriented towards breast cancer risk after MHT stopping, is puzzling due to subgroup analysis of breast cancer risk stratified by BMI and of combining users of progesterone and dydrogesterone; only the leaner patients (BMI $<25\,kg/m^2$) might be at slightly increased breast cancer risk during current MHT use but no longer after stopping, whatever the length of prior use ($\leq$ or >5 years).

Nevertheless, it can nowadays be accepted that MHT using micronized progesterone as the progestogen (when required) confers the best breast safety profile, even if the breast cancer risk might possibly become somewhat increased in the long term (after 5–10 years of utilization). The latter suggestion, however, comes from a subgroup analysis stratified according to the delay (gap time) from menopause onset to MHT initiation[41]. Although the published paper claimed that it concerns patients having initiated MHT <3 years from menopause, their initial categorization (as found in Appendix Table A2 in that paper) shows that, in fact, it concerned only patients having initiated MHT <1 year from their final menstrual period and that it did not concern women with a gap time between 1 and 3 years (no significant *p* trend for this latter group) (http://ascopubs.org/doi/full/10.1200/JCO.2008.21.6432). Therefore, their finding should be confirmed and it should be substantiated whether progesterone really modulates in any way the long-term estrogenic effect before drawing any firm conclusion and recommendation.

Transdermal estradiol administration: advantages

Quite a number of advantages of this route have been previously described[6,7], such as in regard to fasting glucose, insulin resistance in women with metabolic syndrome and even in diabetics; blood pressure can also benefit. A lower myocardial infarction rate has been reported in a large Scandinavian register database[42], as well as lower rates of overall cardiovascular diseases (including VTE and stroke) in a large matched-cohort study based on 'real-world' data (US insurance companies)[43].

Venous thromboembolic events

Oral estrogens indisputably bear an increased risk of VTE events, mostly during the first year(s) of use. As a matter of fact, it is the only risk that remained statistically significant in WHI studies after proper adjustment (such as by the Bonferroni correction) for the number of parameters studied (for seven of them, the significant threshold becomes 0.007 instead of 0.05). Any systemic non-oral route avoids the 'first-pass effect' and thus will minimize estrogenic liver impact

that stimulates the coagulation cascade (including thrombin generation and resistance to activated protein C), leading to increased VTE risk. All studies after the Estrogen and THromboEmbolismRisk Study group (ESTHER)[44] have confirmed that this thrombogenic effect of oral estrogens can be avoided by its administration through the skin (but it would probably be similarly safe through the vaginal mucosa), as recently extensively reviewed[45] and commented[31]. The results of one of these studies[46], using the UK General Practice Research Database (GPRD), are summarized in Table 1. It clearly shows that the dose–effect relationship well recognized for oral estrogens does not apply to transdermal estradiol. Moreover, as reviewed in reference[47], transdermal estradiol also does not confer any additional VTE risk in women at high risk such as from obesity, prothrombotic mutations and a personal VTE history. Therefore transdermal estradiol is not contraindicated in these patients who thus may benefit from MHT if required.

Ischemic stroke

Although somewhat different in premature ovarian failure, an association between MHT and the occurrence of ischemic stroke in postmenopausal women is now widely admitted[48]. In young postmenopausal women, ischemic stroke related to MHT could partly be of thrombogenic rather than of atherogenic nature[49]. On the contrary in older women, it is considered to result mainly from atherosclerosis, through destabilization and rupture of established plaques; this event occurs in part via matrix metalloproteinases (such as MMP-9) that are increased by oral estrogens but not by transdermal estradiol[50,51]. Both mechanisms can explain why and how transdermal estradiol would not increase ischemic stroke risk, contrary to oral estrogens. Indeed, two large, nested case–control studies reported no increased ischemic stroke risk in transdermal estradiol users, as compared to non-users and contrary to oral estrogens users; one utilized the UK GPRD study[52] and the other the National Health Insurance database and National hospital data for all French women aged 51–62[30]. Table 2 describes and compares the results of these studies, which are in general agreement despite different stratification of the estrogen dose. A strong dose–effect relationship of oral CEE, apparently not related to the timing of MHT initiation, had already been reported in the Nurses' Health Study observational study[53]. In transdermal estradiol users, such a dose relationship was suggested in the GPRD study but not found in the French one (Table 2)[30].

Table 1. Relative risks (RR) of thromboembolic accident in users of menopausal hormone therapy (estrogens-only and combined estrogen–progestogens) according to the route of estrogen administration. Adapted from Renoux *et al.* (*J Thromb Haemost* 2010;8:979–86).

