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Hormone therapy in the postmenopausal years: considering benefits and risks in clinical practice

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BACKGROUND: Menopausal symptoms can be very distressing and considerably affect a woman's personal and social life. It is becoming more and more evident that leaving bothersome symptoms untreated in midlife may lead to altered quality of life, reduced work productivity and, possibly, overall impaired health. Hormone therapy (HT) for the relief of menopausal symptoms has been the object of much controversy over the past two decades. At the beginning of the century, a shadow was cast on the use of HT owing to the concern for cardiovascular and cerebrovascular risks, and breast cancer, arising following publication of a large randomized placebo-controlled trial. Findings of a subanalysis of the trial data and extended follow-up studies, along with other more modern clinical trials and observational studies, have provided new evidence on the effects of HT.

OBJECTIVE AND RATIONALE: The goal of the following paper is to appraise the most significant clinical literature on the effects of hormones in postmenopausal women, and to report the benefits and risks of HT for the relief of menopausal symptoms.

SEARCH METHODS: A Pubmed search of clinical trials was performed using the following terms: estrogens, progestogens, bazedoxifene, tibolone, selective estrogen receptor modulators, tissue-selective estrogen complex, androgens, and menopause.

OUTCOMES: HT is an effective treatment for bothersome menopausal vasomotor symptoms, genitourinary syndrome, and prevention of osteoporotic fractures. Women should be made aware that there is a small increased risk of stroke that tends to persist over the years as well as breast cancer risk with long-term estrogen–progestin use. However, healthy women who begin HT soon after menopause will probably earn more benefit than harm from the treatment. HT can improve bothersome symptoms, all the while conferring offset benefits such as cardiovascular risk reduction, an increase in bone mineral density and a reduction in bone fracture risk. Moreover, a decrease in colorectal cancer risk is obtainable in women treated with estrogen–progestin therapy, and an overall but nonsignificant reduction in mortality has been observed in women treated with conjugated equine estrogens alone or combined with estrogen–progestin therapy. Where possible, transdermal routes of HT administration should be preferred as they have the least impact on coagulation. With combined treatment, natural progesterone should be favored as it is devoid of the antiapoptotic properties of other progestogens on breast cells. When beginning HT, low doses should be used and increased gradually until effective control of symptoms is achieved. Unless contraindications develop, patients may choose to continue HT as long as the benefits outweigh the risks. Regular reassessment of the woman's health status is mandatory. Women with premature menopause who begin HT before 50 years of age seem to have the most significant advantage in terms of longevity.

WIDER IMPLICATIONS: In women with bothersome menopausal symptoms, HT should be considered one of the mainstays of treatment. Clinical practitioners should tailor HT based on patient history, physical characteristics, and current health status so that benefits outweigh the risks.

Key words: menopause / estrogens / progestogens / androgens / tibolone / tissue-selective estrogen complex

Introduction

The history of hormone therapy (HT) for the menopause began in 1942 when the US Food and Drug Administration (FDA) approved the use of conjugated equine estrogens (CEE), a mixture of more than ten estrogenic compounds isolated from the urine of pregnant mares, for the treatment of symptoms resulting from estrogen deficiency (Stefanick, 2005). Over the next three decades, the drug became an established treatment for the relief of menopausal symptoms, supported by independent studies. In 1972, the FDA published a Federal Register notice indicating that estrogen products, including CEE, were effective in treating menopausal symptoms (Stefanick, 2005). However, in 1975 critical studies associated the use of estrogens with endometrial cancer (Ziel and Finkle, 1975), causing the FDA to issue a bulletin warning of this risk with prolonged use of these hormones. This problem was readily overcome by combining estrogens with a progestin molecule in women with a uterus. During the decades that followed, several products containing different estrogenic compounds and different progestins, using different routes of administration, were developed to treat not only short-term but also long-term consequences of menopause. HT was proposed as a treatment for a broad range of ailments associated with aging.

Data from observational studies and the 1995 Postmenopausal Estrogens Progestins Interventions (PEPI) trial suggested benefits of HT on cardiovascular disease markers (The Writing Group for the PEPI Trial, 1995). The PEPI trial enrolled healthy women with a uterus, aged 45–64 years, who were at least 1, but not more than 10, years postmenopausal and tested four different regimens (CEE 0.625 mg daily, CEE 0.625 daily plus medroxyprogesterone acetate (MPA) 10 mg on Days 1–12 per 28-day cycle, CEE 0.625 daily plus MPA 2.5 mg daily, or CEE 0.625 daily plus micronized progesterone (MP) 200 mg on Days 1–12 per 28-day cycle) against placebo. In the PEPI, estrogen alone or combined with a progestin improved lipoprotein profile and lowered fibrinogen levels, two important risk factors for cardiovascular disease, compared to placebo (The Writing Group for the PEPI Trial, 1995). The most important lesson learned from PEPI was that the regimens using natural progesterone were the best tolerated metabolically and caused the most beneficial changes in lipids and lipoproteins as they resulted in an high-density lipoprotein (HDL)-C level comparable to that with oral CEE alone, but lacked the 'attenuation effect' of MPA on this rise (The Writing Group for the PEPI Trial, 1995). The theory that HT could be beneficial for heart disease prevention was challenged by the Heart and Estrogen/Progestin Replacement Study (HERS) (4), in which nonhysterectomized older women and with established cardiovascular disease were randomized to HT (oral 0.625 mg of CEE plus 2.5 mg of MPA daily) or placebo. During an average follow-up of 4.1 years, treatment with oral CEE plus MPA did not reduce the overall rate of coronary heart disease (CHD) events in postmenopausal women with coronary disease (Hulley *et al.*, 1998) and increased the rate of thromboembolic events. Although it

was a secondary prevention trial, the publication of the HERS study by Hulley *et al.* (1998) strongly affected the clinical recommendations on the use of HT for prevention of CHD.

Meanwhile, in 1993, the Women's Health Initiative (WHI), a nationwide US study, was launched. The WHI enrolled 161 808 women, aged 50–79 years, in a long-term national health study that concentrated on stratagems for preventing heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women. One component of the WHI, the WHI HT, was two placebo-controlled trials of CEE-MPA (oral 0.625 mg of CEE plus 2.5 mg of MPA daily) in nonhysterectomized women (n = 16 608) and CEE-alone in hysterectomized women (n = 10 739), on the prevention of heart disease and osteoporotic fractures, and associated risk for breast cancer. The average age of women in the WHI HT was 63 years, with a mean of 12 years since menopause (Writing Group for the Women's Health Initiative Investigators, 2002). In July 2002, the estrogen plus progestin arm of the study was halted, 3 years before its scheduled conclusion, because of a small increase in heart disease, stroke, and venous thromboembolism (VTE) in the women who took the HT (Writing Group for the Women's Health Initiative Investigators, 2002). A slight rise in breast cancer, although not statistically significant, was also found (Writing Group for the Women's Health Initiative Investigators, 2002). At this point, many practitioners advised their patients to abandon HT, perhaps overly influenced by health scare headlines of the media. In March 2004, the CEE-only trial was also terminated prematurely because of increased stroke risk and because extending the trial to its full duration would not result in a statistically significant finding for a primary or the composite endpoints (The Women's Health Initiative Steering Committee, 2004). However, the authors also stated positive outcomes in that the use of CEE-alone did not increase CHD incidence in postmenopausal women and there was a trend toward a reduction in breast cancer risk that required further investigation (The Women's Health Initiative Steering Committee, 2004). Moreover, in both studies, HT was proven to prevent osteoporotic fractures, with benefits for many women. Nevertheless, the consequence of the extreme attention offered by the media to the declared hazards of HT deeply affected not only public opinion but also physicians' prescribing patterns, and the use of HT continued to drop considerably.

Between 2004 and 2007, there was a crucial turnabout thanks to the publication of further analyses of the WHI trial, indicating that that risks for certain aspects had been overestimated. By stratifying the WHI cohort by age, they found that the data pointed toward a reduced risk of heart disease, a lower risk of death from any cause, and no apparent increased risk of stroke in women initiating HT between the ages of 50 and 59 years, or less than 10 years past the menopause in contrast to women starting HT after the age of 60 years (Rossouw *et al.*, 2007). These findings led to the foundation of the 'timing hypothesis', according to which there is a window of opportunity where HT initiation could positively influence cardiovascular disease risk in younger women. Even extended postintervention follow-up studies showed favorable outcomes for myocardial infarction, all-cause mortality, and a global index in women in the CEE-alone, 50–59 years group (Harman, 2014). Furthermore, and very importantly, the authors of the WHI publications affirmed that the use of CEE-alone did not affect the overall invasive breast cancer incidence and was associated with statistically significant reduced rates in ductal breast cancer (Manson *et al.*, 2013). The WHI remains the most significant and the only randomized placebo-controlled trial to date on outcomes of disease and death after HT, and the data must be taken into account.

In time, two more essential studies were designed to specifically evaluate the safety of HT in healthy, early postmenopausal women: Kronos Early Estrogen Preventin Study (KEEPS) (Miller *et al.*, 2009) and Early versus Late Intervention Trial with Estradiol (ELITE) (Hodis *et al.*, 2016). In KEEPS, a 4-year randomized, placebo-controlled, double-blind prospective trial, there were no beneficial or harmful effects of HT (oral CEE 0.45 mg/day or transdermal estradiol 50 µg weekly, both in combination with cyclic oral MP 200 mg for 12 days per 28-day cycle) on atherosclerosis progression assessed by carotid intima-media thickness or coronary arterial calcification. The ELITE study was explicitly intended to test the timing hypothesis, by comparing women in early postmenopause and older women treated with HT (oral estradiol 1 mg per day, plus progesterone (45 mg) vaginal gel administered sequentially once daily for 10 days per 28-day cycle) versus placebo (Hodis *et al.*, 2016). Over 5 years, the progression of atherosclerosis was slower for the group of women <6 years past menopause treated with estradiol (E2), compared to their counterparts taking placebo, while there was no benefit for women ≥10 years past menopause.

Two extensive studies were also vital in changing the viewpoint on HT. The Danish Osteoporosis Prevention Trial (Schierbeck *et al.*, 2012) was an open-label and nonplacebo-controlled longitudinal study with a follow-up period of 10 years. In this trial, women receiving HT (oral E2 2 mg/day or oral estrogen-norethisterone acetate trisequential therapy (2 mg E2 for 12 days, 2 mg E2 plus 1 mg norethisterone acetate for 10 days, and 1 mg E2 for 6 days)) had a significantly reduced risk of cardiovascular events such as heart failure and myocardial infarction. A large Finnish study based on the National Death Registry found an elevated hazard ratio (HR) for cardiac death and stroke in the first year for women who stopped HT compared to women who continued using it (Mikkola *et al.*, 2015). Women on HT had used one of the following regimens: E2 associated with a levonorgestrel-releasing intrauterine device (IUD) , or various progestins, of which the most common were norethisterone acetate (44%), MPA (27%), dydrogesterone (12%), for 10–14 days a month, or at 3-month intervals, or continuously. However, no similar increase in cardiovascular disease (CVD) events occurred after stopping HT in the WHI trials (Manson *et al.*, 2013).

In the last 5 years, major scientific societies have issued new recommendations regarding the treatment of menopausal symptoms with HT (Sarri *et al.*, 2015; Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017) based on data from the trials mentioned above, among others, to guide physicians in the practice of menopausal medicine. These recommendations reassure about the fact that, with the appropriate use of HT, the benefits from hormones generally outweigh the risks. European studies have opened

the way to alternative routes of administration, primarily the transdermal route, which can influence cardiovascular risk positively.

In the last 70 years, history has also changed for women in westernized countries. First of all, the life expectancy for women has increased by approximately 18 years in the last century, thereby extending life beyond the final menstrual period in a meaningful manner. Moreover, the social role of women has evolved. In most westernized countries, women account for a significant component of the labor force. Childbearing has also been postponed to an older age. At the time of menopause, a woman is often handling a full-time job, caring for her family, and often also caring for aging parents. The menopause will very often bring on vasomotor and urogenital symptoms that can be very distressing and considerably affect personal and social life. Negative changes in mood, sleep, memory, and overall quality of life may ensue.

Moreover, approximately 30–40% of women report that menopausal symptoms reduce performance in the workplace, apart from producing feelings of shame or embarrassment or worsened social desirability (Griffiths *et al.*, 2016). Healthcare providers caring for women at all levels of the healthcare system must be well prepared to guide patients and provide advice to improve their quality of life. HT could be an option. A woman's choice to use hormones needs to be a personal one, and fully informed regarding the possible risks and benefits. The decision to continue HT in the long term should be revisited regularly based on health status.

The goal of this review is to appraise the most significant clinical literature on the effects of hormones in postmenopausal women, and to report on the benefits and risks of HT for the relief of menopausal symptoms.

Indications for hormone therapy

Estrogens exert critical signaling in a range of human target organs and tissues. Consequently, the fall in estrogen levels that comes with menopause sets off a series of bothersome, and at times distressing, symptoms.

First, 75% of women experience vasomotor symptoms (VMS) when facing menopause (Woods and Mitchell, 2005), starting as early as 11 years before the final menstrual period (FMP) and continuing for as long as 11–12 years after the FMP (Politi *et al.*, 2008; Freeman *et al.*, 2011; Gartoulla *et al.*, 2018), well into their sixties (Gartoulla *et al.*, 2018). Hot flashes and sweating diminish the daytime functioning of women; however, many women lament nocturnal symptoms as well, with greater restlessness in bed, lower sleep efficiency, and a lesser feeling of rest in the morning (Pien *et al.*, 2008). A decline in sleep quality has been related to menopause-related symptoms, namely hot flashes and depressive symptoms, in a longitudinal population study (Kravitz and Joffe, 2011). The presence of moderate–severe VMS seems to be associated with more memory functioning complaints (Drogos *et al.*, 2013). Moreover, because sleep is vital for learning and memory consolidation (Medic *et al.*, 2017), disordered sleeping likely contributes to the memory lapses lamented by many menopausal women.

Symptoms that are seldom reported by women but that can be very problematic are vaginal dryness, dyspareunia, vulvar itching and burning, and dysuria, urinary frequency, urgency, and recurrent lower urinary tract infections (Nappi *et al.*, 2019). Urogenital changes may have a tremendously negative impact on quality of life (Nappi *et al.*, 2016) and, together with a reduced hormone-driven sexual desire (Avis *et al.*, 2009), may cause sexual dysfunction in women coping with menopause (Avis *et al.*, 2009).

One of the significant health problems caused by menopause-related estrogen deficiency is the loss of bone strength, which becomes symptomatic when it causes postmenopausal osteoporotic fractures of the spine, hip, or wrist (Cummings and Melton, 2002). Bone mineral density (BMD) seems to change little during the pre- or early perimenopause but then declines considerably during the late perimenopause, increasing the risk of disabling bone fractures (Finkelstein *et al.*, 2008). A reduction in muscle tropism and tone may favor these events (Maltais *et al.*, 2009).

One of the governing principles of the leading menopause societies is that HT is the most effective therapy for VMS and urogenital atrophy (Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017). Moreover, HT has a proven positive effect on osteoporosis and fracture risk prevention in postmenopausal women (Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017). Off-target benefits of HT may include an improvement in mood swings, sleep disturbances, and sexual dysfunction and, in general, quality of life (Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017).

Hormone therapy: benefits and risks

The WHI was a landmark study. To date, there exist no other randomized clinical trials of HT of that magnitude. Unfortunately, research in menopausal medicine was dampened by the negative publicity around HT produced by the WHI, and most of the data regarding the clinical effects with other doses, preparations, and routes of administration of HT remain observational. However, we believe that large cohort studies, especially those based on national registries, may have sufficient numbers to reduce potential biases and reflect actual medical practice and can help us in decision making.

Cardiovascular system and metabolism

HT has the potential to affect both arterial and venous sides of the cardiovascular system through effects on endothelial function, lipid, glucose metabolism, and coagulation.

