Hormonal replacement therapy (HRT) in postmenopause: a reappraisal

Le traitement hormonal de substitution de la ménopause : réévaluation

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Abstract

Hormone replacement therapy (HRT) is the most effective treatment currently available for vasomotor and urogenital symptoms and decreased libido. Because harmful effects were evidenced in some clinical trials, health authorities now consider that risk-benefit considerations do not favour the use of HRT for prevention of cardiovascular diseases and bone fractures in postmenopausal women. However, experimental and clinical studies indicate that adverse effects of HRT may largely depend on the estrogen and progesterone/ progestin formulation, dosage, mode of administration, patient’s age, associated diseases, and duration of treatment. All estrogen formulations and modes of administration have similar beneficial effects on vasomotor and urogenital symptoms and on bone structure. But cardiovascular and invasive breast cancer risks are higher with oral estrogen than with transdermal estradiol, and also higher with many progestin compounds than with micronized progesterone. The combination of transdermal estradiol + micronized progesterone appears to be effective and relatively safe if elementary precautions are taken, and seems to be presently the best choice for HRT in most postmenopausal women. In the author’s — heterodox — opinion, HRT may also be a good therapeutic choice to prevent bone loss, since alternative medications, including raloxifene and bisphosphonates, may have dramatic harmful effects in some patients. It might also have beneficial effects on the development of coronary disease in young postmenopausal women. HRT requires careful adjustment to each individual patient and continuous monitoring of clinical evolution. In the future, this adjustment could benefit from genetic screening to maximize in each individual the ratio between positive and adverse effects.

Résumé

Le traitement hormonal de substitution (THS) est actuellement le traitement le plus efficace des troubles vasomoteurs et urogénitaux et de la diminution de la libido. En raison des effets indésirables observés dans certaines études cliniques, les autorités sanitaires estiment aujourd’hui que le THS est contre-indiqué pour la prévention des fractures et des maladies cardiovasculaires en postménopause. Cependant, les études expéri- mentales et cliniques indiquent que ces effets indésirables dépendent largement de la formulation des molécules (estrogènes et progestérone/progestènes), du dosage, de la voie d’administration, de l’âge des patientes, des pathologies associées et de la durée du traitement. Toutes les formulations estrogéniques ont des effets bénéfiques similaires sur les troubles vasomoteurs et urogénitaux, et sur la structure osseuse, quelle que soit la voie d’administration. Mais les risques de maladies cardiovasculaires et de cancers du sein sont plus élevés lorsque les estrogènes sont administrés par voie orale que par voie transdermique, et plus élevés aussi avec la plupart des progestènes qu’avec la progèstéronne micronisée. L’association estradiol transdermique et progestérone micronisée apparaît à la fois efficace et à moindre risque si l’on respecte certaines précautions élémentaires. L’auteur estime — opinion hétérodoxe — que le THS peut aussi constituer un bon traitement pour la prévention de l’ostéoporose, en raison des effets potentiellement dangereux des traitements alternatifs tels que raloxifène et bisphosphonates chez certaines patientes. Le THS pourrait également avoir des effets bénéfiques dans la prévention de pathologies cardiovasculaires chez des femmes récemment ménopausées. Le THS doit être soigneusement adapté à chaque cas particulier, et faire l’objet d’un suivi attentif. Dans un futur proche, ce traitement pourrait être ajusté selon la carte génétique des patientes.

Keywords: Menopause; HRT (hormone replacement therapy); Estrogens; Progesterone; Transdermal

Mots clés : Ménopause ; Traitement hormonal de substitution (THS) ; Estrogènes ; Progestérone ; Transdermique

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1. Introduction

Menopause is defined as the final menstrual period, resulting from the end of the ovarian activity. Diagnosis of menopause can be ascertained retrospectively after 12 months of amenorrhea. However, menstrual cycle and endocrine changes can already be observed prior to menopause, on average 12-24 months, with irregular cycles and increase in FSH levels. The primary basis of this evolution is oocyte/follicle depletion in the ovary. Peak oocyte complement (6-8 million) is observed during fetal life around week 20-22 of gestation. Thereafter, total oocyte count declines steadily to 1-2 million at the end of gestation, 300,000 to 500,000 at the onset of puberty, then drops exponentially to a few hundred by 50 years of age. Throughout reproductive life, only 400 to 500 oocytes are selected for ovulation. All other oocytes are lost by atresia, i.e. a genetically scheduled apoptotic process [1].