Route of estrogen administration	*Daily estrogen dose*	*Relative risk (95% confidence interval)*
Oral	Low (<0.625 mg CEE or <2 mg E2)	1.19 (1.04–1.35)
	Standard (0.625 mg CEE or 2 mg E2)	1.55 (1.45–1.65)
	High (>0.625 mg CEE or >2 mg E2)	1.84 (1.63–2.09)
Transdermal	Patches ≤50 µg	0.99 (0.87–1.12)
	Patches >50 µg	1.05 (0.81–1.36)

CEE, conjugated equine estrogens; E2, estradiol

Gallbladder disease and cholecystectomy

Oral estrogens increase biliary cholesterol and saturation, promote its precipitation in the bile and also reduce gallbladder mobility, all contributing to gallstone formation. This is not the case with transdermal estradiol which bypasses the liver. In the large prospective MWS cohort[14], similarly to other reports, a dose-related increased risk of hospital admission for gallbladder disease was found over a 5-year period in oral MHT users but much less in transdermal estradiol users; these results are summarized in Table 3.

Considering only surgically treated gallstone disease, the E3N cohort study[15] similarly reported a greater cholecystectomy risk in MHT users, restricted to unopposed oral therapy (adjusted HR 1.38; 95% CI 1.14–1.67); they reported no increased risk with transdermal estradiol use (adjusted HR 1.01; 95% CI 0.94–1.10), whether unopposed or opposed.

Bone health

Only oral CEE, as demonstrated in the WHI studies, have been definitely shown to reduce fracture risk, even in non-osteoporotic women[54,55] but there presently does not exist any clinical trial assessing the impact of transdermal estradiol

Table 3. Relative risk (RR) of hospitalization for gallbladder disease (including cholecystectomy) in actual users of menopausal hormone therapy, according to the route of estrogen administration, compared to never-users. Adapted from Liu *et al.* (*Br Med J* 2008;337:a386).

Route of estrogen administration	*Duration of estrogen use (years)*	*Cases/controls*	*Relative risk (95% confidence interval)*
Oral	6.6	6914/263 871	1.74 (1.68–1.80)
Transdermal	7.2	1249/60 247	1.17 (1.10–1.24)

Table 2. Relative risks (RR) or odds ratios (OR) of ischemic stroke from menopausal hormone therapy (estrogen-only and combined estrogen–progestogens) according to the route of estrogen administration and to the dose administered. Adapted from Renoux *et al.* (*Br Med J* 2010;340:c2519) and from Canonico *et al.* (*Stroke* 2016;47:1734–41).

	Renoux et al., 2010		*Canonico et al., 2016*	
Route of estrogen administration	*Dose*	*Adjusted RR (95% CI)*	*Dose*	*Adjusted OR (95% CI)*
Oral	≤0.625 mg CEE or ≤2 mg E2	1.25 (1.12–1.40)	≤1 mg E2	1.39 (1.00–1.99)
	>0.625 mg CEE or >2 mg E2	1.48 (1.16–1.90)	1.5 mg E2	1.84 (1.02–3.30)
			≥2 mg E2	2.41 (1.43–4.07)
Transdermal	≤50 µg	0.81 (0.62–1.05)	<50 µg	0.69 (0.37–1.28)
	>50 µg	1.89 (1.15–3.11)	50 µg	0.79 (0.40–1.58)
			>50 µg	0.88 (0.57–1.37)

CEE, conjugated equine estrogens; E2, estradiol

on fracture risk. However, as reviewed, numerous studies have consistently demonstrated bone mineral density (BMD) maintenance and improvement among transdermal estradiol users[56]. Since the Food and Drug Administration (FDA) admits BMD as an accurate surrogate for fracture risk prediction, one can reasonably consider that transdermal estradiol will prevent fractures equally to oral estrogens. Furthermore, even very low doses (0.014 mg/day) of transdermal estradiol, as compared to placebo, over 2 years increased significantly ($p < 0.001$) more lumbar spine BMD (+2.6% vs. +0.6%) as well as total hip BMD (+0.4% vs. −0.8%)[57]. It is noticeable that mean plasma estradiol levels increased in the estradiol group from 4.8 pg/ml (baseline) to only 8.6 pg/ml; these levels remained far below those usually found in the premenopause, as well as those traditionally considered to be necessary to treat climacteric symptoms.