Estrogen and estrogen–progestogen combinations

The attempt to reduce CVD with HT in secondary prevention at the end of the 1990s was unsuccessful. The results of the WHI indicating harmful effects of HT in postmenopausal women produced turmoil in the scientific community and women worldwide (Writing Group for the Women's Health Initiative Investigators, 2002). Subsequent subanalyses and follow-up studies of the WHI at 13 years and 18 years postintervention allowed us to better contextualize the earlier

reported findings in women of the younger age range (Rossouw *et al.*, 2007; Manson *et al.*, 2013, 2017). In truth, the relation between HT and CVD risk seems to be a complex one. It depends on chronological age and menopausal age, individual health status, route of delivery of estrogens, and possibly dose, and type of progestogen.

Younger early postmenopausal women versus older late postmenopausal women. By analyzing the data based on chronological age, investigators of the WHI (Rossouw *et al.*, 2007) recognized that HT (combined data CEE and CEE 0.625 mg/day plus MPA 2.5 mg/day) did not cause cardiovascular complications in women of the lower age group (50–59 years). Indeed, the HR for cardiovascular events in this group was 0.93, with an absolute reduction of 2 cases/10 000 person-years, compared to placebo. HR was 0.98 in women aged 60–69 years, with a risk of 1 per 10 000 person-years, while it was only higher (HR 1.26) in the group of women aged 70–79 years, with an excess risk of 19 per 10 000 person-years. CEE alone appeared to be associated with lower risk of CHD than CEE-MPA. The authors reported that, although age and years since menopause were highly correlated, in their analyses years since menopause appeared to influence hormone effects on CHD more than chronological age. Indeed the HR for CHD was 0.76 in women with less than 10 years since menopause, 1.10 for women with 10 to less than 20 years since menopause, and 1.28 for women with more than 20 years since menopause (combined CEE alone and CEE/MPA data). Therefore, younger women, closer to the FMP, experiencing symptoms and requiring HT, may have the added benefit of a reduction in CVD events. Indeed, a subanalysis of the original WHI data showed that women who initiated HT closer to the menopause, aged between 50 and 59 years and within 10 years of their FMP, had a nonsignificant trend toward lowered CVD risk (CHD, coronary artery bypass grafting or percutaneous coronary intervention, and all-cause mortality) (Rossouw *et al.*, 2007). Women further from the menopause, aged 60–69 and 10 years or more from the FMP, on the contrary, experienced a risk increase (Rossouw *et al.*, 2007). The overall WHI cohort hardly represented the younger symptomatic women in the observational studies. It was misinterpreted, but this first reanalysis confirmed the robust previous observational data in favor of HT as a neutral factor for CVD events that had prompted the WHI study in the first place (Stampfer *et al.*, 1985; Bush *et al.*, 1987; Henderson *et al.*, 1991;). In the extended postintervention WHI follow-up of 13 years, the women who had been randomized for treatment with CEE at a younger age (age 50–59 years) had better outcomes for myocardial infarction and all-cause mortality. In older women, age 60–69 years, CEE had a neutral effect on these outcomes; in women aged 70–79 years, CEE determined a trend toward increased risk of these events (Manson *et al.*, 2013). During the 18-year follow-up, results demonstrated no difference in long-term all-cause and cause-specific mortality in women treated with HT versus placebo at any age (Manson *et al.*, 2017). Data from the 2012 randomized open-label Danish trial (DOPS study), including 1006 women, showed that the risk of the composite endpoint of death, heart failure, or myocardial infarction was significantly decreased when HT was started in early postmenopause in healthy women (Schierbeck *et al.*, 2012). The beneficial effect occurred in the 10-year randomization phase and was maintained for an additional 6 years of nonrandomized follow-up (Schierbeck *et al.*, 2012). A recent comparative analysis between data from the Nurses' Health Study (NHS) and the WHI showed that among women aged 50–59 years at HT initiation, associations of CEE alone or CEE+MPA were highly concordant regarding most cardiovascular outcomes (Bhupathiraju *et al.*, 2017). However, for myocardial infarction, results for CEE plus MPA tended toward risk elevation in the WHI and toward risk reduction in the NHS. When examined according to the number of years since the FMP (<10 years) instead of age group, results were nonsignificant and concordant for both studies (Bhupathiraju *et al.*, 2017). Medical practitioners, therefore, need to be aware that age, especially menopausal age, is a determining factor in deciding to administer HT to a patient and that younger patients with less risk factors may enjoy more benefits. Older women, on the other hand, may have more CVD risk factors (Swica *et al.*, 2018) and related events.

Timing hormone therapy: the window of opportunity. Age and time since menopause at HT initiation are two of the most critical factors influencing the effects of HT on chronic disease risk. In our opinion, time since menopause onset is especially important because it is the time spent in the absence of the estrogen effects on the endothelium that makes the difference in terms of atherosclerotic risk (Tuomikoski and Mikkola, 2014). With menopause, the inhibitory effect of estrogens on the growth and proliferation of vascular smooth muscle cells is lost (Mendelsohn, 2000). This leads to an acceleration of the atherosclerosis process and the production of pro-inflammatory cytokines and adipokines in visceral adipose tissue (Pou *et al.*, 2007; Lee *et al.*, 2009). Blood lipid profiles tend to become atherogenic in women within a year of the FMP, with significant increases in total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B (ApoB), independent of ethnicity, age or weight (Matthews *et al.*, 2009). Increases in HDL cholesterol levels are paradoxically associated with a more significant progression of carotid intima-media thickness (El Khoudary *et al.*, 2016). Moreover, blood pressure levels tend to rise in postmenopause (Taddei, 2009).

In the proximity of the menopause, women still have healthy arteries and present a "window of opportunity" for HT to produce beneficial cardiovascular effects. Aging arteries, however, become less responsive to the beneficial effects of estrogens, possibly linked to a down-regulation of estrogen receptors (ER) (Smiley and Khalil, 2009). Estrogens produce different effects on arteries, depending on the stage of the atherosclerotic process. At an early stage, these steroids inhibit or slow down the development of the atherosclerotic plaque by preventing the accumulation of foam cells in the endothelium. At later stages, they exacerbate inflammation, precipitate rupture of vulnerable plaques by increasing expression of matrix metalloproteinases (MMPs) and promote thrombo-occlusive events (Khalil, 2013). Considerable increases in MMPs lead to excessive remodeling and disruption of existing atheromatous plaques (Wingrove *et al.*, 1998). Thus, the prior endothelial condition of a woman is the real determining factor of HT cardiovascular outcome. The vast majority of the women included in the original trial probably had a severely diseased vasculature because of age, the number of years since menopause, and pre-existing cardiovascular risk factors (obesity, high cholesterol, and hypertension). In the WHI, those women who started HT soon after the menopause showed better cardiovascular outcomes, having less advanced atherosclerosis. Indeed, in WHI-CACS, approximately 8.7 years after randomization, women aged 50–59 years receiving CEE only presented a

lower prevalence and quantity of coronary-artery calcium, a marker of atherosclerosis progression, than those receiving placebo (et al., 2007).

Based on this hypothesis, a group of researchers designed the Early versus Late Intervention Trial (ELITE), a randomized, placebo-controlled, double-blind prospective trial to evaluate effects of HT on the progression of atherosclerosis, with carotid intima-media thickness (CIMT) and coronary arterial calcification (CAC) as the outcomes (Hodis et al., 2016). The aim of the ELITE study was specifically to test the timing hypothesis of HT, by comparing these outcomes in women early in postmenopause (<6 years past menopause) and in women late in postmenopause (≥10 years past menopause) (Hodis et al., 2016). CIMT measurements every 6 months, and cardiac computed tomography were carried out on 643 healthy postmenopausal women, randomized to HT or placebo for 6–7 years. The rate of progression of atherosclerosis by CIMT was similar in the E2 and placebo groups in women ≥10 years past menopause. At the same time, it was slower in the group of women <6 years past menopause for women on HT compared with placebo. Computed tomography did not reveal differences for CAC, total stenosis, and plaque between the E2 and placebo-treated women in either the menopausal age group. This may be attributed to the short trial duration with respect to the long incubation period of CAC (Loria, 2007), and therefore, the study may not have lasted long enough to observe a change (Hodis et al., 2016). Moreover, the post-trial analysis of the ELITE data revealed that with higher plasma E2 levels achieved through the therapy, the CIMT progression rate was decreased among women in early postmenopause but increased among women in late postmenopause. These data are perfectly in line with the timing hypothesis (Miller et al., 2020). KEEPS was also designed to focus on the healthy younger women by recruiting subjects within 3 years of menopause and by excluding those with known clinical and subclinical atherosclerosis (Miller et al., 2009). In KEEPS, CIMT increased comparably in treatment and placebo-treated women in a similar fashion over the 4 years of the study. The disalignment between the KEEPS results of no benefit on CIMT progression and the results of the ELITE trial may be explained by a dose-response effect of E2 or a time-dependent effect (Hodis et al., 2016; Sriprasert et al., 2019). Indeed treatment consisted of CEE 0.45 mg/day or transdermal E2 50 mcg/day, both with oral progesterone (200 mg/day for 12 days/month), or placebo pills and patches. Circulating levels of E2 and E1, although both increased with both treatments versus placebo, differed between women assigned to transdermal E2 or oral CEE. Moreover the duration of the study, 4 years, was shorter than that of ELITE.

CIMT was evaluated after a 3-year period of stopping HT or placebo in a subgroup of 76 participants from KEEPS. No accelerated changes occurred in arterial thickness and no differences between treatment groups over time, although for women randomized to oral E2, there was a significant increase in CIMT post-treatment with respect to the years on active treatment (Miller et al., 2019).

A recent report from the Finnish nationwide prescription register reported that HT reduces the death risk related to CHD, the earlier HT is initiated (Savolainen-Peltonen et al., 2016).

Route of administration. Transdermal and vaginal estrogens seem to confer a lower risk of VD events, most probably thanks to the lower impact on liver function. Hepatic hemostatic factors are significantly less affected by nonoral therapy (Canonico, 2014). Nonoral routes of administration respect more closely female physiology as ovarian hormones are released directly into the bloodstream. Observational evidence shows that transdermal estrogen therapy, at the dose of ≤50 μg, is associated with a lower risk of deep vein thrombosis, stroke, and myocardial infarction compared to oral treatment (Simon et al., 2016). The VTE data were confirmed in a recent study using data from UK QResearch and Clinical Practice Research Datalink (CPRD) databases (Vinogradova et al., 2019). Women included in the study had been exposed to oral estrogen-only preparations (CEE and E2) and combined preparations (CEE or E2 with MPA, dydrogesterone, norethisterone acetate, norgestrel/levonorgestrel, or drospirenone) or transdermal E2 alone or combined with a progestin, mainly norethisterone acetate. In this study, no transdermal preparation (E2 alone or combined, combined cyclical or continuous) was associated with an increased VTE risk, and dose (≤ or > 50 μg transdermal E2) did not make a difference (Vinogradova, 2019). Lower incidence of congestive heart failure and VTE were observed in a matched-cohort study involving 5102 women treated with transdermal estrogen therapy versus oral estrogen therapy use; CVD events largely driven by VTE events were 19% lower in the women treated with transdermal E2 (Sriprasert et al., 2019). Compared to oral CEE, transdermal E2 was also associated with a lower risk of CHD and stroke, although nonsignificantly (Shufelt et al., 2014). Interestingly, data from the WHI observational study (Crandall et al., 2017) showed that oral CEE below 0.625 mg/d was found to be equally safe as compared to transdermal E2, when global index (defined as CHD, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death) was considered. Vaginal E2 (25 μg twice-weekly tablets or 7.5 μg/day ring) to alleviate vaginal atrophy also seems to be beneficial, with the mortality from CVD having been significantly decreased with this therapy in a nationwide Finnish cohort study of 195 756 women (Mikkola et al., 2016). These findings were confirmed by data of the Women's Health Initiative Observational Study, where the risks of CHD and all-cause mortality were lower in users than in nonusers of vaginal estrogens in a population of prevalently white, lean women with a higher education and income. At the same time, the chances of stroke and pulmonary embolism/deep vein thrombosis were similar (Crandall et al., 2018). Finally, very recent data from the NHS confirmed the cardiovascular safety of vaginal estrogens (Bhupathiraju et al., 2018).

Type of oral estrogen used. Among oral preparations, CEE have been associated with higher risks of VTE with respect to oral E2 in a very recent observational study (Vinogradova et al., 2019).

Progestogen used in combination therapy. The observation, from the WHI study, that more favorable cardiovascular outcomes were obtained in the estrogen-only arm compared to the estrogen–progestogen arm prompted the question as to whether the progestogen component could oppose the well-known effects of estrogen on the cardiovascular system. For example, among women in the age group of 50–59 years, the frequency of cardiac episodes was lower (HR = 0.63 (0.36–1.09)) in the group receiving CEE than in the group receiving CEE/MPA (HR = 1.29 (0.79–2.12)) (Rossouw et al., 2007). As described earlier, MPA has a wide variety of effects owing to its ability to interact with various endocrine receptors. Indeed, in nonrandomized controlled trials (RCTs) MPA and norpregnanes, such as nomegestrol

acetate and promegestone, determined a significant increase in the risk of venous complications (Scarabin, 2018; Vinogradova *et al.*, 2019). Progesterone and pregnane derivatives, such as dydrogesterone and chlormadinone acetate, on the other hand, were found to be neutral on the risk of VTE (Canonico *et al.*, 2010; Vinogradova *et al.*, 2019). Observational data indicate that highest VTE risk seems to be associated with the use of HT formulations containing MPA (Sweetland *et al.*, 2012; Vinogradova *et al.*, 2019). In the report of the UK CPRD databases, the risk for VTE with CEE/MPA was 2.1, very close to that reported by the WHI for the same formulation (Scarabin, 2018). As for stroke risk, no association was found with the use of progesterone, pregnane, and nortestosterone-progestins, while a positive association has been reported for formulations containing norpregnane derivatives (Canonico *et al.*, 2016).

Dose. HT may have beneficial cardiovascular effects in postmenopausal women without overt clinical disease even at lower doses (Casanova *et al.*, 2015). In a subset of 1246 women of the WHI observational study, followed during a median of 10.4 years, oral low-dose CEE (<0.625 mg/day) was associated with nonsignificantly lower rates of CHD, total CVD and CVD mortality compared to women who used oral conventional-dose CEE (0.625 mg/day) (Shufelt *et al.*, 2014). Findings regarding stroke risk are not homogenous. Low-dose HT (equivalent to 0.3 mg of oral conjugated estrogens (CE) daily) was not associated with an increased risk of stroke as compared to conventional-dose HT in the NHS (Grodstein *et al.*, 2000). Another study from the French National Health insurance database identified an increasing dose-dependent ischemic stroke risk with oral estrogen in a population of women between 51 and 62 years of age; risk was borderline significant with a low to medium estrogen dose (<1 mg/day) and greater in those using high (>1 mg/day) estrogen doses (Canonico *et al.*, 2016). Stroke risk was not found to increase with increasing doses of transdermal estrogens (Canonico *et al.*, 2016). In the WHI observational study, no significant difference in stroke risk was seen when low (≤0.625 mg) and medium oral CEE doses were compared (>0.625 mg) (Shufelt *et al.*, 2014). However, at least in theory, beginning HT with low doses, especially in women who are older and further from the FMP, could be a wise approach as E2 increases MMP activity and possibly causes disruption of atheromatous plaques in a dose-dependent manner (Wingrove *et al.*, 1998).

Data on the interaction between the diverse estrogen–progestin preparations and the female cardiovascular system are very difficult to interpret and much debated. They have been illustrated in detail for this reason. However, these findings require confirmation through RCTs.

Selective estrogen receptor modulators and tissue-selective estrogen complex

Raloxifene. The 4-year Multiple Outcomes of Raloxifene Evaluation (MORE) osteoporosis treatment trial and the 4-year follow-up Continuing Outcomes Relevant to Evista (CORE) trial, designed to determine the effect of raloxifene on the incidence of invasive breast cancer, produced a first set of data on the cardiovascular safety profile of this drug. In postmenopausal women at relatively low risk of cardiovascular events participating in these trials (Ensrud *et al.*, 2006), there was no evidence of an impact of raloxifene on the incidence of cardiovascular events overall or coronary or cerebrovascular events.