According to several epidemiologic studies, median age of natural menopause is presently estimated to be 51.3-51.4 years in Western countries. The timing of menopause is primarily genetically driven, although it may be modulated by environmental factors (for instance, menopause occurs earlier in lean than in obese women, and smoking lowers the age of menopause by 1-2 years [2]). Indeed, the age of natural menopause has changed little for the last 2,000 years and remained fairly constant from 1850 to the present [2], on the contrary of the menarcheal age, which fell by several years over the last 150 years [3]. During the last century, life expectancy in industrialized countries increased by about 30 years. For example, in France, life expectancy rose from 62 years in 1936 to 81 years in 1990 [2]. Thus, while at the beginning of the 20th century, most women survived only a few years to menopause, now a healthy woman is expected to spend nearly 40% of her life span in postmenopause [2]. Therefore, prevention and treatment of menopause associated clinical disorders progressively became a public health issue and, until the last decade, it was widely admitted that most postmenopausal women would clearly benefit from prolonged hormonal replacement therapy (HRT) with estrogens and progestins. Indeed, most of those disorders are likely to result, directly or indirectly, from the dramatic decrease in gonadal steroids levels after menopause.

However, HRT in postmenopausal women can hardly be considered as a physiological hormonal replacement therapy (except in premature ovarian failure resulting from surgical, vascular, infectious, autoimmune, toxic or iatrogenic pathological conditions). Indeed, natural menopause is not a pathological condition, but is part of the normal ageing process. Restoring in older postmenopausal women hormonal levels normally found in young menstruating women must be considered as a pharmacological treatment, susceptible to induce adverse as well as beneficial effects, according to the patient’s age, the compound used, its dosage, its route of administration and the duration of treatment. Not surprisingly, a number of studies have recently evidenced that potential risks could sometimes exceed expected benefits, leading European and U.S. health authorities to conclude — maybe too hastily — that risk-benefits considerations do not favour the use of HRT for prevention of chronic diseases associated with menopause.

In this paper, we will briefly review the clinical symptoms associated with menopause, as well as long-term consequences assumed to result from — or to be amplified by — the brutal drop in sexual hormone levels; review the physiological and pharmacological effects of estrogen and progestin compounds currently used in HRT; analyse the results of the major clinical trials of hormone therapy conducted over the last decade; and try to delineate a strategy regarding HRT in postmenopausal women. This review will be limited to estrogen and progestin therapy. Androgen therapy will be reviewed in another paper.

2. Major clinical features associated with menopause

Vasomotor symptoms. Hot flushes are a hallmark of the menopausal transition, experienced by 40 to 70% of postmenopausal women [4]. Hot flushes are transient and recurrent episodes of intense heat in the upper arms and face, frequently followed by profuse sweating, flushing of the skin, and chills. They may be accompanied by palpitations and anxiety. They are temporally related to secretory LH pulses (but not all LH pulses are accompanied by hot flushes). Night-time episodes are consistently associated with transient awakenings. Hot flushes appear to result from a deterioration of the central thermoregulatory mechanism, due to increased central noradrenergic activity and decreased endogenous opiates [5,6]. While the exact mechanism of those alterations is still unknown, appearance of hot flushes is clearly associated with the dramatic drop of estradiol levels observed at menopause. Hot flushes may cause considerable distress, fatigue, memory defects, irritability, acute physical discomfort, and therefore negatively impact the quality of life [7]. They usually regress five years after menopause, but may persist all life long [8].