Vaginal administration of sex steroids

Estradiol

Estradiol can be administered vaginally in the form of tablet, suppository, ring or even cream. Very low to low estradiol doses (7.5–25 μg/day) are sufficient to treat genitourinary symptoms[58] and should therefore be preferred, although registered products delivering higher doses remain available in some countries; used at doses >50 μg/day, the latter are also effective in relieving vasomotor symptoms. As reviewed by Santen[59], significant systemic absorption depends on the dose, type of delivery and degree of vaginal mucosa preestrogenization; chronic use leads to lower blood levels than acute. Systemic effects can be produced, even with a 7.5-μg vaginal ring or a 10-μg tablet. The local biological effects clearly predominate over systemic effects but risks of endometrial hyperplasia and cancer have not been thoroughly evaluated, especially in the long term (no safety data available for use longer than 1 year, as reported in a systematic review)[60], despite some evidence of a preferential absorption into the endometrium[61]. For low-dose estrogen vaginal administration, it is customary not to recommend progestogen supplementation but an elevated endometrial cancer risk (RR 1.96; 95% CI 1.77–2.17) has been reported in a large Danish cohort[62]. Unopposed vaginal estradiol may thus warrant endometrial echographic monitoring, while any case of vaginal bleeding requires thorough evaluation. Though admitted by some societies, low-dose vaginal estradiol could be hazardous in breast cancer survivors. Indeed, even the low estradiol blood levels arising from low-dose vaginal estradiol could still exhibit some cardiovascular protection, as evidenced by a decreased risk of coronary heart disease and stroke death in a large Finnish cohort[63].

Conjugated equine estrogens

Conjugated equine estrogens remain available in some countries in the form of a cream that delivers greater estrogen doses than necessary to treat genitourinary symptoms. Since it is widely recommended to use the smallest effective dose in this indication, it should not be used chronically for atrophic vaginitis. A recently updated Cochrane review[64] concluded to a low-quality evidence of increased endometrial thickness for CEE cream users compared to estradiol ring users; the authors attributed this difference to higher estrogen doses used in the cream but it could also be attributable to the difference in the estrogen used. In this review, the authors recall that its 2006 update reported evidence of more incidents of vaginal bleeding from use of CEE cream. Similarly, an open-label randomized study comparing use for 24 weeks of vaginal estradiol tablets (25 μg daily) vs. vaginal CEE cream (2 g daily =1.25 mg CEE, a higher dose than usual in clinical practice) showed a significant ($p < 0.001$) greater proportion of patients with increased estradiol levels above the normal postmenopausal range (>49 pg/ml) in the CEE group; in the latter group, more patients had signs of endometrial proliferation (including hyperplasia)[65].

Estriol

Vaginal estriol is quite efficient in treating the genitourinary syndrome of menopause. Recent RCTs have demonstrated its superiority over placebo at ultra-low vaginal doses of 20–50 μg[66–68]. It has previously been recalled[9] that estriol is considered as a weak estrogen (lower affinity and shorter binding time to the estrogen receptor) devoid of any stimulatory effect on breast and endometrium at classical doses. Thus, wherever registered estriol medications are available, they could be considered to treat genitourinary syndrome of menopause instead of estradiol, preferably at low to ultra-low doses. Similarly, it could be acceptable to use vaginal low-dose estriol in custom-compounded hormone therapy despite the presently negative FDA advice, considering its efficacy and apparent safety. Notice that registered vaginal estriol preparations have been widely available and utilized in this indication since the 1950s in Europe and many countries round the world.

At comparable low doses, vaginal estriol probably would appear to be even less risky than estradiol for cancer survivors, although this is purely conjectural.

Progesterone

As reviewed[69], vaginal progesterone administration is quite attractive since there apparently occurs a so-called uterine first-pass effect for progesterone[70], as shown for estradiol. Even micronized progesterone can be used vaginally and all preparations provide a relatively sustained absorption with higher blood concentrations than by the oral route.

In a 3-year prospective study, in which 30 women received transdermal estradiol gel and vaginal 100 mg progesterone capsules every other day, endometrial histology showed atrophy in all cases and amenorrhea was achieved in 92.6% of cycles[71]. It seems possible to reach high local concentrations in the uterus with less systemic distribution of the hormone by use of a continuous low-dose progesterone administration through a vaginal ring[72], with satisfactory endometrial protection in this pilot study. A new vaginal insert delivering effervescent micronized progesterone (100

and 200 mg twice daily) provided rapid progesterone absorption and ten times higher endometrial tissue concentrations[73], with lower systemic progesterone levels than after intramuscular administration in oil, although the latter route of administration leads to excessive blood levels.