In the milestone Raloxifene Use for the Heart (RUTH) trial, women who were 55 years of age or older, 1 year or more postmenopausal, with established CHD or at increased risk for CHD, treated with raloxifene orally at the dose of 60 mg/day for a median of 5.6 years, did not develop more coronary events or CHD (Barrett-Connor *et al.*, 2006). The overall risk of stroke was not increased although in women with elevated stroke risk score the incidence of fatal stroke rose by 49%. Raloxifene also caused an increased risk of VTE. The overall risk of death from cardiovascular causes or death for any reason was not significantly affected by raloxifene administration over that time (Barrett-Connor *et al.*, 2006).

In a *post-hoc* analysis of the RUTH trial data, postmenopausal women with CHD risk factors or those with established CHD aged < 60 years did not experience an increase or decrease in the incidence of coronary events with raloxifene treatment (Barrett-Connor *et al.*, 2006). The incidence of coronary events was significantly lower in postmenopausal women <60 years of age assigned raloxifene compared with placebo. Indeed, the HR was 0.59 with an absolute risk reduction of 36 cases/1000 women (Collins *et al.*, 2009). Moreover, raloxifene did not cause early CHD harm at any age (Collins *et al.*, 2009). Raloxifene did not affect the incidence of coronary events in any other subgroup (Collins *et al.*, 2009).

Tissue-selective estrogen complex (BDZ/CE). In healthy postmenopausal women, orally administered BZA/CE at the daily doses of CE 0.45 mg/BZA 20 mg (n = 1585) or CE 0.625 mg/BZA 20 mg (n = 1583), any BZA/CE dose (n = 4868), for 2 years was shown to have an acceptable cardiovascular safety profile, with rates of stroke and CHD comparable to placebo (n = 1241). The risk of VTE was low (Komm *et al.*, 2015).

Tibolone

There are little data from RCTs on the cardiovascular effects of tibolone. Results of the OPAL study (Bots *et al.*, 2006), a three-arm, randomized, placebo-controlled, double-blind study to determine the effect of orally administered tibolone (2.5 mg daily) and CEE/MPA (0.625/2.5 mg daily) in 866 healthy postmenopausal women aged 45–79 years, have shown a more significant progression of CIMT of both hormone treatments versus placebo. In the LIFT study (Cummings *et al.*, 2008) a randomized study carried out in 4538 women, aged between 60 and 85 years, Tibolone administered orally at the daily dose of 1.25 mg/day (mean age 68 years) determined an increase in stroke events. Women treated with Tibolone had an increase in the absolute risk of stroke of 2.3 (95% CI, 0.4–4.2) per 1000 person-years and an increase in the relative hazard of 2.19 (95% CI, 1.14–4.23). The risk of stroke was higher (6.6 per 1000 person-years) in women older than 70 years of age treated with tibolone versus 3.4 per 1000 person-years treated with placebo. The conclusions that arose are that, as risk of stroke rises exponentially with age, tibolone should generally not be used in elderly women. Moreover, it should not be administered to women who have strong risk factors for stroke, such as hypertension, smoking, diabetes, and atrial fibrillation (Cummings, 2008). Tibolone does not seem to confer an increased VTE risk (Barrett-Connor *et al.*, 2006) or increase of CHD events (Cummings *et al.*, 2008).

Androgens

Short-term (24 weeks) transdermal testosterone treatment (300 μg/day) does not produce serious adverse events (Achilli *et al.*, 2017). Moreover, the effect on serum lipid profile, carbohydrate metabolism, and renal and liver function as assessed by serum chemistry and hematology indices seems to be neutral (Achilli *et al.*, 2017). Transdermal testosterone (300 μg/day) was also evaluated in a double-blind, randomized, placebo-controlled study in women with heart failure; the 24-week treatment was associated with significant functional improvements, compared to placebo, in terms of peak oxygen consumption and distance walked over the 6-minute walking test (Iellamo *et al.*, 2010). Long-term studies, however, are lacking.

Vaginal dehydroepiandrosterone (DHEA) treatment (6.5 mg/day) does not increase circulating levels of DHEA, E2, or testosterone above the normal postmenopausal range and data of a 52-week trial in otherwise healthy postmenopausal women did not reveal significant adverse effects (Sauer *et al.*, 2018). No robust studies have specifically investigated the cardiovascular effects of systemic DHEA treatment in postmenopausal women.

Body weight, fat distribution, and glucose metabolism

Estrogen and estrogen–progestogen combinations

Central fat distribution is intricately linked to insulin resistance and metabolic syndrome and hence increased CVD risk. Menopause results in an increase in central visceral fat (Genazzani *et al.*, 2006). It is a known fact that HT will not help with weight loss but may help prevent the menopausal changes in body fat distribution, with a decrease in visceral fat mass (Jensen *et al.*, 2003; Papadakis *et al.*, 2018). The Danish Osteoporosis Prevention Study (DOPS) showed that women on HT gain less fat than controls (Jensen *et al.*, 2003). An observational, longitudinal 2-year study in women taking prevalently oral CEE 0.625 mg/day continuously combined with MPA 2.5 mg/day yielded similar results (Gower *et al.*, 2006).

The PEPI trial reported mean fasting insulin levels that were 16.1% lower, mean fasting glucose levels 2.2 mg/dl lower in women randomized to CEE 0.625 mg/day with or without a progestational agent with respect to placebo. Two-hour glucose levels were, however, significantly higher, possibly indicating a slower glucose blood clearance in women on HT (Espeland *et al.*, 1998).

The WHI showed a small but statistically significant decrease in BMI and waist circumference during the first year of treatment in women assigned to HT (Margolis *et al.*, 2004). Similar results were found in HERS, where women assigned to HT experienced slight but significant weight loss, decreased BMI, and displayed a decreased waist-hip ratio, and waist circumference during follow up compared with placebo (Kanaya *et al.*, 2003). As a consequence, HT improves insulin resistance and lowers the incidence of diabetes in postmenopausal women. In HERS and WHI (Kanaya *et al.*, 2003; Margolis *et al.*, 2004), the incidence of type 2 diabetes mellitus (T2DM) in the HT arm was reduced by 35% and 21%, respectively. These data are in agreement with those of extensive observational studies, the NHS (Manson *et al.*, 1992), and the French E3N cohort study where women were exposed to oral or transdermal E2 alone or combined with progesterone, MPA or dydrogesterone (de Lauzon-Guillain *et al.*, 2009). Consistent with the effect of HT, in the postintervention follow up of the WHI trials, the diabetes risk reductions disappeared in the years after discontinuation of HT (Manson, 2013). HT has a favorable effect on glucose metabolism, even in women with pre-existing T2DM (Salpeter *et al.*, 2006; Slopien *et al.*, 2018).

In KEEPS, insulin resistance tended to decrease in both HT groups (oral CEE (0.45 mg/day) or transdermal 17β-E2 (50 μg/day)), both with progesterone (200 mg/day for 12 days/month), which is consistent with the previously reported data (Miller *et al.*, 2019) .

Selective estrogen receptor modulators and tissue-selective estrogen complex

In healthy postmenopausal women, raloxifene treatment (60 mg/day) administered over 12 months was shown to prevent body weight gain and favored gynoid-type fat distribution (Francucci *et al.*, 2005). In another study, raloxifene administered for the same period remarkably altered body composition by increasing fat-free mass and total body water (Jacobsen *et al.*, 2010). One small trial reported that a 12-month raloxifene treatment (60 mg/day) did not modify fasting glucose or glucose tolerance; however, it decreased insulin sensitivity (Lasco *et al.*, 2004).

In a meta-analysis of five Selective Estrogens, Menopause, and Response to Therapy (SMART) RCTs in postmenopausal women, oral bazedoxifene (BZA) 0.45 mg/CE 0.625 mg treatment for 2 years did not affect body weight (Black *et al.*, 2016). In the SMART-1 trial, BZA/CE improved lipid parameters and homocysteine levels, and did not significantly change fasting blood glucose or insulin levels over a 12-week period (Lobo *et al.*, 2009). Obese women treated with BZA/CE, on the other hand, in a randomized placebo-controlled pilot 12-week study, benefited from an improvement in fasting pancreatic beta-cell function and glucose concentrations (Lovre *et al.*, 2019).

Tibolone

In a randomized placebo-controlled trial, tibolone (2.5 mg/day) was shown to reduce insulin sensitivity. Therefore, it may not be advisable to prescribe tibolone to women with, or at increased risk for, diabetes (Manassiev, 2013).

Central nervous system

Basic science and animal studies have taught us that E2 exerts beneficial effects on the brain, such as maintaining synaptic integrity (Tang, 2004), facilitating the production of soluble β-amyloid, and increasing the number of dendritic spine numbers in the prefrontal cortex and the hippocampus (Jaffe *et al.*, 1994; Hara *et al.*, 2015). However, clinical data have been equivocal and controversial as to the benefits of HT in the brain of postmenopausal women.

Vasomotor symptoms

Estrogen and estrogen–progestogen combinations. There is no doubt that estrogen or estrogen–progestogen HT is the best treatment option to alleviate VMS in women (Maclennan *et al.*, 2004) to the point that all major scientific societies recommend HT use for this purpose (Sarri *et al.*, 2015; Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017). Combination estrogen–progestogen HT is more effective than estrogen alone in treating hot flashes (Maclennan *et al.*, 2004). Data from KEEPS recently confirmed decades of studies (Santoro *et al.*, 2017). Low doses were proven efficient in resolving VMS in almost all

symptomatic women (Santoro *et al.*, 2017). For this reason, in clinical practice, it is appropriate to begin HT at low dosages and to increase them gradually in case of symptom persistence.

Selective estrogen receptor modulators and tissue-selective estrogen complex. While raloxifene worsens hot flashes (Yang *et al.*, 2013), the BZA/CE (BZA 20 mg/day/CE 0.45 mg) combination is efficient and, thanks to the CE component, is effective and approved for the treatment of VMS (Komm *et al.*, 2014).

Tibolone. Tibolone (2.5 mg/day) is more effective than a placebo in reducing VMS, however, less successful than combined HT in postmenopausal women (Formoso *et al.*, 2016).

Cognitive decline

Estrogen and estrogen–progestogen combinations. Cognition. Studies of healthy community-dwelling women are concordant about the observation that women who use HT (either unopposed estrogens or estrogens plus progestogen) perform better than nonusers on a broad spectrum of cognitive skills (Maki *et al.*, 2001; Miller *et al.*, 2002; Sherwin, 2003; Whitmer *et al.*, 2011). This is particularly true for women undergoing surgical menopause (Verghese *et al.*, 2000). In the Study of Women's Health Across the Nation (SWAN), women who started HT before their FMP had a positive cognitive effect. In contrast, those who initiated HT long after the FMP had a worse effect on cognitive performance (Greendale *et al.*, 2009). The NHS, however, found no significant improvement in cognition from the long-term use of HT (Kang *et al.*, 2004). Also, women who had started HT long after their FMP exhibited a more rapid cognitive decline (Kang *et al.*, 2004). WHIMS, an ancillary study of the WHI, aimed to evaluate the effect of estrogen plus progestogen on the incidence of dementia or mild cognitive impairment compared with placebo (Shumaker *et al.*, 2003). Rates of dementia in women aged 65 years or older randomized to CEE plus MPA were increased, but not in those taking CEE alone. At the early termination of the study, 40 women were diagnosed with probable dementia (HR 2.05) in the treatment group, after an average follow-up of 4.05 years, versus 21 in the placebo group. The incidence of mild cognitive impairment did not differ between groups. However, the women enrolled in the WHIMS clinical trial were, on average, 72 years old at the time of HT initiation, approximately 15 years after their FMP. This leads us to hypothesize that, as for CVD, there is a window of treatment opportunity for cognitive decline prevention in early postmenopause. Indeed, contemporary studies have shown a protective effect of HT against cognitive decline, in women subjected to oophorectomy, when they start close to the surgical menopause (Bagger *et al.*, 2005; Rocca *et al.*, 2007). This effect persists, even years after treatment cessation. In a cross-sectional study involving 428 subjects, women receiving HT before the age of 56 years scored higher on a test of global cognitive function and had better attention compared with those who started therapy after 56 years of age (MacLennan *et al.*, 2006).

Moreover, women who started therapy after the age of 56 years performed worse than those who never used HT (MacLennan *et al.*, 2006). The biological plausibility of the phenomenon lies in the evidence from basic science that the density of brain ER declines after menopause and with aging (Jaffe *et al.*, 1994), and that the beneficial metabolic and endothelial effects of E2 on cell function in healthy brain tissue are supplanted by detrimental effects in unhealthy age-damaged tissue (Clarkson, 2007; Brinton, 2008). So far, randomized placebo-controlled trials to test this hypothesis have shown a neutral effect of HT on cognition in women started on the treatment close to the menopause. The KEEPS-Cog, another RCT, recruited younger women (Gleason *et al.*, 2015) (mean age 52.6 years, mean menopausal age 1.4 years). Six hundred and ninety-three women were randomized to either daily oral CEE or transdermal E2 plus MPA (12 days per month), or placebo. No benefit or harm, therefore, a neutral effect, was reported on cognitive measures of women treated with HT compared to placebo. The WHIMS-Young (WHIMS-Y) study investigated 1326 women who had taken part in the WHI CEE-based RCTs at the age of 50–55 years (Espeland *et al.*, 2013). An average of 14.2 years after randomization to treatment and 7.2 years after treatment cessation, when women were 67.2 years of age on average, a battery of cognitive tests was administered via a telephone interview.

Contrary to the initial WHI results, these data indicated neither harm nor benefit to cognitive ability in women initiating HT early in postmenopause. The absence of cognitive effects during and immediately after HT is also consistent with the Early versus Late Intervention with Estradiol Study in recently menopausal women (Henderson, 2016). Many factors may affect cognition in women, and this area of gender medicine still needs much research to clarify the conflicting results yielded from observational and RCTs. To date, no RCTs have confirmed the window of opportunity for cognition. However, in a most recent analysis of the Cache County 12-year longitudinal population-based study of over 2000 healthy women, it was found that the greatest benefit of HT on objective measures of cognition was obtained when exposure to therapy, whether estrogen-only or combined, began within 5 years of the menopause, consistent with this hypothesis (Matyi *et al.*, 2019). HT initiated more than 5 years after the menopause nevertheless still produced beneficial effects compared to never use (Matyi *et al.*, 2019).

Alzheimer's disease. Observational studies have also provided indications for the view that the timing of HT initiation might be protective against the development of Alzheimer's disease (Zandi *et al.*, 2002; Henderson *et al.*, 2005; Imtiaz *et al.*, 2017), a typically gender-related disorder.

In an extensive observational study, the Cache County Study (Matyi *et al.*, 2019), HT exposure was associated with improved global cognition and attenuated decline over a 3-year interval. In women who received HT for more than 10 years in the same study, the excess gender-related risk of Alzheimer's disease disappeared. A post-WHI reanalysis (Shao *et al.*, 2012) of the same data, with extended follow-up, showed that women who had used any type of HT within 5 years of the menopause had 30% less risk of Alzheimer's disease, especially if therapy was protracted for 10 years or more. Alzheimer's disease risk was not reduced among those who had initiated HT 5 years or more after the menopause (Shao *et al.*, 2012).

Finnish researchers very recently reported that the prolonged E2 exposure, especially for over 10 years beyond the natural menopausal age with the use of HT, might determine a small increase in the risk of Alzheimer's disease (Savolainen-Peltonen *et al.*, 2019). However, this study suffers from several important biases among which the most influential, in our opinion, is that the women prescribed HT had VMS and, because of this, were more prone to developing cognitive dysfunction independently from the use of HT (Maki and Henderson,

2016). The association between HT use and Alzheimer's disease in this study, therefore, does not imply a causal relationship.

Stress and cognition. Stress exposure around the menopause may interfere with prefrontal cognitive processes, such as working memory (Kudielka and Kirschbaum, 2005; Ycaza Herrera and Mather, 2015), and this is mediated by a response in cortisol secretion (Oei *et al.*, 2006). A substudy of the ELITE trial demonstrated that HT limits the effects of stress on working memory, perhaps by aiding in the maintenance of proper hypothalamus–pituitary–adrenal axis reactivity (Herrera *et al.*, 2017). Long-term HT seems to reduce the free cortisol response to physical stress, independent from time of HT initiation (less than or more than 6 years postmenopause) (Ycaza Herrera *et al.*, 2015). Furthermore, it seems to benefit cognitive performance following an episode of acute stress compared to a placebo (Greendale *et al.*, 2009).