Urogenital symptoms, resulting from atrophy of estrogen dependent mucosa, occur very early after menopause in up to 50% of menopausal women [9]. Vaginal dryness may cause dyspareunia and even bleeding during sexual intercourse. Urinary incontinence and recurrent urinary tract infections, causing discomfort in passing urine, may severely affect sexual, familial, social and professional life.

Depressed mood, including possible true depression, is a common complaint during the menopausal transition. The exact mechanism is not elucidated, but is probably related to the deprivation of sexual hormones availability at the brain level.

Sleep disorders are the most common complaints in postmenopausal women. They could result from estrogen and progestosterone deficit, since these hormones have sleep-promoting effects.

Libido: due to all those disturbances, libido is frequently decreased during the early post menopausal years. The importance of this trouble may also of course depend on the sexual partner. In return, this decrease of libido accentuates the vaginal dryness, resulting in a vicious circle.
Skin dryness and atrophy appear progressively and may cause itching.

3. Major long-term consequences of estrogen deficit

Cardiovascular disease. More than 30 years ago, epidemiologic studies suggested that endogenous estrogens have protective cardio-vascular effects. In the Framingham observational study, after adjusting for potential confounding factors, including age, the incidence of cardiovascular events was found to be markedly increased in postmenopausal women as compared to pre-menopausal women [10]. In another observational study, cardiovascular mortality in women over 65 years of age was inversely related to the menopause age [11]. Experimental studies indicate that those protective effects result from the action of estradiol on endothelial function [12-14]. Estrogen receptor has been evidenced in cultured endothelial cells [12], and apoptosis of endothelial cells is inhibited by estradiol [14].

Osteoporosis. Estrogen deficiency is always associated with bone loss and is a major cause of osteoporosis in postmenopausal women, resulting in vertebral and hip fractures. In premenopausal women, it has also been suggested that luteal defect could be associated with bone loss, but the evidence is still controversial.

4. Experimental studies with hormonal compounds currently used in postmenopausal HRT

For most endocrine glands, hormonal replacement is performed using only synthetic compounds structurally identical to native human hormones (thyroxine, hydrocortisone, etc.). This is -not yet- true for sex steroids, in particular for estradiol and progesterone.

4.1. Estrogens

For many years, conjugated equine estrogen (CEE), extracted from urine of pregnant mare, has been the estrogen compound most widely used for HRT in postmenopausal women. Thus, CEE is a mixture of at least ten very potent animal placental estrogens, including compounds present only during gestation. Actually, until recently, CEE was the only estrogen compound largely used for HRT in USA. Besides the potential risks linked to the purification process, biologic activity may vary from one batch to another. CEE is administered orally. More recently, synthetic estradiol was made available in Europe, and only lately in USA. This pure compound may be delivered by the oral, the transdermal (gel or patches), or the transnasal route, or as an implant. In France, transdermal gel and patches are now the most widely used way of estrogen administration in postmenopausal women.

Whatever the mode of treatment –oral or transdermal- and the compound used –CEE or estradiol-, estrogens are similarly effective to reduce circulating levels of LH and FSH, suppress hot flushes, relieve urogenital symptoms and prevent osteoporosis. However, experimental studies indicate that orally administered estrogens –but not transdermal estradiol- exert major pharmacological effects on hepatic protein synthesis, resulting in specific endocrine, metabolic and cardiovascular alterations as a consequence of the first pass hepatic action resulting in estradiol concentrations which are four to five times higher than in the systemic circulation [15]. Moreover, it remains to be investigated whether in some tissues, estradiol and CEE might not exert different, and possibly antagonistic, effects on estrogen receptors.

Somatotropic axis. Estrogen treatment in postmenopausal women exerts route-dependent effects on growth hormone (GH) and insulin-like growth factor-I (IGF-I) secretion. Different oral estrogen formulations induce a dose dependent decrease in IGF-I levels and a concomitant two to four fold increase in circulating GH levels [16]. The decrease in IGF-I concentrations is likely to result from estrogen inhibition of hepatic IGF-I mRNA generation, as demonstrated in the rat [17], while the concomitant elevation of GH levels is explained by reduced negative inhibition of pituitary GH by IGF-I. Very high doses of transdermal estradiol may also decrease IGF-I levels [18]. However, at doses habitually used in postmenopausal women, transdermal estradiol administration results in unchanged or slightly increased circulating IGF-I concentrations, without any change in GH levels [16,19].