There is good evidence to consider that vaginal progesterone (even off-label, but it is registered in many countries as vaginal gel or tablets) could satisfactorily protect the endometrium, but only few epidemiological data are available. Micronized progesterone can be used vaginally in women suffering from excessive sedation with oral micronized progesterone, though it very seldom occurs at doses of 100–200 mg daily.

Dehydroepiandrosterone

Only one significant benefit of dehydroepiandrosterone (DHEA) has emerged – improvement of vaginal atrophy when vaginally administered[74]. Thus, postmenopausal women with moderate to severe dyspareunia or pain at sexual activity benefited significantly from daily administered 6.5 mg vaginal DHEA for 12 weeks[75]. Like the oral route, it should be devoid of any noxious effect and thus could probably be safely used for treatment of genitourinary syndrome of menopause. It probably would be clinically much more easy than the recently introduced selective estrogen receptor modulator ospemifene[76]; it would bring about less potential problems than estriol and a registered product will become available since it has recently been approved by the FDA.

Testosterone

In a small and short RCT, topical testosterone propionate cream (300 μg daily) induced a significant improvement in vaginal trophism in women with vaginal atrophy[77]. It, however, seems completely illogical, for this indication, to prefer testosterone (with proven undesirable side-effects) over (or even to combine it with) other steroids.

Conclusion

The administration of the 'natural', body-identical, sex hormones (estradiol and progesterone) seems definitely to bear some advantages over other hormonal products with diverse biological activities, such as synthetic progestogens and, on the other hand, conjugated equine estrogens, a complex mixture of human and equine sex steroids. Furthermore, a more physiological route of estradiol administration (namely systemic rather than oral) eliminates the increased risks of VTE, ischemic stroke and gallbladder events that result from oral estrogens.

Indeed, pending a clear and definite demonstration in RCTs, MHT combining transdermal (or percutaneous) low estradiol doses together with micronized progesterone would appear to be optimal, conferring a very good risk–benefit balance: decreased overall and cardiovascular mortality, improved quality of life and fracture prevention, without any increased risk of thromboembolic events, ischemic stroke, gallbladder disease and probably breast cancer. This favorable risk–benefit balance is illustrated in Figure 1, published already in 2013 in a previous paper[7]. It certainly might allow its continued use for long periods, including for fracture prevention, now that there no longer exists any injunction mandatorily to stop MHT after 60 or even 65 years of age. This MHT could also be optimal for symptomatic patients with various health risk factors such as risk factors for venous thromboembolism and ischemic stroke, hypertension, diabetes mellitus, metabolic syndrome, obesity, smoking, and especially for (very) elderly people[7]. We also could call it again hormone replacement therapy.

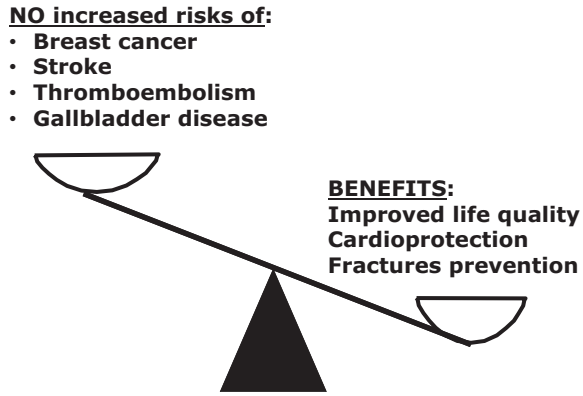

Figure 1. Risk–benefit balance for symptomatic women treated with an optimized hormone replacement therapy delivering estradiol by the transdermal route, in combination, if appropriate (women with an intact uterus), with micronized progesterone as the progestogen required for endometrial protection. This ratio remains favorable in asymptomatic women despite the lack of improved quality of life. From L'Hermite (*Climacteric* 2013;16(Suppl 1):44–53).

Furthermore, despite some remaining negative opinions, some authors now consider that prevention of coronary heart disease should objectively be reconsidered as an indication for MHT, even in asymptomatic postmenopausal women, in addition to lifestyle changes[78,79].

Conflict of interest Lately M. L'H. has occasionally received consultancy honoraria and/or lecture fees from Besins Health Care International, TEVA and Merck/MSD.

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