Dehydroepiandrosterone. Higher endogenous dehydroepiandrosterone sulfate (DHEAS) levels are independently and positively associated with several measures of cognitive function, such as executive function, concentration, and working memory (Genazzani *et al.*, 2006). Consequently, DHEA supplementation may seem an exciting treatment opportunity. DHEA treatment in postmenopausal women can induce the synthesis of neuroactive steroids, particularly allopregnanolone, and neuropeptides, such as β-endorphin, which are crucial for the modulation of mood, memory, and feeling of well-being during reproductive aging (Genazzani *et al.*, 2006). Moreover, under DHEA supplementation, women display a lower response to ACTH in terms of cortisol production, while the response of other adrenal steroids is preserved (Pluchino *et al.*, 2008). Our most recent data show that in postmenopausal women with lower (5th percentile) baseline DHEAS levels, even low-dose oral DHEA (10 mg/day) administration improves climacteric symptoms (Genazzani *et al.*, 2006) and reverses some age-related changes of adrenal enzymatic pathways (Genazzani *et al.*, 2006). In our study, cortisol secretion was blunted to a greater extent in DHEA-treated women (oral DHEA 25 mg/day) than in HT-treated (transdermal E2 50 µg/day plus MP 100 mg/day) women, an effect we believe could be beneficial for long-term cognitive functioning, in agreement with previously described data (Herrera, 2017).

Mood

Until only a few years ago, data from RCTs pointed toward the efficacy of E2 as an antidepressant only in depressed perimenopausal, but not postmenopausal, women (Rubinow *et al.*, 2015). On the other hand, the use of estrogen to treat depressed women who are more than several years postmenopause is bound to be a failure (Rubinow *et al.*, 2015). This finding is consistent with the 'critical window hypothesis', which suggests that E2 exerts beneficial effects only if it is administered close to cessation of ovarian activity. In the KEEPS trial, CEE (0.45 mg/day, with cyclic progesterone) but not transdermal E2 (50 µg/day, with cyclic progesterone) improved depressive symptoms compared to placebo (Gleason *et al.*, 2015). A very recent trial, for the first time, demonstrated that a 12-month administration of transdermal E2 (0.1 mg/day) and MP (200 mg/day for 12 days every 3 months) was more effective than placebo even in preventing the development of clinically significant depressive symptoms among euthymic perimenopausal and early postmenopausal women (Gordon *et al.*, 2018).

Effect of progestin component of hormone therapy on mood. Progestogens may dampen the antidepressant effect of estrogen therapy in nondepressed women (Sherwin, 1991; Zweifel and O'Brien, 1997). In a cross-sectional survey carried out in 176 healthy, mostly postmenopausal women, oral MP proved to be more neutral on mood than MPA (Fitzpatrick *et al.*, 2000). In a double-blind crossover study, cyclic oral MPA (10 mg/day for 12 days per 28-day cycle), in turn, was better on mood than cyclic oral norethisterone acetate (1 mg/day for 12 days per 28-day cycle) in women without a history of premenstrual syndrome receiving E2 2 mg/day continuously (Björn *et al.*, 2000). Women with a history of premenstrual syndrome experienced adverse mood effects with both progestogens (Björn *et al.*, 2000).

Route of administration may affect the influence of progesterone on mood. In a study on community-dwelling postmenopausal women, transdermal E2 associated with synthetic progestin caused an increased risk of depressive symptoms, while transdermal E2 alone or in combination with natural progesterone had a neutral effect (Scali *et al.*, 2010).

Progestin dosage may influence response in mood symptoms. In a randomized, double-blind cross-over study, women receiving 2 mg oral E2 continuously combined with 10 mg or 20 mg oral MPA sequentially for 12 days per cycle, both women with and without a history of premenstrual syndrome responded with more negative mood symptoms with the lower dose of MPA. In women with a history of premenstrual syndrome, the higher dose of MPA enhanced positive mood symptoms (Björn *et al.*, 2002). In a randomized, placebo-controlled, double-blind, crossover study, natural vaginal progesterone, similarly caused adverse mood effects in women without prior premenstrual syndrome, when administered at a lower dose of 400 mg compared to a higher dose of 800 mg (Andréen *et al.*, 2003). In contrast, women with previous premenstrual syndrome reported no progesterone-induced symptom cyclicity (Andréen *et al.*, 2003).

Sleep

Estrogen and estrogen–progestogen combinations. The vast majority of RCTs comparing HT to placebo have found that HT improves perceived sleep quality and self-reported sleeping problems more than placebo (Hays *et al.*, 2003; Brunner *et al.*, 2005; Welton *et al.*, 2008; Cintron *et al.*, 2017;). A recent meta-analysis of the literature revealed that HT is associated with improved sleep quality in women with sleep disturbance associated with VMS (Hays *et al.*, 2003) but that the effect of HT in women without VMS is not clear (Cintron *et al.*, 2017). In the recent KEEPS report (Cintron *et al.*, 2018), overall sleep quality was improved by both HT regimens (oral CEE 0.45 mg/day versus transdermal E2 50 µg/day) compared with placebo. However, transdermal E2 performed modestly better than oral CEE. Alleviation of VMS was positively associated with improvements in overall sleep quality, confirming previous reports (Cintron *et al.*, 2018). Therefore, it seems that it is the sleeping disturbances accompanied by nocturnal hot flashes that are most responsive to HT. Small studies have suggested natural progesterone improves subjective sleep quality and benefits selected polysomnography-based sleep parameters more than MPA in combination therapies (Montplaisir *et al.*, 2001; Gambacciani *et al.*, 2005). This effect is biologically plausible thanks to the prompt

metabolization of natural progesterone to allopregnanolone, a GABAergic agonist hypnotic inducer.

Tissue-selective estrogen complex. Data from the SMART-5 trial indicate that the BZA 20 mg/CE 0.45 mg/day combination has favorable effects on sleep. These effects were observed in postmenopausal women, both with moderate to severe and milder VMS (Pinkerton *et al.*, 2014).

Musculoskeletal system

Bone

Estrogen and estrogen–progestogen combinations. Conventional-dose HT prevents all fractures, including vertebral and hip fractures (Marjoribanks *et al.*, 2017). The WHI data were the first to provide substantial evidence of this fact (Writing Group for the Women's Health Initiative Investigators, 2002; Cauley *et al.*, 2003, 2006). Indeed women under HT benefited from a 34% reduction in hip fractures and a 24% reduction in total fractures (Writing Group for the Women's Health Initiative Investigators, 2002). HT also causes a decrease in vertebral fractures (Zhu *et al.*, 2016). This is paralleled by an increase in BMD (Manson *et al.*, 2013), an effect that had already been shown in PEPI (The Writing Group for the PEPI Trial, 1995) and other trials. HT is the only therapy available with proven efficacy of fracture reduction in patients without osteoporosis in early postmenopausal years (Bagger *et al.*, 2004). The preventive effect of HT, however, is probably attenuated when it is begun after 60 years of age (Zhu *et al.*, 2016). Stopping HT has no rebound effect on bone as no increased fracture risk, either sustained or transient, has been reported for former HT users compared with former placebo users in postintervention follow-up (Watts *et al.*, 2017). Although some studies have reported a loss in BMD after stopping HT (Karim *et al.*, 2011; Zhu *et al.*, 2016), WHI data indicate a significant residual benefit for total fractures that persisted over 13 years in the years following cessation of therapy in women assigned to CEE plus MPA (Manson *et al.*, 2013).

Low-dose HT may improve BMD in treated women (1 mg E2 + 0.5 mg norethisterone acetate or 0.5 mg of 17beta-E2 and 0.25 mg of norethisterone acetate); however, there are no results to date on fracture prevention (Gambacciani *et al.*, 2008; Zang *et al.*, 2010).

Raloxifene and tissue-selective estrogen complex. Raloxifene and BZA are ER agonists in the bone. As for raloxifene, two large studies, the MORE and RUTH trials, both showed a reduction in vertebral fracture risk but not in the incidence of hip fracture (Delmas *et al.*, 2002; Collins *et al.*, 2009). BZA 20 mg/day has shown to similarly reduce vertebral fracture risk, particularly in women with higher fracture risk (Reginster *et al.*, 2014; Palacios *et al.*, 2015). There are no data on fracture risk with BZA 20 mg/CE 0.45 mg/day, but improvement in total hip and femoral neck BMD was observed in a large RCT versus placebo (Lindsay *et al.*, 2009). When compared to estrogen–progestin therapy, tissue selective estrogen complex (oral BZA 20 mg/CE 0.45) BMD improvements were lower than in the women treated with oral CE 0.45 mg/MPA 1.5 mg (Pinkerton *et al.*, 2014).

Tibolone. Randomized, controlled studies show that tibolone, even at low doses (1.25 mg/day), increases BMD and reduces fracture risk (Ettinger 2007; Cummings *et al.*, 2008; Biglia *et al.*, 2010; Zang *et al.*, 2010). Tibolone (2.5 mg/day) was shown to have equal effectiveness to combined estrogen–progestin therapy (Biglia *et al.*, 2010) over the long term (Rymer *et al.*, 2002) (over 10 years), both in early and late postmenopause and in women with established osteoporosis. In women older than 60 years of age treated with tibolone (Cummings *et al.*, 2008), this benefit is overshadowed by the increase in stroke risk.

Muscles

In women at midlife, lean muscle mass, contrary to fat mass, seems to decrease, thus contributing to the change in body composition. Sarcopenia is more manifest in aging women than aging men and, although it cannot be attributed to the menopause, this degenerative process seems to evolve more rapidly after the FMP (Bondarev *et al.*, 2018). However, HT does not seem to confer a benefit in terms of gain in lean body mass. Although earlier studies had indicated preservation of muscle in women treated with HT (oral E2/norethisterone acetate) compared to placebo (Sipila *et al.*, 2001; Sorensen *et al.*, 2001), data from more recent large trials have not confirmed these results (Kenny *et al.*, 2005; Sites *et al.*, 2005; Thorneycroft *et al.*, 2007; Bea *et al.*, 2011;). Data from WHI BMD centers (Bea *et al.*, 2011) showed that lean body mass loss was smaller with either estrogen or estrogen–progestin treatment compared to placebo at 3 years. This result, however, was lost by 6 years, resulting in no differences between placebo and HT treatment groups. DOPS, likewise, found no significant difference for change in lean body mass between treatment and control over 5 years (Jensen *et al.*, 2003).

Joints

WHI data have revealed that estrogen and estrogen–progestin treatments result in less joint pain compared to placebo (Barnabei *et al.*, 2005; Chlebowski *et al.*, 2018). Moreover, women treated with HT develop less carpal tunnel syndrome (Al-Rousan *et al.*, 2018). The WHI has also demonstrated a reduction in the percentage of women who undergo joint replacement surgery among women taking HT compared to placebo, possibly indicating a role for HT in the preservation of cartilage (Cirillo *et al.*, 2006).

Intervertebral discs

Estrogen–progestogen treatment seems to have a positive effect on intervertebral disc height, which correlates with T-score (Muscat Baron *et al.*, 2007; Baron *et al.*, 2009). Adequate disc height is vital for the maintenance of shock-absorbing properties of the intervertebral disc and protecting the spine from vertebral compression fractures (Muscat Baron *et al.*, 2007; Baron *et al.*, 2009).

Skin and hair

The use of estrogen after the menopause increases collagen content, and therefore, the ability to retain water, with higher dermal thickness and elasticity (Calleja-Agius *et al.*, 2013). Prevention of skin aging seems to be maximal with the use of HT during the perimenopause (Phillips *et al.*, 2008). HT may exert a beneficial effect on the facial skin appearance by increasing rheological properties, however, not limiting the number and depth of wrinkles (Phillips *et al.*, 2008; Owen *et al.*, 2016). Through an improvement of skin blood flow, HT may positively affect wound healing and prevention. Elderly HT users, in a study of the UK General Practice Research Database, were reported to

develop fewer chronic leg ulcers and pressure-induced ulcers than nonusers (Margolis et al., 2002).

Urogenital system

The menopause leads inevitably to a constellation of urogenital symptoms, such as vaginal dryness, dyspareunia, vulvar itching and burning, dysuria, urinary incontinence, and recurrent lower urinary tract infections, termed the genitourinary syndrome of the menopause. Although the impact of genitourinary symptoms is comparable to that of severe medical conditions (Di Bonaventura et al., 2015), women are reluctant to report these disturbances, and so they are often neglected.

Vulvovaginal atrophy

Estrogen or estrogen–progestogen combinations. Symptoms of vulvovaginal atrophy can be treated with either topical or systemic estrogen therapy (Rahn et al., 2014). Estrogen therapy restores the normal vaginal flora, lowers pH, and thickens and revascularizes the vaginal lining. Thanks to its efficacy and excellent safety profile (Marjoribanks et al., 2017; Crandall et al., 2018), vaginal estrogen is generally the first-line approach to treat symptoms of vulvovaginal atrophy in the majority of women. Indeed, while systemic HT eliminates the symptoms of vulvovaginal atrophy in 75% of cases, vaginal therapy succeeds in 80–90% of cases (Goldstein, 2010). Local estrogenic compounds for genitourinary syndrome include E2, estriol, CEE, promestriene.

Low-dose vaginal estrogen is preferable and is available in the form of 4 µg vaginal inserts, a 7.5-µg vaginal E2 ring, or 10-µg E2 tablet (Zdravkovic et al., 2001; Constantine et al., 2018). By definition, low-dose vaginal estrogen is characterized by systemic absorption within normal postmenopausal E2 levels and, importantly, does not induce endometrial hyperplasia (Zdravkovic et al., 2001).

Selective estrogen receptor modulators and tissue-selective estrogen complex. Ospemifene. Ospemifene is the first nonestrogen treatment approved for moderate to severe dyspareunia in women with vulvovaginal atrophy (Paton, 2014). The effect of ospemifene on symptoms of vaginal atrophy and dyspareunia, vaginal epithelium, and pH of the vagina are comparable to those of vaginal estrogens (Goldstein, 2010). Improved histological features of the vaginal lining, with a reduction in parabasal cells and an increase in superficial cells are attainable with this therapy (Di Donato et al., 2019). In healthy postmenopausal women, ospemifene administered orally 60 mg/day for up to 52 weeks is safe. Although studies on ospemifene have been of short duration, no increase in cardiovascular, thromboembolic events has been reported with respect to placebo over a period of 52 weeks (Di Donato et al., 2019). Ospemifene treatment is statistically associated with a greater endometrial thickness in women with an intact uterus both at 12 weeks and at 52 weeks; however, this increase is not clinically relevant and has not resulted in endometrial pathology in women treated over this period (Di Donato et al., 2019).

Androgens: DHEA and testosterone. Vaginal DHEA. Vaginal DHEA goes through local conversion by enzymes (intracrine metabolism) into estrogens and androgens such as androstenediol, androstenedione, testosterone, and DHT (Labrie et al., 2015). In placebo-controlled clinical trials (Parish, 2013; Archer, 2015; Labrie et al., 2015; Sauer et al., 2018), the daily application of 0.50% (6.5 mg) DHEA improved objective parameters of vaginal atrophy: vaginal pH, vaginal epithelial maturation index, epithelial thickness and integrity, and lubrication (Labrie et al., 2016). Activation of the estrogen and androgen receptors through DHEA metabolites in the vagina, affects all three layers of the vaginal wall, including the fibers of the basal membrane collagen and the muscle wall, and results in significant improvement of dyspareunia (Labrie et al., 2016).

Vaginal testosterone. Researchers are evaluating intravaginal testosterone for improvement of vulvovaginal atrophy; this may be a promising new option for breast cancer survivors treated with aromatase inhibitors (Santen et al., 2017; Davis et al. 2018), for whom available options are very scanty. In a randomized placebo-controlled trial (Davis et al., 2018), intravaginal testosterone was tested in the form of a self-administered cream (300 µg per dose) daily for 2 weeks and then thrice weekly for 24 weeks.

Tibolone. Tibolone reduces vulvovaginal atrophy symptoms to a similar extent as conventional low-dose continuous combined hormone therapy, both at the dose of 2.5 mg (Swanson et al., 2006; Hammar et al., 2007) and 1.25 mg/day (Swanson et al., 2006).