Glucose metabolism. Estradiol increases insulin secretion and insulin sensitivity [20]. However, oral estrogen treatment may affect carbohydrate metabolism because elevated GH levels impair insulin action [21,22]. In contrast, insulin resistance is not observed under transdermal treatment.

Substrate oxidation. GH is known to regulate substrate oxidation and body composition [23–25]. When compared to transdermal administration, oral estrogen induces a greater suppression of lipid oxidation, resulting in a decrease in lean body mass and an increase in whole body fat mass [26]. These findings suggest that hepatic estrogen accumulation may direct fatty acids away from oxidative into lipogenic pathways.

Bone and connective tissues. The effects of estrogens on skeletal and connective tissues metabolism are route dependent. Under estrogen treatment, changes in biochemical markers of osteoblast function (osteocalcin and procollagen I) and fibroblast function (procollagen III) correlate positively with changes in circulating levels of IGF-I. Thus levels of those biochemical markers increase during transdermal as compared to oral estrogen administration [27].

Cholesterol and triglycerides. Both oral and transdermal estrogens increase HDL-cholesterol and decrease LDL- and total cholesterol, but those effects are more pronounced under oral treatment [28]. However, transdermal administration decreases triglycerides and increases the size of LDL-cholesterol particles, while oral formulation has opposite effects [28–31]. Thus, oral administration could actually reduce the antiatherogenic effects of estradiol.

Cardiovascular system. Numerous studies indicate that physiological parenteral replacement of estradiol in ovariec-
pendently of serum lipid patterns [32]. However, trials in oophorectomized monkeys showed coronary benefits only when hormonal therapy started shortly after menopause [35]. Vascular endothelial and smooth muscle cells contain estrogen receptors and it has been shown that estradiol inhibits smooth muscle cell proliferation and neointimal formation, reduces infarct size after induction of myocardial ischemia [36] and accelerates endothelial recovery after arterial injury [32–34, 37]. On the other hand, oral, but not transdermal, estrogens raise circulating levels of coagulation factors, decrease coagulation inhibitors [38–42], and increase C-reactive protein (CRP) levels, an excellent marker of cardiovascular morbidity [43–45].

**Breast.** The majority of breast cancers express estrogen receptors. In these cases, estrogens are likely to promote tumour growth. Moreover, in postmenopausal women, breast adipose tissue (and most breast carcinomas) acquire aromatase to synthesize estrone from circulating androstenedione. Estrone (and estrone sulfate) acts as a pool which can be converted as needed to the more active estradiol, which triggers proliferation of normal epithelial cells and progression of breast cancer cells [46]. Elevated aromatase levels in postmenopausal obese women are likely to explain the higher incidence of spontaneous breast cancer as compared with lean women [47]. In obese women, estrogen replacement therapy does not further increase aromatase levels and breast cancer risk [47]. In lean women, aromatase levels rise under estrogen treatment, increasing the estrone pool—especially when using the oral route [48]—and therefore possibly activating the proliferation of breast cancer cells [49]. Moreover, oral, but not transdermal, estrogens were found to activate the production of potentially toxic estradiol metabolites, particularly in smokers, thus further increasing the risk of developing breast cancer [50,51].

**Ovaries, uterus.** Estrogen receptors are present in ovarian and in uterine endometrial cells. Estrogens induce uterine endometrial hyperplasia and increase the risk of uterus and ovarian cancer [52].

**Nervous system.** A few studies suggest that estrogens may have protective effects on cognitive functions if treatment is started soon after the deprivation of ovarian steroids [53–55].

### 4.2. Progesterone and progestins

Besides synthetic progesterone, identical to the endogenous hormone, a large variety of progesterone analogues, referred to as progestins, are currently used. Most of them are derived from progesterone (19-norprogesterone derivatives) or from testosterone (19-nor-testosterone derivatives). The various molecules differ widely from each other in their chemical structure, pharmacokinetics, metabolism and potency. They all interact with the progesterone receptor, but most progestins also interact with other steroid receptors, such as the glucocorticoid, the mineralocorticoid and the androgen receptors [56]. For instance, medroxyprogesterone acetate (MPA), a widely used progestin, exhibits androgenic and glucocorticoid activity in addition to its progestogenic activity [57,58]. Because transdermal formulations provide insufficient concentrations, the oral route is mainly used in postmenopausal women. Vaginal, intra-uterine and intramuscular routes may also be used.

Progesterone and all progestin compounds prevent the elevated risk of estrogen-induced uterine endometrial hyperplasia and the risk of uterus and ovary cancer. Therefore, except in hysterectomized women, HRT always includes a combination of estrogen with progesterone or progestin. However, due to differences in the pharmacology of the molecules, progesterone and the various progestin compounds may exert different, and even opposite, effects in several tissues.

**Cardiovascular system.** In animal studies, progesterone, but not MPA, was found to restore the endothelial control of vascular tone in the mesenteric artery of ovariectomized rats [59]. Moreover, MPA was found to prevent the cardio protective and anti-inflammatory effects of estradiol [36,56,60], while drospirenone, a progestin derived from spironolactone, which closely matches the pharmacological profile of natural progesterone and has antimineralocorticoid and antiandrogenic potency [61–63], was reported to have beneficial effects [56].

**Breast.** In progesterone knockout mice, the mammary tumour incidence after treatment with a carcinogen was found reduced when compared to wild-type mice [64]. However, both in vitro and in vivo studies have shown that endogenous (in premenopausal women) and exogenous progesterone down-regulate estradiol receptors within normal breast epithelial cells and stimulate estradiol conversion to less potent estrone [46,65–67]. Thus, in normal human breast epithelial cells, progesterone inhibits the cell proliferation induced by estradiol [46,68]. Similarly, in breast cancer, progesterone was found to inhibit cell growth and promote apoptosis [69]. Moreover, a recent study in postmenopausal rhesus monkeys indicated that a combination of estradiol and progesterone did not stimulate breast epithelial proliferation [70]. On the contrary, androgenic progestins may up-regulate estradiol receptors. Norgestrel, norethisterone and MPA stimulate estrone conversion to estradiol [71]. In normal postmenopausal breast, MPA increases the cell proliferation induced by estradiol [70,72]. Combination of CEE and MPA was found to stimulate cell proliferation and inhibit apoptosis [73]. In monkeys, combination of estradiol and MPA was found mitogenic for breast cells [70].

**Bone.** Progesterone might stimulate bone formation [74], but so far there is no clear evidence for a significant bone-protective effect in postmenopausal women.

**Nervous system.** Progesterone regulates vital neuronal and glial functions and therefore exerts neuroprotective, neurotrophic and promyelinating effects. It might also revert age-dependent changes and dysfunctions [75]. On the contrary, MPA was found to exert damaging effects [75].

### 4.3. Tibolone

Tibolone is a synthetic steroid with weak estrogenic, progestogenic and androgenic properties, always administered orally. Tibolone has beneficial effects on hot flushes, vaginal
dryness and prevention of bone loss, and does not induce endometrial hyperplasia or carcinoma [76]. It was reported to inhibit smooth muscle cell proliferation [77] and might therefore exert a protective action against coronary heart disease [78]. Tibo-lone was reported to reduce mammary density, decrease proliferation and promote apoptosis of normal breast epithelial cells [73], and to inhibit invasion of human mammary cells in vitro [79], but was found to have no significant effect on the growth of human breast tumours implanted in ovariectomized nude mice [80].