Urinary incontinence

The vaginal route is preferred for the estrogenic treatment of urinary symptoms, such as frequency, nocturia, overactive bladder, and urge incontinence (Nappi and Davis, 2012). Vaginal estrogen therapy may also help prevent recurrent urinary tract infections with vaginal estrogens (Constantine et al., 2018). No benefit, on the other hand, is achievable on stress incontinence (Townsend et al., 2010; Cody et al., 2012; Nappi and Davis, 2012).

As for systemic HT, findings from the HERS trial revealed a negative impact of 0.625 mg of CE plus 2.5 mg MPA in older postmenopausal women with incontinence, which already became evident by 4 months of treatment (Grady et al., 2001). WHI follow-up data confirmed the data in women assigned to CEE plus MPA (Hendrix et al., 2005) and showed that the same trend occurred with CEE alone (Manson et al., 2013). The negative effects were attenuated but persisted after stopping in both trials (Manson et al., 2013).

A recent observational study showed that the exposure to systemic HT regimens, as well as vaginal E2, may favor the *de novo* development or worsening of pre-existing stress urinary incontinence (Rahkola-Soisalo et al., 2019).

HT may weaken pelvic floor muscles and also provoke pelvic organ prolapse (Rahkola-Soisalo et al., 2019). Women with this problem seeking relief for menopausal symptoms need to be made aware of this risk.

Sexuality

Throughout the 5 years following the FMP, sexual activity slowly decreases, independently of vaginal dryness, lubricant use, or mood disorders (Avis et al., 2017). Further on, the consolidation of vulvovaginal symptoms and the consequent dyspareunia can aggravate this and lead to avoidance of sexual intimacy altogether (Nappi et al., 2016).

Estrogen and estrogen–progestogen combinations

Postmenopausal HT has proven benefits on sexual function (Nappi et al., 2009). With estrogen or estrogen–progestogen therapy, a significant improvement in sexual function is attained, mainly through

improvement of dyspareunia, when used in women with menopausal symptoms or early postmenopause (Nastri *et al.*, 2013; Taylor *et al.*, 2017). Indeed, vaginal atrophy is the strongest predictor of sexual activity (Gass *et al.*, 2011). Recent findings from KEEPS, however, show that HT with transdermal E2 may perform better than oral CE on psychological domains of sexual function, possibly owing to the lack of sex hormone-binding globulin (SHBG) induction in the liver and consequent sequestration of circulating androgen levels (Taylor *et al.*, 2017). Indeed, besides ameliorating vaginal lubrication, transdermal E2 improves desire, arousal, orgasm, and sexual satisfaction, suggesting that the effect of this treatment on psychological aspects of the sexual response is independent of that on physiological aspects (Taylor *et al.*, 2017).

Dehydroepiandrosterone

DHEA ameliorates many aspects of sexuality, such as sexual interest, lubrication, arousal, orgasm, and increases sexual frequency (Scheffers *et al.*, 2015; Peixoto *et al.*, 2017). In a meta-analysis of studies involving the daily oral administration of DHEA between 10 mg and 1600 mg, with over 90% using ≤50 mg/day, positive effects were reported for women with sexual dysfunction, especially in perimenopausal and postmenopausal women (Scheffers *et al.*, 2015). Low endogenous DHEAS levels are negatively correlated with domains of sexual function in pre- and postmenopausal women more than testosterone levels. Our data showed that a 1-year treatment using oral DHEA 10 mg daily in symptomatic early postmenopausal women may improve sexual function and increases the number of sexual encounters (Genazzani *et al.*, 2011). Oral DHEA is not available as an approved pharmacological formulation but is marketed as a dietary supplement.

Vaginally administered DHEA has shown improvement in vaginal pain levels and lubrication along with an increase in the scores of sexual desire/interest, arousal, orgasm, and a decrease in pain with sexual activity compared to the use of a placebo (Peixoto *et al.*, 2017; Sauer *et al.*, 2018).

Testosterone

Even with adequate estrogen replacement, many women experience a persistent decrease in libido. Exogenous testosterone has been recognized to play a role in improving sexual desire (Somboonporn *et al.*, 2005; Achilli *et al.*, 2017). Randomized placebo-controlled trials have demonstrated that adding transdermal testosterone (300 µg/day) to HT or giving transdermal testosterone alone improves desire, the number of satisfying sexual events and of orgasms, and reduces personal distress (Achilli *et al.*, 2017). This is particularly true for women undergoing surgical menopause who experience an abrupt decline in testosterone levels (Braunstein *et al.*, 2005; Buster *et al.*, 2005; Simon *et al.*, 2005). However, the therapeutic use of testosterone can determine supra-physiologic levels of this steroid and can cause side effects such as acne and hirsutism.

Moreover, the long-term health implications of testosterone use on CVD and breast cancer risk in postmenopausal women are unclear to this date. This therapeutic strategy may offer benefit but must be restricted to a select subset of healthy women who continue to suffer from sexual dissatisfaction despite the establishment of an optimal HT regimen, and for a limited amount of time (6 months) (Baber *et al.*, 2016). A first Global Position Statement on the use of testosterone in the treatment of women was published just recently (Davis *et al.*, 2019), stating that testosterone is an effective treatment for hypoactive sexual disorder in postmenopausal women. Owing to the lack of available female formulations, male formulations of transcutaneous testosterone may be used as long as circulating testosterone levels are maintained within the physiological premenopausal range (Davis *et al.*, 2019).

Tibolone

In the *Livial International Study in Sexual Arousal Disorders* (LISA) and Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) studies, tibolone 2.5 mg/day proved to be as effective as estrogen–progestogen therapy in improving libido and sexual function (Biglia *et al.*, 2010). The effects of tibolone on sexual function may be mediated by its Δ^4-isomer metabolite, which stimulates the androgen receptor. Also, tibolone may increase the bioavailability of testosterone by reducing SHBG concentrations (Dören *et al.*, 2001).

Quality of life

Women's priority symptoms when evaluating their impact on the quality of life are mostly vasomotor, but also sleep, concentration, and fatigue (Carpenter *et al.*, 2015). These are central nervous system (CNS)-related disturbances and often come in clusters (Cray *et al.*, 2012), and can interfere with daily performance as well as well-being at the workplace and in the household. HT represents the most effective treatment to alleviate bothersome symptoms and improve quality of life. This fact is true for most estrogen–progestogen formulations, oral and transdermal, as well as for tissue selective estrogen complex and tibolone (Maclennan *et al.*, 2004; Welton *et al.*, 2008; Pinkerton *et al.*, 2014; Paoletti *et al.*, 2015; Simon *et al.*, 2019). Severely symptomatic women are the ones that experience the most significant improvement in the quality of life (Utian and Woods, 2013). WHI data, on the other hand, have not revealed significant benefits in terms of health-related quality-of-life outcomes in a subset of women 50–54 years of age with moderate-to-severe VMS treated with CEE, alone or in combination with MPA (Hays *et al.*, 2003; Brunner *et al.*, 2005).

It is important to comment that many scales used in past research investigated mostly disease symptoms and may not have picked up specific changes in quality of life. New scales, such as the Utian QOL scale, explicitly developed for the study of the sense of well-being in women, as distinct from menopausal symptoms, may reveal enhancements in quality of life even in women with no health-related issues (Utian *et al.*, 2018).

Well-being begins in the central nervous system. Transition states, such as the menopausal one, require a restructuring of regulatory networks, in other words adaptation to a new neuroendocrine status, that can take years (Petricka and Benfey, 2011). There are many hormonal targets for estrogens in the female brain. Acyclical fluctuations of E2 and sudden E2 withdrawal, which, in turn, cause secondary changes in the release and metabolism of neurotransmitters (such as serotonin, dopamine, and acetylcholine), neuropeptides and β-endorphin, as well as neurosteroids (namely allopregnanolone and dehydroepiandrosterone), account for the CNS-related menopausal symptoms (Genazzani *et al.*, 2007; Gordon *et al.*, 2016). According to an attractive theoretical model, changes in E2 and progesterone levels may cause fluctuations in progesterone-derived neurosteroids, particularly allopregnanolone, providing the basis of menopause-associated mood

symptoms (Slopien et al., 2018). In vulnerable women, the GABA A receptor, the main target of neurosteroids, may fail to adapt to changes in allopregnanolone levels (Slopien et al., 2018). In a very recent study it was shown that, in early postmenopausal women, falling allopregnanolone circulating levels correlate with Hamilton depression index and, in women during the late menopausal transition and early postmenopause, to the presence of specific depressive symptoms (shallow sleep and symptoms of the digestive tract in women during the late menopausal transition; feelings of guilt, sleep disorders and general somatic symptoms) (Slopien et al., 2018). The more symptomatic women are possibly the ones that adapt less well to the new menopause-induced hormonal status and are the ones who benefit the most from HT. HT has been shown to restore neurosteroid allopregnanolone and beta-endorphin levels in different estrogen-sensitive brain areas of ovariectomized rats (Stomati et al., 2002; Bernardi et al., 2006; Pluchino et al., 2009) and, in postmenopausal women, to increase circulating levels of GABA-A agonist allopregnanolone and beta-endorphin (Stomati et al., 1997; Pluchino et al., 2005).

Aging process

Telomeres are noncoding portions of chromosomal DNA. The shortening of telomere length (TL) is associated with mitotic aging, and the rate at which this occurs is proportional to disease risk and mortality (Blackburn et al., 2015). In the NHS, neither age at menopause nor duration of total or estrogen-only HT use were correlated with leucocyte TL (Prescott et al., 2012). Other observational studies have found an absence of correlation between exogenous hormone use and blood cell TL and telomerase activity (Dalgård et al., 2015; Kresovich et al., 2018). An earlier study suggested that longer endogenous estrogen exposure, in terms of reproductive years, is associated with greater TL and with lower telomerase activity, however, the length of exogenous HT was not associated with TL or telomerase activity (Lin et al., 2011). The results suggest that the endogenous estrogens may be associated with a deceleration of cellular aging. Interestingly, a small randomized longitudinal study showed that postmenopausal women carriers of apolipoprotein E (APOE)-e4, a major genetic risk factor for cognitive decline, Alzheimer's disease and early mortality, may benefit from HT started early in that it seems to decelerate telomeric shortening. In the same study, no protective effect was found for noncarriers. The researchers concluded that, in women with a genetic vulnerability to cognitive decline, HT may reduce TL attrition and neurological aging (Jacobs et al., 2013).

Cellular aging may proceed through pathways operating independently from TL. An emerging marker of nonmitotic cellular aging is epigenetic age calculated from DNA methylation and is strongly correlated with chronological age (Horvath and Raj, 2018). Menopause is associated with accelerated epigenetic aging through increased DNA methylation (Levine et al., 2016). In an extensive study examining the data from four large observational studies, a longer time since menopause (irrespective of age at menopause) was found to be associated with increased epigenetic aging. Surgical menopause was also associated with increased biological aging in both blood and saliva. This finding may in part explain the increasing evidence that both spontaneous or surgical primary ovarian insufficiency is associated with an increased risk of CVD, and all-cause mortality (Honigberg et al., 2019). A very recent study has demonstrated that worse VMS, the hallmark of menopause, are associated with accelerated epigenetic aging, particularly if these are late-occurring (Thurston et al., 2020). Exposure to menopausal hormone therapy was found to be associated, on the contrary, with decreased epigenetic aging of the buccal epithelium (Levine et al., 2016).

HT may have differential effects on cell aging; this area of medicine deserves to be further explored and may represent to grounds for true tailoring of hormone therapy.

Hormone therapy and cancer

Breast cancer

Estrogen and estrogen–progestogen combinations

The causality of HT in breast cancer risk is very complicated. Breast cancer is the main reason for women not initiating or stopping HT. This is because the media gave incredible resonance to the slightly increased risk observed in the combined estrogen–progestin (CEE/MPA) arm of the WHI, with consequences on public opinion (Writing Group for the Women's Health Initiative Investigators, 2002). Within the WHI trial, results for breast cancer were divergent in the two arms (CEE-alone vs CEE/MPA), with increased risk in the women randomized to CEE/MPA and borderline/reduced risk in those randomized to CEE alone during the intervention period (Writing Group for the Women's Health Initiative Investigators, 2002). It is important to remark that, in the women who had never been treated with hormones before entering the study, there was no excess risk of breast cancer. The increased risk was seen in women who were previously exposed to 5–10 years of HT (Anderson et al, 2006; Prentice et al., 2008).

Moreover, the increased breast cancer risk, and more advanced cancers seen in the combined HT arm, may have reflected the effect of the changes in the hormonal environment on previously existing tumors in a population of women whose age was, per se, a risk factor for breast cancer. Poststopping follow-up showed persistence of a slight risk in the CEE/MPA arm, corresponding to less than one additional case of breast cancer diagnosed per 1000 users of combination hormone therapy annually (Manson et al., 2013). However, more specific time-dependent analyses identified risk attenuation with time since cessation of use (Chlebowski et al., 2010). In the CEE-alone arm of the WHI, a protective effect against breast cancer was observed, that became significant over the early postintervention phase but dissipated during the late postintervention follow-up (Manson et al., 2017). Many observational studies agree in affirming that HT carries a slightly increased breast cancer risk (Kerlikowske et al., 2003; Bakken et al., 2011; Chlebowski et al., 2015; Collaborative Group on Hormonal Factors in Breast Cancer, 2019;), especially with use over 5 years (Lyytinen et al., 2006). In a very recent report of the Danish Diet, Cancer and Health Cohort study, higher breast cancer mortality (HR 1.34; 95% CI 1.05–1.72) only became evident in HT users after 15 years of follow-up (Holm et al., 2019). According to other studies, exposure to estrogen-only treatment does not increase breast cancer incidence (Manson et al., 2013; O'Brien et al., 2015; Jones et al., 2016;). Moreover, mortality from breast cancer in HT users is reduced (Mikkola et al., 2016; Chen et al., 2016).

Robust observational data seem to indicate that women younger than 50 years do not have increased risk of breast cancer under HT (O'Brien *et al.*, 2015), and this is very reassuring for all those women who develop primary ovarian insufficiency (Chen *et al.*, 2002; Ewertz *et al.*, 2005). This is true even for those women with a family history of young-onset breast cancer (Mikkola *et al.*, 2016). An analysis by subgroups study has demonstrated that the risk of developing breast cancer depends on the type of formulation and regimen of therapy (Simin *et al.*, 2017).

Type of estrogen. CEE is protective against breast cancer in the population of women randomized to this treatment in WHI. This is the first evidence of this kind. A working biological theory on the argument states that estrogen triggers apoptosis in estrogen-deprived breast cancer cells (Jordan, 2015). Whether this theory extends to all estrogens is questionable.

Route of estrogen administration. The route of systemic HT does not seem to make a difference in breast cancer incidence (Farrell *et al.*, 2016). However, estrogens delivered vaginally do not increase breast cancer incidence (Crandall *et al.*, 2017) also due to the extremely low systemic exposure to these hormones. In this regard, vaginal estrogen has been advocated, in co-ordination with the oncologist, in survivors of breast cancer who are unresponsive to nonhormonal remedies (American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and Farrell, 2016).

Type of progestin. Based on the divergent breast cancer incidence between CEE-alone and the CEE/MPA arm, a causal role for MPA was hypothesized in breast cancer development (Writing Group for the Women's Health Initiative Investigators, 2002). However, other progestins may confer an increased risk of breast cancer, as reported by the Million Women Study, in which the current use of HT preparations containing estrogen plus progestogens determined a substantially higher risk for breast cancer than any other type of HT (estrogen-only, tibolone) (Beral, 2003). A large longitudinal study, including older naturally menopausal women, has shown on the other hand that MP and dydrogesterone are associated with a lower risk of invasive breast cancer compared to that observed with other progestogens (Chen *et al.*, 2006; Fournier *et al.*, 2008; Fournier *et al.*, 2014).

Tibolone

LIBERATE, a randomized, placebo-controlled double-blind, parallel-group trial was designed to demonstrate that tibolone 2.5 mg/day was noninferior to placebo on breast cancer recurrence in women with climacteric symptoms and a history of breast cancer (Bundred *et al.*, 2012). However, in the study subjects, the incidence of breast cancer recurrence increased and was highest in the group with women with normal BMD, which probably had a higher lifetime exposure to estrogen, compared to those with low BMD (Bundred *et al.*, 2012). The joint analysis of RCTs indicates that tibolone does not increase the risk of breast cancer development compared with placebo (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). Finally, a 1-year tibolone treatment has proven to decrease breast density, thanks to a reduction in proliferation and a stimulation of apoptosis (Valdivia *et al.*, 2004).