4.4. Phytoestrogens

Phytoestrogens are plant-derived chemicals with estrogenic activity [81]. They are found in high concentrations in soy products and red clover (isoflavones), hop (flavonones) and also in fruits and vegetables (flavones, lignans, coumestans), or in grape skins and red wine (stilbenes). Those compounds, always administered orally, have weak estrogenic effects: their affinity for estrogen receptors is at least 1,000 to 10,000 times lower than that of estradiol. Since in some Eastern countries such as Japan, the incidence of breast cancer is about one-third that of Western countries, while the average daily intake of iso- flavones is three times higher, it has been suggested that phytoestrogens could represent a safe alternative to conventional HRT [81]. However, the overall evidence of experimental studies shows no consistent effects of dietary phytoestrogens on cell proliferation in normal human breast tissue, and indicates that those compounds might even stimulate proliferation of existing breast cancer [81]. It has been hypothesized that exposure to relatively high concentrations of phytoestrogens during gestation or early life might be more important in programming an individual’s risk to develop cancer [81]. Moreover, phytoestrogens extracts of soy and red clover appear to have little or even no effect on hot flushes [82,83]. Effects may differ according to the compound and the dose, and long-term deleterious effects cannot be excluded. Of major concern is the fact that phytoestrogens supplements are often considered as over-the-counter “natural” compounds: for women who do not find relief with recommended doses, it is easy and tempting to increase the dosage and achieve circulating concentrations that may have deleterious effects.

4.5. SERMs (selective estrogen receptor modulators)

Synthetic SERMs may act as estrogen agonists or antagonists, depending on the target tissue. They are administered orally. Tamoxifen acts as an estrogen antagonist in breast tissue and is therefore used for the adjuvant treatment of breast cancer, but it increases the risk of endometrial cancer. Ralox-ifene acts as an estrogen antagonist in the breast and the endometrium, and as an agonist on bone and lipid metabolism [84, 85]. It has no beneficial action on major subjective symptoms of menopause and was even found to increase the frequency of hot flushes, legs cramps and peripheral edema [86]. Other SERMs, with variable tissue specificity and potency, are currently under investigation.

5. Clinical trials

Clinical trials report either observational or prospective studies. Those (very) large scale field investigations try to assess the balance between beneficial and harmful effects of HRT in “real life” conditions. At first glance, the results of those trials appear inconsistent. However, those discrepancies result from considerable heterogeneity in their design, inclusion and exclusion criteria, compounds, doses and modes of administration. Actually, most results are in line with data obtained in experimental studies. In this section, we will briefly review the conclusions of major clinical trials published over the last decade.

5.1. Effects of HRT on cardiovascular system

Several studies have investigated the risk of coronary disease, ischemic stroke, and venous thromboembolism under HRT. Substantially lower coronary heart disease rates in postmenopausal women under estrogen, or estrogen + progestin, therapy had been reported in observational studies [87]. On the other hand, the WHI (Women’s Health Initiative) trial [88–91] was a prospective randomized, double-blind, placebo controlled study of CEE + MPA treatment involving a total of 16,608 postmenopausal women, aged 50–79 years (mean 63.3 years) at enrolment. BMI averaged 28.5 kg/m², and 45% of women had a BMI ≥ 30 kg/m². About 8% and 16% of patients included in the study reported previous history of cardiovascular attack and breast cancer, respectively. About 36% and 4% were treated for hypertension and diabetes, respectively. About one-half were current or previous smokers. Doses of CEE (0.625 mg daily) and of MPA (2.5 mg daily) were identical in all volunteers and kept constant throughout the trial. Under CEE + MPA treatment, the risks of fatal and non-fatal coronary heart disease [88], fatal and non-fatal ischemic stroke [89], venous thromboembolic disease (including pulmonary embolism) [88] were all significantly increased. Possible interaction between HRT and age or associated diseases was not assessed. The treatment was associated with elevated CRP levels, and high CRP values were associated with increased risk of coronary disease [90]. Interestingly, use or non use of HRT was less important as a predictor of cardiovascular risk than did baseline CRP levels [90]. Similar conclusions were reached in the HERS (Heart and Estrogen/progestin Replacement Study) trial, a prospective randomized, blinded, placebo-controlled study of the effects of CEE + MPA on cardiovascular functions in 2,763 women (mean age 66.7 years) with prior coronary disease [92]. In contrast, the NHS (Nurses’ Health Study), a prospective case control epidemiological trial [93] from an initial cohort of more than 100,000 female nurses, found that women initiating either CEE + MPA or unopposed CEE treatment within 4 years of menopause had a reduced risk of coronary disease, while there was no relation between HRT...
and coronary disease in women who started therapy at least 10 years after menopause [93].