Selective estrogen receptor modulators and tissue-selective estrogen complex

Raloxifene prevents ER-positive breast cancer regardless of a woman's baseline breast cancer risk; however, it does not affect the risk of non-invasive or ER-negative breast cancers. The ability of raloxifene to prevent invasive breast cancer has earned its approval in the USA as a prevention treatment for breast cancer. This effect has been observed during treatment and persists for at least 5 years after treatment cessation (Grady *et al.*, 2008; Cuzick *et al.*, 2013). Tissue selective estrogen complex has not been adequately tested for breast cancer risk as yet, although a neutral effect on the breast was observed over 2 years in randomized clinical trials (Pinkerton and Conner, 2019). In truth, the SMART trials were not powered for breast cancer as a clinical outcome. BZA has not been found to increase breast density, which correlates with breast cancer risk (Pinkerton *et al.*, 2013).

Effects in carriers of breast cancer gene 1/2 gene mutation

With the advent of genetic testing for the breast cancer gene (BRCA) 1/2 gene mutation to determine predisposition for breast and ovarian cancer, many women are choosing to undergo bilateral salpingo-ovariectomy in premenopause. Although these women can benefit significantly from HT in terms of quality of life and mortality risk reduction owing to CVD (Parker *et al.*, 2013), there is concern that exposure to this treatment can oppose the achievement of optimal breast cancer risk reduction. Observational studies have shown that the use of systemic HT is associated with a neutral or reduced risk of breast cancer in these women (Rebbeck *et al.*, 2005; Eisen *et al.*, 2008). In a very recent cohort study during a 7.6-year follow-up, with the use of any type of HT, there was no increase in breast cancer in these patients, when comparing HT users versus nonusers (Domchek *et al.*, 2011). However, there was a significant difference between breast cancer risk when comparing estrogen-alone therapy versus estrogen plus progestogen, with a higher risk in combined therapy users (Domchek *et al.*, 2011). Based on the available literature, breast cancer risk reduction following salpingo-ovariectomy in premenopausal BRCA carriers without a history of breast cancer is not affected by HT (Kotsopoulos *et al.*, 2018). Estrogen-only HT is preferable over progestin-containing methods in BRCA mutation carriers (Gordhandas *et al.*, 2019). For women taking estrogen/progestin, options to minimize systemic progestin include intermittent progestin withdrawal every 3 months or the use of a progestin containing IUD (Kotsopoulos *et al.*, 2018) or hysterectomy, given that these patients may be at increased risk of uterine cancer when exposed to HT (Kotsopoulos *et al.*, 2018).

Ovarian cancer

Estrogen and estrogen–progestogen combinations

In the CEE/MPA arm of the WHI trial, a nonsignificantly elevated risk of ovarian cancer was identified over 13 years of cumulative follow-up (Manson *et al.*, 2013). Data from a Danish registry study reported a risk of ovarian cancer in HT users that approximates one extra ovarian cancer for roughly 8300 women taking HT each year (Mørch *et al.*, 2009). A huge meta-analysis by the Collaborative Group on Epidemiological Studies of Ovarian Cancer reported that ovarian

cancer is significantly increased in current users (Beral et al., 2015). However, the increase is essentially limited to the two most common histological types, serous and endometrioid estrogen-only and of estrogen–progestogen preparations, or between women who had begun HT before or after the age of 50 years (Beral et al., 2015). However, there is a lack of experimental evidence to explain the biological plausibility of the implication of HT in ovarian carcinogenesis.

Selective estrogen receptor modulators and tissue-selective estrogen complex

BZA does not seem to increase the incidence of ovarian cancers (Pinkerton et al., 2009).

Endometrial cancer

Estrogen and estrogen–progestogen combinations

In postmenopausal women, the addition of a continuously combined progestin to estrogen decreases endometrial cancer incidence (Chlebowski et al., 2015). The recent observation of an increase in endometrial cancer rate in the USA was associated with a decrease in the use of approved estrogen–progestogen therapy post-WHI (Constantine et al., 2019). The increased use of compounded hormone therapy following the WHI, with a perhaps inappropriate progestogen opposition, may be a contributing factor (Dubaut et al., 2018). In the Million Women Study, the use of continuous combined preparations was associated with a lowered risk of endometrial cancer, especially in obese women who usually have a higher incidence of endometrial cancer than nonobese women (Beral et al., 2005).

Selective estrogen receptor modulators and tissue-selective estrogen complex

BZA does not increase the incidence of endometrial cancer (Pinkerton et al., 2009).

Colorectal cancer

Both observational and randomized clinical trials have reported that women using combined estrogen–progestogen HT have a lower risk of developing colorectal cancer (Grodstein et al., 1998; Writing Group for the Women's Health Initiative Investigators, 2002; Morois et al. 2012), while E2 use may increase the risk of developing adenoma (Morois et al., 2012). This risk-reducing effect on cancer tends to persist for 4 years after stopping HT. Similar results were found for tibolone treatment in a population of women aged 60–79 years (Bots et al., 2006).

Prescribing hormone therapy: evaluating risk

The challenge of modern menopausal medicine is creating a benefit-risk profile and tailoring HT to each woman seeking relief for menopausal symptoms.

Concerning CVD risk, although chronological age is an essential determinant of global health status, cardiovascular status plays a more significant role in determining whether a woman is a good candidate for HT. In WHI, it is the women with elevated LDL-cholesterol concentrations, other dyslipidemias, or metabolic syndrome, but not those without these risk factors, that had increased risks of coronary events while using HT (Aedo et al., 1990; Manson et al., 2013; Wild et al. 2013; Bassuk and Manson, 2014). Healthy women, on the other hand, may benefit from a reduction in cardiovascular risk and stroke (Bray et al., 2008).

BMI plays a significant role in determining VTE risk (Heit, 2015). Indeed, women with a BMI $<25\,kg/m^2$ tend to have a lower risk than women in the overweight or obese categories (Heit, 2015). Moreover, excluding thrombophilic conditions and personal predisposition to VTE could be very important. A nested case–control study in the two Women's Health Initiative hormone trials demonstrated that D-dimer testing in advance of HT prescription might help to identify women for whom the risk is higher (Cushman et al., 2018). In the study, women with D-dimer >0.54 mg/l (top quartile) had nearly a 3-fold higher risk of future VTE than women in the lowest quartile on HT and a risk six times that of women with lower D-dimer on placebo (Cushman et al., 2018). Altered protein C and free protein S, prothrombin fragment 1.2, and plasmin–antiplasmin complex levels were also associated with the risk of future thrombosis to a lesser extent (Cushman et al., 2018). With further confirmatory studies, soon, a panel of biomarkers could be adopted in menopausal medicine as a decision-making tool to select and reassure women with a low VTE risk about taking HT. In any case, physicians can choose to prescribe transdermal HT, which does not appear to increase the risk of thrombosis in women with thrombophilic conditions (Rott, 2014). Transdermal estrogen formulations represent an appropriate choice for all women, especially older menopausal women, and those who are overweight or obese (Oliver-Williams et al., 2019) or have diabetes (Oliver-Williams et al., 2019). Moreover, a progestogen with neutral effects on glucose and lipid metabolism, such as MP, can also be used in women with increased baseline thromboembolic and cardiovascular risk (Slopien et al., 2018). Owing to higher absolute risks of CHD, stroke and VTE in women 10 years after the menopause or >60 years old, HT should be initiated for the shortest time possible, at the lowest possible dose and preferably by transdermal administration (<50 µg/day of estrogen) (Laliberté et al., 2018; Oliver-Williams et al., 2019).

As for breast cancer risk, one must keep in mind that estrogens and progestogens are not cancerogenic compounds. They promote already existing tumors for which menopausal women must undergo timely screening, especially before starting HT. It was indeed estimated that 93.3% of the breast cancers in the WHI CEE/MPA trial were occult tumors (Beral, 2003). It was estimated that CEE/MPA simply decreased the average doubling time from 200 to 150 days (Santen et al., 2012). The endogenous risk of breast cancer is 2.8% by age 60 years, while the putative risk of breast cancer increases to 3.37% with HT use for 5 years; the absolute increase is 0.67% (Santen et al., 2012). This is inferior to the risk of developing breast cancer conferred by obesity, by being a flight attendant, or by other common exposures (Bluming and Tavri, 2012). Finally, appropriate follow-up during HT usually allows diagnosing tumors with no discernible difficulty compared to nonusers (Cheek et al., 2002).

Absolute contraindications to HT are as follows and must be ruled out before commencing HT: all estrogen-sensitive diseases such as breast or endometrial hyperplasia and cancer, severe active liver disease, CHD, stroke, dementia, a personal history or inherited high risk of thromboembolic disease, porphyria cutanea tarda, or

hypertriglyceridemia (Sarri *et al.*, 2015; Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017).

Some existing conditions may worsen with HT and must be weighed against the benefits of this therapy. Migraine headaches may increase while on HT (MacGregor, 2018). However, there is no contraindication to the use of physiological doses of natural estrogen in women with migraine with or without aura. It is advisable to use the lowest doses of transdermal estrogen, and continuous progestogens are preferable compared to cyclical progestogens to avoid setting off headaches (MacGregor, 2018). In women with psychiatric conditions, it is crucial to choose the proper treatment to prevent interaction with psychotropic drugs; in these women, natural vaginal progesterone or levonorgestrel (LNG)-releasing IUD are preferable (Brzezinski *et al.*, 2017). Women with a history of endometriosis must be well advised on a possible recurrence of the disease with HT. Current recommendations advocate the use of continuous combined preparations instead of unopposed estrogens for women with a history of endometriosis, even when subjected to hysterectomy (Gemmell *et al.*, 2017). Other gynecological conditions, such as stress urinary incontinence, genital prolapse (Nappi *et al.*, 2016; Rahkola-Soisalo *et al.*, 2019) and uterine leiomyomas (Sommer *et al.*, 2015), may worsen with systemic HT.

Hormone therapy regimens in clinical practice

Hormone therapy prescription: finding the right fit

Systemic treatment

Translating data from the literature to daily practice is not an easy task. We have identified six types of menopausal women (Figs 1, 2, 3, 4, 5, and 6) and provide evidence-based advice for HT prescription. Keeping in mind that the safeguard of the patient's health is of utmost importance, it is crucial to choose formulations that will produce benefits, while minimizing risks. Circulating hormone levels attained with various formulations depend on the dose and route of administration (Table I).

Figure 1a depicts a healthy early menopausal woman (≤6 years of the FMP (Harlow *et al.*, 2012)), who may require standard medium starting doses of oral (0.625 mg/day CEE, 1–2 mg/day E2) or transdermal estrogens (50 µg/day E2 patch, 1–2 mg/day E2 gel), combined with appropriate doses of endometrial-protective progestogens according to sequential or continuous combined regimen (5–10 mg/day dydrogesterone, 100–200 mg/day MP, 2 mg/day drospirenone, 1 mg/day norethisterone acetate) in women with a uterus. Progestogens may be added cyclically (12–14 days per 28-day cycle) within the first year of the FMP and continuously after that because of the better endometrial protection that the latter regimen offers (Beral *et al.*, 2005). Although this device is not officially approved for menopausal HT, an LNG-IUD releasing 20 µg/day may be used for endometrial safety. Alternatively tibolone may be used (1.25–2.5 mg/day), although this product is less efficient for the resolution of vasomotor symptoms (VMS) (Formoso *et al.*, 2016). Tissue selective estrogen complex (CEE 0.45 mg/-BZA 20 mg) is an innovation in terms of HT and may be particularly indicated in women with dense breasts (Pinkerton *et al.*, 2013), as this specific formulation is neutral on this feature.

With age, circulating DHEA concentrations will decrease to approximately 20% of those present in early adult life. In some women, there may be a correspondence between below reference range DHEAS levels and symptoms of fatigue, depression, and reduced sexual desire (Peixoto *et al.*, 2017). Although there are no clinical recommendations endorsing the use of DHEA supplementation in postmenopausal women, it is the author's experience that a benefit may come from a trial of oral DHEA at the starting dose of 10 mg/day up to 25 mg/day alone or as an adjunct to systemic HT (Genazzani *et al.*, 2006; Pluchino *et al.* 2008). Figure 2 portrays a healthy late postmenopausal women (>10 years past the FMP (Harlow *et al.*, 2012)) who should continue, rarely begin, treatment with ultra-low or low doses of oral (1 mg E2, 0.3–0.45 mg CEE), but preferably low doses of transdermal estrogens (25 µg/day E2 patch, 0.50–1 mg E2 gel) or tibolone (1.25 mg/day) (Fig. 2). Indeed, lower doses of estrogens have been shown to confer a lower risk of stroke and VTE (Grodstein *et al.*, 2000; Renoux *et al.*, 2010a, b; Canonico *et al.*, 2016; Shufelt *et al.*, 2019), the incidence of which increases in all women with age (Heit, 2015). Ultra-low doses of transdermal E2 (14 µg/day) are indicated for bone preservation and may not provide relief from VMS (Ettinger *et al.*, 2004). Drospirenone (2 mg/day) in a fixed dose associated with E2, may be used owing to its favorable effects on systolic and diastolic blood pressure, and myocardial perfusion reserve (White *et al.*, 2005; Knuuti *et al.*, 2007). Natural progesterone (100 mg/day) or its isomer, dydrogesterone (5 mg/day), administered continuously are highly recommended for endometrial protection in nonhysterectomized women, owing to the lower impact on the risk of VTE (Canonico *et al.*, 2010; Vinogradova *et al.*, 2019) and breast cancer (Beral, 2003), the incidence of which increases in all women with age (Barginear *et al.*, 2014). Oral DHEA supplementation at the starting dose of 10 mg/day up to 25 mg/day may be attempted, alone or as an adjunct to systemic HT for the reasons described above (Genazzani *et al.*, 2006; Pluchino *et al.*, 2008).

Figure 3 illustrates an overweight (BMI > 25) early menopausal woman (≤6 years of the FMP (Harlow *et al.*, 2012)). In this type of woman, transdermal estrogens (25–50 µg/day E2 patch, 1–2 mg/day E2 gel) are more appropriate because of the lower impact on VTE (Canonico *et al.*, 2007; Shufelt *et al.*, 2014; Simon *et al.*, 2016), the incidence of which increases with body weight (Heit, 2015). Where indicated, MP or dydrogesterone should be preferred for the same reason (Vidder *et al.*, 2010; Vinogradova *et al.*, 2019) (Fig. 3) in a cyclic fashion (200 mg/day MP, 10 mg/day dydrogesterone) within the first year following FMP, or a continuous fashion (100 mg/day MP, 5 mg/day dydrogesterone). Moreover, MP or dydrogesterone are seemingly neutral on breast cancer risk, which per se is higher in obese women (Chen *et al.*, 2002). Higher-than-standard doses of progestogens may be required for endometrial protection in women with high BMI (Baber *et al.*, 2016). The insertion of an LNG-IUD releasing 20 µg/day may be considered owing to the superior endometrial-protective effect in obese women that carry a baseline increased risk for endometrial hyperplasia (Ciccone *et al.*, 2019).

Figure 4 displays the older overweight (BMI > 25) late menopausal woman (>10 years past the FMP (Harlow *et al.*, 2012)) who should continue, seldom begin, treatment with ultra-low to low doses of transdermal E2 (transdermal estrogens (14–25 µg/day E2 patch,

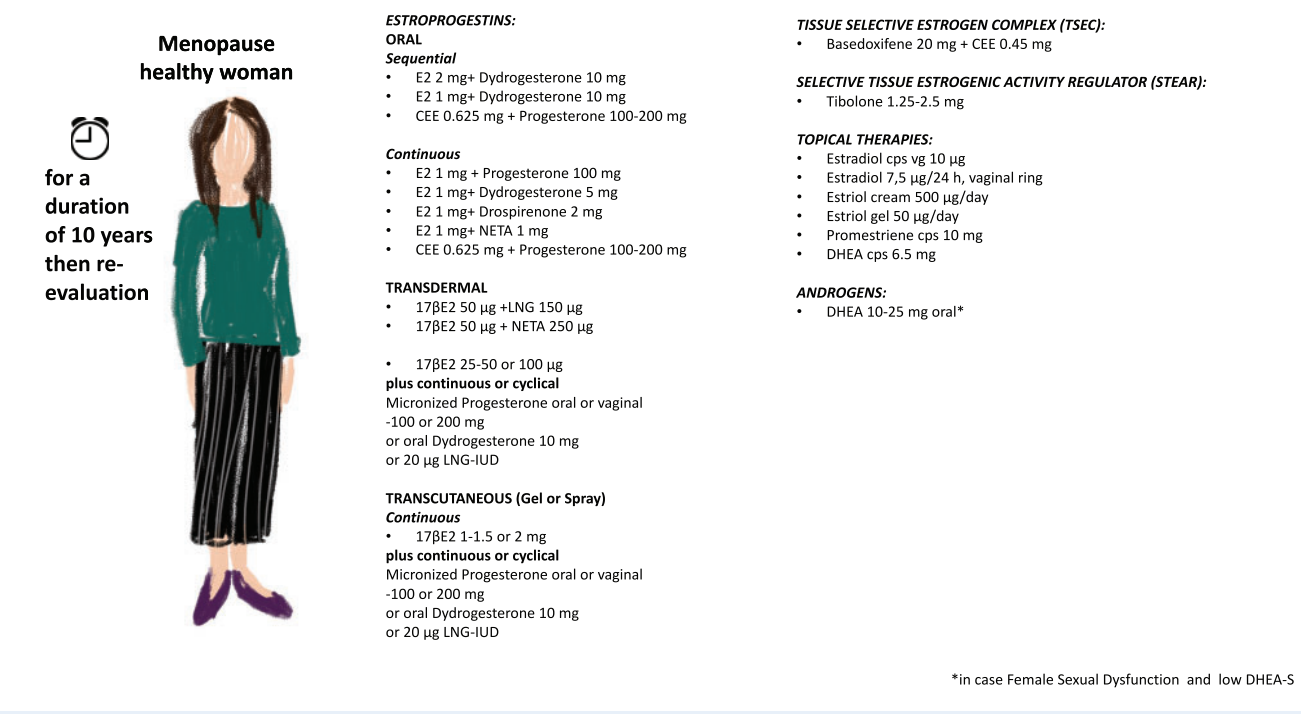


Figure 1 Recommended hormone therapy regimens for young, healthy early menopausal women. This category of patients can take all commercially available hormone therapies (HT) according to their preferences and needs for10 years and then they should be re-evaluated clinically. Sequential or continuous oral, transdermal and transcutaneous estroprogestins compounds, tissue selective estrogen complex (TESC), different doses of Tibolone, topical therapies and different doses of oral dehydroepiandrosterone (DHEA) are available for climacteric symptoms of these women.

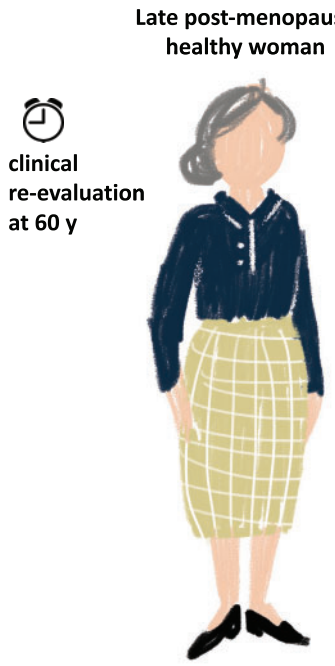
0.50–1 mg E2 gel)) after fully considering the risks associated with HT . Where indicated, MP or dydrogesterone (100 mg/day MP, 5 mg/day dydrogesterone) (Fig. 4) should be administered continuously.

Figure 5 depicts a woman who has undergone surgical menopause. This woman is particularly susceptible to developing menopausal symptoms because of the sudden deprivation of ovarian steroid hormones. Medium to high doses of oral (0.625 mg/day CEE, 1–2 mg/day E2) or transdermal estrogens (50–100 µg/day E2 patch, 1.5–2 mg/day E2 gel) are usually required, in combination with appropriate doses of progestogens where indicated (5–10 mg/day dydrogesterone, 100–200 mg/day MP, 2 mg/day drospirenone, 1 mg/day oral norethisterone acetate). Fixed transdermal E2 (50 µg/day) associated with 250 µg/day transdermal norethisterone acetate or 150 µg/day LNG may be used. The addition of testosterone therapy may be of benefit when hypoactive sexual desire disorder is diagnosed. Many countries do not have female formulations of testosterone, therefore, approved male transdermal 1% gel formulations may be used off-label in healthy women, provided that circulating testosterone levels do not exceed typical female range values (Davis *et al.*, 2019). In women with persisting low libido and fatigue, a trial of oral DHEA supplementation at the starting dose of 10 mg/day up to 25 mg/day may be used, alone or as an adjunct to systemic HT (Genazzani *et al.*, 2006; Pluchino *et al.*, 2008).

Figure 6 portrays a woman with primary ovarian insufficiency, who may be treated with medium to high doses of E2 (0.625 mg/day CEE, 2 mg/day E2) or transdermal estrogens (50–100 µg/day E2 patch, 1.5–2 mg/day E2 gel), combined with appropriate doses of progestogens where indicated (5–10 mg/day dydrogesterone, 100–200 mg/day MP, 2 mg/day drospirenone, 1 mg/day oral norethisterone acetate). Transdermal E2 (50 µg/day) associated with 250 µg/day transdermal norethisterone acetate or 150 µg/day LNG may be used. Contrary to other types of women where the treatment goal is to alleviate symptoms, in these subjects the goal is to achieve the average physiological serum E2 circulating levels of approximately 100 pg/ml at least until age 50 years, the average age at natural menopause (Nelson, 2009). However, in women desiring hormonal contraception, oral low-dose estrogen–progestin formulations (Santoro, 2015), such as E2 valerate 1–3 mg/day + dienogest 2 mg/day or E2 1.5 mg/day + nomegestrol acetate 2.5 mg/day, may be used . Contraception, improvement of VMS, and correction of erratic bleeding may also be obtained by using an LNG-containing IUD with supplemental transdermal estrogen, which has proven effective for perimenopausal women (Santoro et al., 2015). Transdermal 1% gel formulations may help improve hypoactive sexual desire disorder in these women.

Topical treatment

Vaginal estrogens may be used alone, or they may be added at standard doses to systemic (oral or transdermal) treatment when it does not fully alleviate genito-urinary symptoms. In the absence of contraindications, vaginal estrogen therapy may be administered without restriction for as long as it is needed because of the low systemic impact (Bhupathiraju *et al.*, 2018).



ESTROPROGESTINS:
ORAL
Continuous
- E2 1 mg + Progesterone 100 mg
- E2 1 mg + Dydrogesterone 5 mg
- E2 1 mg+ Drospirenone 2 mg
- CEE 0.45-0.3 mg + Progesterone 100 mg

TRANSCUTANEOUS (GEL)
Continuous
- 17βE2 0.50-1 mg

plus continuous
Micronized Progesterone oral or vaginal 100 mg or oral Dydrogesterone 5 mg

TRANSDERMAL
- 17βE2 25 µg

plus continuous
Micronized Progesterone oral or vaginal 100 mg or oral Dydrogesterone 5 mg

- 17βE2 ultra-low dose 14 µg

SELECTIVE TISSUE ESTROGENIC ACTIVITY REGULATOR (STEAR):
- Tibolone 1.25 mg

***TOPICAL THERAPIES* (Twice/week):**
- Estradiol cps vg 10 µg
- Estradiol 7,5 µg/24 h, vaginal ring
- Estriol cream 500 µg/day
- Estriol gel 50 µg/day
- Promestriene cps 10 mg
- DHEA cps 6.5 mg

ANDROGENS:
- DHEA 10-25 mg oral*

*in case Female Sexual Dysfunction and low DHEA-S

Figure 2 Recommended hormone therapy regimens for healthy late postmenopausal women. This category of patients can take all commercially available hormone therapy (HT) according to their preferences and needs but they should be re-evaluated clinically at 60 years to assess any acquired risk factors or contraindications. Continuous low doses of oral, transderamal and transcutaneous estroprogestins compounds, TESC, different doses of Tibolone, topical therapies and low doses of oral DHEA are available for climacteric symptoms of these women. DHEA, dehydroepiandrosterone.

Vaginal Prasterone treatment may be considered for the treatment of genitourinary syndrome in young prematurely, naturally or surgically menopausal, sexually active women, whether healthy or overweight, because of its proven positive effects on arousal/lubrication, orgasm, and dryness (Labrie *et al.*, 2009).

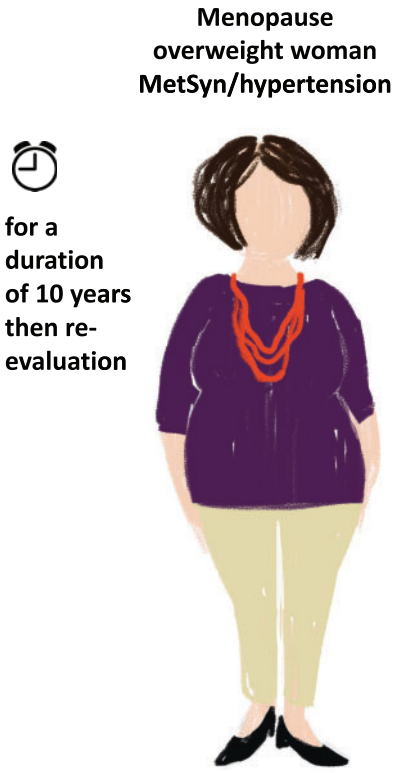
Dose titration and tapering

It is recommended to begin HT with ultra-low, or low doses (Sarri *et al.*, 2015; Baber *et al.*, 2016; The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017) and then titrate until VMS control is achieved. This is especially important for women with cardiovascular risk factors. Randomized placebo-controlled trials have shown that ultra-low doses of estrogen–progestogens (0.5 mg 17β-E2 combined with 2.5 mg dydrogesterone or 0.5 mg 17β-E2 combined with either 0.1 mg or 0.25 mg NETA) (Panay *et al.*, 2007; Stevenson *et al.*, 2010), and low doses (1 mg 17 β-E2 combined with 5 mg dydrogesterone) can significantly reduce reduced moderate to severe VMS (Hammar *et al.*, 2007; Zang *et al.*, 2010; Santoro *et al.*, 2017). All the while, beginning HT with low doses can increase tolerability and compliance by reducing irregular vaginal bleeding and breast tenderness (Zang *et al.*, 2010). Moreover, it has been suggested that lower doses of HT lower the risk of cardiovascular events: both stroke (Grodstein *et al.*, 2000; 2008) and VTE (Casanova *et al.*, 2015). In the observational NHS, ultra-low dose treatment with CEE demonstrated no increased risk of stroke (Grodstein *et al.*, 2000, 2008). However, these hypotheses must be confirmed by sufficiently powered trials. Ultra-low-dose oral HT with 0.5 mg 17β-E2 combined with 0.25 mg NETA/day has been used effectively to increase BMD at the lumbar spine and hip when compared to low-dose MHT (Huang *et al.*, 2007; Gambacciani *et al.*, 2008). However, the effects of estrogen on bone are dose dependent and there is some concern that not all women may have a significant benefit on BMD with low doses (Huang *et al.*, 2007). Indeed, the percentage of nonresponders increases as doses decrease. Moreover, there are no data on fracture risk reduction. Women needing HT for fracture risk prevention must be monitored more closely in order to modify treatment accordingly.

On stopping HT, women should be made aware that menopausal symptoms may recur (Brunner *et al.*, 2010). Unfortunately, tapering the therapy does not seem to offer greater benefits in the long term compared to stopping abruptly (Haskell *et al.*, 2009). Symptoms of urogenital atrophy will also recur with discontinuation of HT (Gass *et al.*, 2018).

Future perspectives

The WHI and large observational studies have taught us a lot about the effects of HT in postmenopausal women of different ages/conditions. Nonetheless, there are many unanswered



ESTROPROGESTINS:
TRANSCUTANEOUS (Gel or Spray)

Continuous
- 17βE2 1-1.5 or 2 mg

plus continuous or cyclical
Micronized Progesterone oral or vaginal -100 or 200 mg
or oral Diyhdrogesterone 5-10 mg
or 20 µg LNG-IUD

TRANSDERMAL
- 17βE2 25-50 µg

plus continuous or cyclical
Micronized Progesterone oral or vaginal -100 or 200 mg
or oral Dydrogesterone 5-10 mg
or 20 µg LNG-IUD

TOPICAL THERAPIES:
- Estradiol cps vg 10 µg
- Estradiol 7,5 µg/24 h, vaginal ring
- Estriol cream 500 µg/day
- Estriol gel 50 µg/day
- Promestriene cps 10 mg
- DHEA cps 6.5 mg

Figure 3 Recommended hormone therapy regimens for young early menopausal overweight or obese women with metabolic syndrome or hypertension. The therapeutical options for this category of women are limited to transcutaneous or transdermal compounds. For this type of patient, transcutaneous or transdermal continuous estrogens plus continuous or cyclical progestogens compounds and/or topical therapies should be preferred once the key risk factors have been assessed and according to their relative contraindications.

questions and there is still room for research. The main obstacles in furthering our knowledge in this area of medicine are the financial and time commitments required to design and carry out randomized placebo-controlled trials to ensure adequate power and a long enough follow-up. The many conflicting results, moreover, presented by the media, have led to a loss of interest in education and research in menopausal medicine. Modern midlife women, however, are highly engaged in important roles in society and need qualified support to maintain a suitable quality of life. Future research must concentrate on the following issues.