The effects of CEE alone were also investigated in another arm of the WHI trial, conducted in 10,739 postmenopausal women, aged 50-79 years (mean 63.6 years) with prior hysterectomy [94]. The treatment did not affect the incidence of coronary heart disease but increased the risks of stroke and pulmonary embolism [94]. However, when the occurrence of coronary heart disease was related to the age of the participants at baseline, the risk under CEE, as compared with placebo, was decreased in women aged 50 to 59 years, similar in women aged 60 to 69 years, and increased in women aged 70 to 79 years [95].

The WEST (Women’s Estrogen for Stroke Trial) trial was a prospective randomized, double-blind, placebo controlled study of oral estradiol treatment conducted in 664 postmenopausal women (mean age 71 years) with recent history of ischemic stroke or transient ischemic attack. There was no detectable effect on cerebral stroke incidence, but a higher risk of fatal stroke [96].

The ESTHER (Estrogen and Thromboembolism Risk) group investigated the impact, on the risk of venous thromboembolism, of the route of estrogen administration and of the progestosterone or progestin type in a prospective case-control study involving a total of 871 postmenopausal women 45-70 years of age [97]. Oral estrogen as well as some progestin derivatives (promegestone and nomegestrol acetate) were associated with an increased venous thromboembolism risk. In contrast, transdermal estradiol, oral micronized progesterone and some other progestin derivatives (medrogestone, MPA, cyproterone acetate, and chlormadinone acetate) had no effect on venous thromboembolism incidence [97]. The importance of the ESTHER trial was underlined in an editorial of Circulation [98].

The RUTH (Raloxifene Use for The Heart) study [86] investigated in a prospective randomized, double-blind, placebo controlled study the effects of raloxifene, conducted in 10,101 postmenopausal women (mean age 67.5 years). Raloxifene had no effects on the incidence of primary coronary events, but was associated with increased risk of venous thromboembolism and fatal stroke [86].

5.2. Effects of HRT on invasive breast cancer risk

A meta-analysis of 51 epidemiological studies involving a total of 161,116 women had shown a higher incidence of breast cancer in postmenopausal women under CEE with or without progestin [99]. In the WHI trial, the risk of invasive breast cancer was increased under CEE + MPA treatment [88] but not under CEE alone [94]. The Million Women Study [100] included 1,084,110 postmenopausal women aged 50-66 years in a prospective case control epidemiological investigation. BMI was not reported. The invasive breast cancer risk was increased under unopposed oral estrogen (ethinylestradiol or CEE) as well as under tibolone treatment, and was even more important under estrogen-progestin treatment (progestin formulations included MPA, norethisterone, norgestrel and levonorgestrel) [100]. Conversely, the risk of invasive breast cancer was reduced under raloxifene treatment in the RUTH study [86].

The E3N cohort study was a prospective case-control study investigating the impact, on the risk of invasive breast cancer, of the route of estrogen administration and of the progesterone or progestin formulation. This study involved a total of 80,377 postmenopausal women 40-66 years old (mean 53.1 years) [101]. Only 4.5% of the women had a BMI > 30 kg/m². Estrogen alone was associated with increased risk of breast cancer, whatever the route of administration (oral or transdermal). Breast cancer risk was also increased when estrogen was combined with some progestin compounds (namely medrogestone, promegestone, MPA, norethisterone acetate, cyproterone acetate, chlormadinone acetate). On the other hand, this risk was not increased under a combination of estrogen and oral micronized progesterone, or of estrogen and the progestin compound dydrogesterone [101]. It is noteworthy that estrogen alone was associated with a greater breast cancer risk in the Million Women Study [100] and in the E3N study [101], but not in the WHI trial [94], presumably because of the high proportion of obese patients in this last group.

5.3. Effects of HRT on ovarian cancer risk

The NHS included 82,905 postmenopausal women in a prospective observational study. The ovarian cancer risk was found increased under estrogen alone but not under combined estrogen and progestin treatment [52]. In the Million Women Study, an increased risk of ovarian cancer was evidenced under unopposed estrogen treatment, whatever its formulation or mode of administration. The risk increase was still present when estrogen was combined with norethisterone, norgestrel or levonorgestrel, but not when estrogen was associated with MPA [102].

5.4. Effects of HRT on endometrial cancer risk

In the WHI study, the incidence of endometrial cancer was unaffected by CEE + MPA treatment [88]. In the Million Women Study, estrogens as well as tibolone increased the risk of endometrial cancer, while progestins counteracted these adverse effects of estrogens [103].

5.5. Effects of HRT on bone (hip and vertebral) fracture risk

As expected, the fracture risk was reduced under CEE + MPA, or under CEE alone, as compared with placebo, in the WHI trial [88,94], and under raloxifene in the RUTH trial [86].

5.6. Effects of HRT on colorectal cancer risk

The incidence of colorectal cancer was reduced under CEE + MPA treatment, but not under CEE treatment alone, in
the WHI trial [88,94]. The mechanisms underlying those effects remain unclear.

5.7. Effects of HRT on cognitive function

This was assessed in the WHIMS (Women’s Health Initiative Memory Study) [104,105], a subgroup of 4,532 postmenopausal women from the WHI trial. Cognitive function was not improved under CEE + MPA [104]. Moreover, the incidence of dementia was increased [105], possibly resulting from vascular alterations.

6. Conclusions

Hormone replacement therapy (HRT) is the most effective treatment currently available for vasomotor and urogenital symptoms and for decreased libido. However, because harmful effects have been evidenced in a number of clinical trials, US and European health authorities now consider that risk-benefit considerations do not favour the use of HRT for prevention of chronic diseases in postmenopausal women [106]. However, experimental studies as well as clinical trials and simple common sense indicate that adverse effects of HRT may largely depend on the estrogen and progesterone/progestin formulation, dosage, mode of administration, patient’s age, associated diseases and duration of treatment.

All estrogen formulations and modes of administration have similar beneficial effects on vasomotor and urogenital symptoms and on bone structure. But cardiovascular, thromboembolic and invasive breast cancer risks are higher with oral estrogen than with transdermal estradiol, and also higher with a number of progestin compounds than with oral micronized progesterone. While new estradiol or progesterone specific analogues, with all desired effects and none of the harmful consequences, might in the future further improve HRT efficiency and safety, today the combination transdermal estradiol + micronized progesterone appears to be the best choice when HRT is needed in postmenopausal women. Indeed, this combination is effective and relatively safe if elementary precautions are taken.

In the author’s –heterodox– opinion, HRT may also be a good therapeutic choice to prevent bone loss, since alternative medications, including raloxifene and bisphosphonates, may have dramatic harmful effects in some patients. It might also have beneficial effects on the development of coronary disease in young newly postmenopausal women. (Two new ongoing clinical trials, KEEP (Kronos Early Estrogen Prevention Study) and ELITE (Early versus Late Intervention Trial with Estradiol) are presently investigating the effects of transdermal versus oral estrogen in younger postmenopausal women).

Such as for any prolonged hormone therapy, HRT requires careful adjustment to each individual patient and continuous monitoring of clinical evolution. The lowest effective dose should be used, and it is of interest to stress that this dose generally decreases with aging. In a near future, this adjustment could benefit from genetic screening to maximize in each individual the ratio between positive and adverse effects [107].

References