Duration of hormone therapy

Current international guidelines recommend initiation of HT in healthy women within 10 years of their FMP with moderate-to-severe VMS. Still, there is less clarity on when to stop HT. The decision to continue or discontinue HT should involve ongoing counseling, with periodic re-evaluation, and should be made on an individual basis. Annual reassessment is mandatory to make sure that treatment goals are being met and that new contraindications have not arisen. In the absence of contraindications, some guidelines advise that HT can be used for as long as the woman feels that the benefits outweigh the risks for her. Indeed, for a significant proportion of women, bothersome menopausal symptoms persist well into advanced age and constitute a problem (Gartoulla *et al.*, 2018). Menopausal VMS have been shown to continue, on average, for 7.4 years, and up to 12 years (Avis *et al.*, 2015). In women who are started on HT, early discontinuation and annual discontinuation is not a good practice, particularly in recently menopausal women. In women who discontinue HT, VMS recur in 50% of cases, regardless of whether HT is stopped abruptly or tapered (Brunner *et al.*, 2010). Discontinuation of HT may set off depressive symptoms in 5–10% of women (Grady *et al.*, 2003; Ockene *et al.*, 2005; Ness *et al.*, 2006; Brunner *et al.*, 2010;). These data were substantiated by a study on women with a history of perimenopausal depression who exhibited a rapid increase in depressive symptoms following an abrupt experimental withdrawal from E2 (Schmidt *et al.*, 2015). More importantly, in a recent large-scale population study, the discontinuation of HT was accompanied by risk elevations of 26–66% for cardiac or stroke death; women who were younger than 60 years at the initiation or discontinuation of HT use had the higher risk. The authors of the research paper hypothesized that acute withdrawal of vasodilatory estrogen might result in constriction of coronary arteries and fatal thrombogenic events, especially in younger women with preserved cardiovascular sensitivity to estrogens (Mikkola *et al.*,

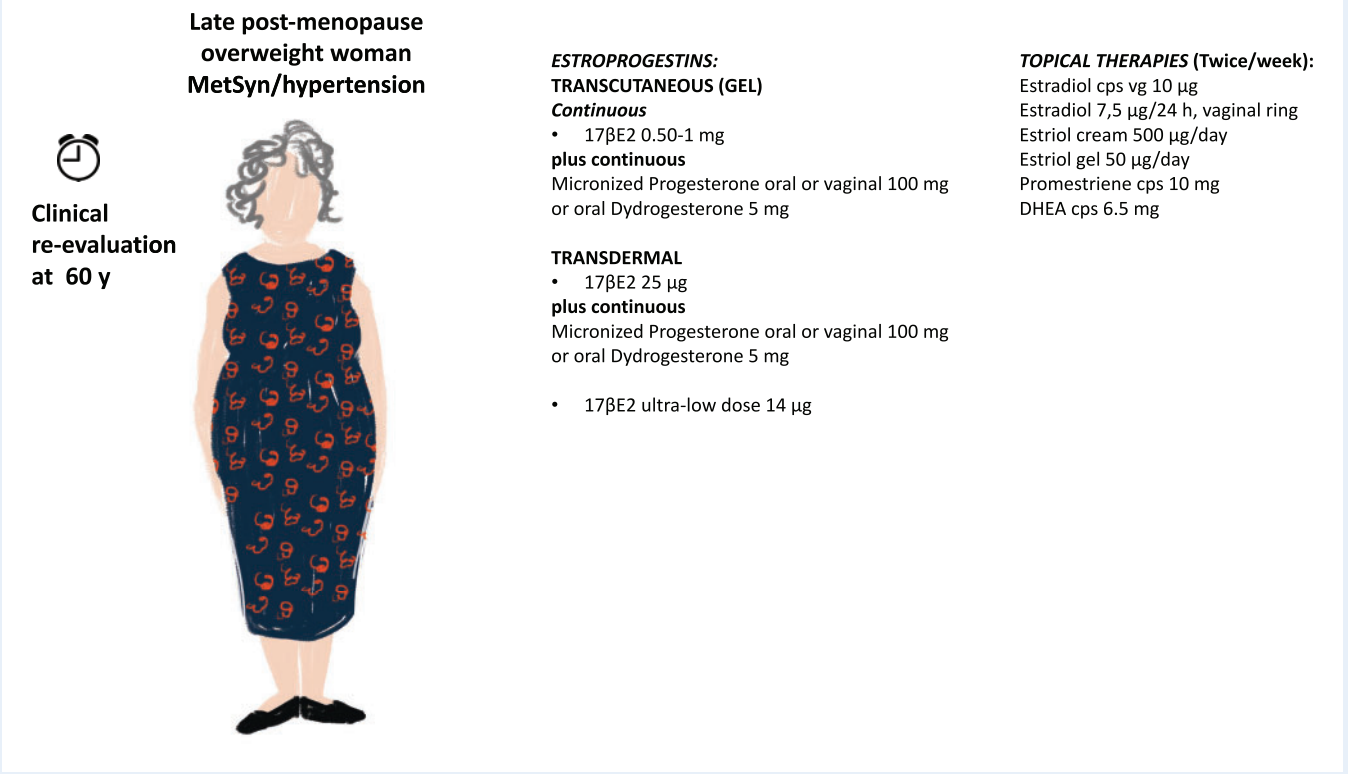


Figure 4 Recommended hormone therapy regimens for late menopausal overweight or obese women with metabolic syndrome or hypertension. The therapeutical options for this category of women are limited to transcutaneous or transdermal compounds. For this type of patient, transcutaneous or transdermal continuous low and ultra-low doses of estrogens plus continuous or cyclical progestogens compounds and/or topical therapies should be preferred once the key risk factors have been assessed and according to their relative contraindications.

2015). There is a need for RCTs on the impact of long durations of HT, initiated in the early postmenopause.

Cardiovascular risk and hormone therapy

The observed risk for CVD and thromboembolic events is not proportionate to the number of years of HT use. Findings from the WHI trial did not indicate an association between the duration of oral CEE and CEE/MPA use and CHD risk (Prentice *et al.*, 2009). Although, an increased stroke risk after ≥5 years of HT use was suggested (Prentice *et al.*, 2009), other studies found a null effect of HT duration on stroke risk (Schneider *et al.*, 2009; Casanova *et al.*, 2015). The Danish Osteoporosis Study reported no increased risk of stroke after 16 years of follow-up in recently menopausal women (Schierbeck *et al.*, 2012). On the other hand, HT can induce some cardiovascular benefits only if continued for long enough. In a population-based cohort study using the UK Biobank data, postmenopausal women free of known CVD who took HT for at least 3 years displayed better cardiac structure and function compared to those who had never used HT (Sanghvi *et al.*, 2018). Finally, the risk of VTE in women taking HT is higher within the first 2 years of use compared to subsequent years (Prentice *et al.*, 2009). RCTs are needed to assess the long-term cardiovascular safety, both in terms of CVD and VTE, of estrogens delivered through different routes (transdermal vs oral) combined with different types of progestogens.

Breast cancer risk and hormone therapy

In WHI, the risk of breast cancer observed in women treated with CEE/MPA was higher in older rather than younger women, and the risk did not increase for 7 years in women who have never received hormones in the past (Manson *et al.*, 2013). In contrast, those using CEE plus MPA had a nonsignificant increase in the risk of new breast cancer after 3–5 years (Manson *et al.*, 2013). In the DOPS, the use of E2 and norethindrone acetate did not cause an increase in breast cancer for up to 11 years of therapy and a 16-year follow-up period (Schierbeck *et al.*, 2012). In an observational study of hysterectomized women using CEE 0.625 mg/day, breast cancer risk did not increase for at least 15 years; this was mostly true for lean women (Chen *et al.*, 2006). In this study, the increased breast cancer risk emerged after 10 years of estrogen therapy but did not become statistically significant until after 20 years of ongoing estrogen use (Chen *et al.*, 2006). In the latest report of the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2019), the 20-year risk for 5 years current use followed by 15 years of past use was about 8.3% for estrogen combined with continuous progestogen, and 7.7% for estrogen plus cyclical progestogen, versus 6.8% for estrogen-only therapy. The 20-year excess risks with 10 years of use from age 50 years were estimated to be approximately double those with 5 years of use (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). However, most of the individuals

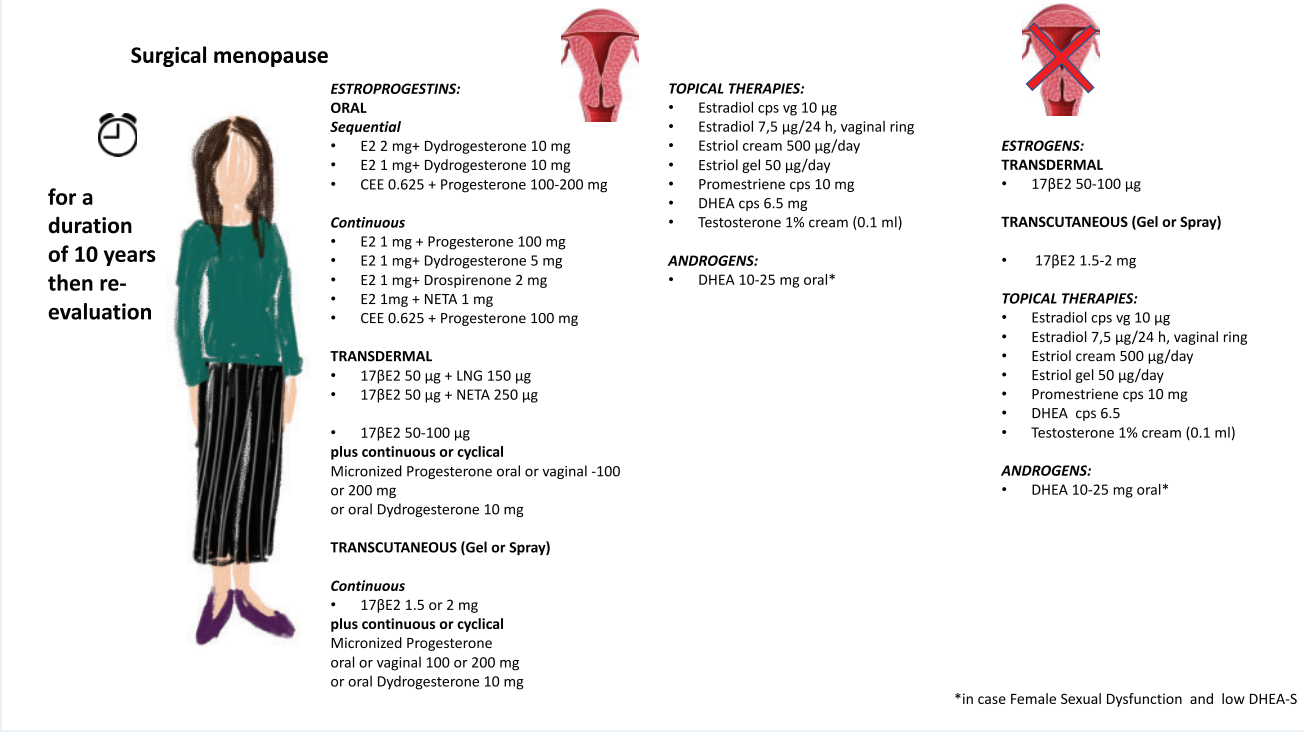


Figure 5 Recommended hormone therapy regimens for women who undergo surgical menopause. Nonhysterectomized patients can take several commercially available hormone therapy (HT). Sequential or continuous oral, transderamal and transcutaneous estroprogestins compounds, topical therapies and different doses of oral DHEA should be recommended for climacteric symptoms of these women. For hysterectomized women, continuous transderamal and transcutaneous estrogens, topical therapies and different doses of oral DHEA should be recommended. Both hysterectomized and nonhysterectomized patients can take the aforementioned therapies according to their preferences and needs for 10 years and then they should be re-evaluated clinically. DHEA, dehydroepiandrosterone.

included in the study used MPA and norethisterone acetate, the harmful effects of which have been studied on breast cells and revealed in the past decade (Lyytinen *et al.*, 2009; Courtin *et al.*, 2012; Ruan and Mueck, 2018). The study data reaffirm that the influence of progestogens is highly significant in determining the risk of breast cancer associated with HT (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). Randomized placebo-controlled clinical trials comparing the long-term risk of breast cancer in menopausal women treated with different progestogens are lacking. Moreover, there is a need for studies on the safety and effectiveness of tissue selective estrogen complex, selective estrogen receptor modulators or low-dose vaginal estrogen therapy or prasterone to treat menopausal symptoms in women who have a history of breast cancer.

Fracture risk prevention and hormone therapy

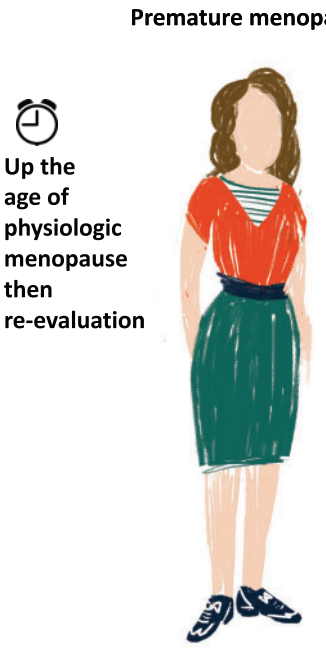
Osteoporosis-related bone fractures decrease with years of HT use (Manson *et al.*, 2013). Even after stopping HT, the benefits seem to last for years (Manson *et al.*, 2013). Research, however, is still lacking and should be promoted for a comprehensive understanding of the effects of HT when initiated early after the menopause. Moreover, the long-term effectiveness of low-dose and ultra-low dose HT on fracture prevention needs to be investigated. Finally, answers are still lacking on the comparison of osteoporosis prevention in women with primary ovarian insufficiency between HT and combined hormonal contraceptives.

Dementia and hormone therapy

Data on the prevention of cognitive decline and HT are most controversial. First, it is important to remove bias due to patient selection. Studies should be performed clearly separating healthy postmenopausal women from those with a genetic risk for Alzheimer's disease and from those with a cardiovascular risk for vascular dementia. Second, randomized placebo-controlled studies should be implemented to test the 'timing hypothesis' with regards to this particular health domain. This is especially important for women with early and surgical menopause who are most susceptible to a loss of cognitive function (Verghese, 2000).

Conclusion

Changes in mood, sleep patterns, memory, and body shape, as well as the onset of vasomotor and urogenital symptoms will often startle women as they begin the menopausal transition. Distress caused by these symptoms may considerably affect a woman's personal and



ESTROPROGESTINS:

ORAL

Contraception need

- 17βE2+ NOMAC
- E2V+Dienogest

Non contraception need

Sequential

- E2 2 mg+ Dydrogesterone 10 mg
- CEE 0.625 + Progesterone 100-200 mg

TRANSCUTANEOUS (Gel or Spray)

Continuous

- 17 βE2 1,5-2 mg

plus continuous or cyclical

Micronized Progesterone oral or vaginal 100- 200 mg
or Dydrogesterone 10 mg oral

TRANSDERMAL

- 17βE2 50 µg +LNG 150 µg
- 17βE2 50 µg + NETA 250 µg

- 17βE2 50-100 µg

plus continuous or cyclical

Micronized Progesterone oral or vaginal 100 or 200 mg
or Dydrogesterone 10 mg oral
or 20 µg LNG-IUD

TOPICAL THERAPIES:

- Estradiol cps vg 10 µg
- Estradiol 7,5 µg/24 h, vaginal ring
- Estriol cream 500 µg/day
- Estriol gel 50 µg/day
- Promestriene cps 10 mg
- DHEA cps 6.5 mg
- Testosterone 1% cream (0.1 ml)

ANDROGENS:

- DHEA 10-25 mg oral*

*in case Female Sexual Dysfunction and low DHEA-S

Figure 6 Recommended hormone therapy regimens for women who experience primary ovarian insufficiency. Patients who experience premature menopause can take several commercially available hormone therapy (HT) up to the age of physiologic menopause and then they should be re-evaluated clinically. Oral contraception or sequential estroprogestins compounds, transcutaneous or transdermal continuous estrogens plus continuous or cyclical progestogens compounds or levonorgestrel (LNG)-IUD, topical therapies and different doses of oral DHEA should be recommended for these women. DHEA, dehydroepiandrosterone.

Table I Therapeutic ranges for estradiol and progesterone hormone therapy in postmenopausal women.

Progestogen	Daily dose (mg)			
	Oral		Intrauterine/implants	Vaginal
	Sequential	Continuous		
Micronized progesterone	200–300	100	–	100–200
Dydrogesterone	10–20	2.5–10	–	–
Medroxyprogesterone acetate	5–10	2.5	–	–
Nomegestrol acetate	5–10	2.5	–	–
Norethisterone acetate	1–2	0.5–1.0	–	–
Dienogest	3–4	–	–	–
Levonorgestrel	–	–	0.075–0.15	–
Norgestimate	–	–	0.09	–
Drospirenone	–	2	–	–

(-), not determined.

social life and therefore healthcare providers must be well prepared to guide patients and provide advice that will benefit their quality of life. A concept is emerging that some menopausal symptoms might be predictive of future health complications. Indeed, severe vasomotor symptomatology and poor quality of sleep have been found to be associated with an increased risk of CVD (Thurston *et al.*, 2008; ., 2011; Matthews *et al.*, 2013; Thurston 2017) and perimenopausal depression (de Kruif *et al.*, 2016). In turn, depressive symptoms, VMS, and sleep

disorders may increase the risk of developing cognitive dysfunction (Ownby et al., 2006). An increased risk of osteoporosis and bone fracture has also been found in women suffering from severe hot flashes (Crandall et al., 2015). Finally, insomnia has been linked to decreased sexual function (Kling et al., 2017). It is quite clear, therefore, that leaving bothersome symptoms untreated in midlife women may lead not only to altered quality of life and reduced work productivity but also overall impaired health.

HT is an effective treatment for bothersome menopausal disturbances. Future studies are needed to verify whether targeting menopausal VMS can influence and benefit other domains of a woman's health. By adequately evaluating cardiovascular risk factors and VTE risk factors, health hazards can be minimized. Moreover, promoting a healthy lifestyle and eliminating any modifiable risk factors, such as obesity, alcohol, and tobacco consumption, can help to overcome a woman's risk of developing cancer. Finally, where possible, the transdermal route of HT administration should be preferred as it has the least impact on coagulation, glucose, and lipid metabolism. With combined treatment, natural progesterone should be favored as it is devoid of the antiapoptotic properties of other progestogens on breast cells. When starting HT, low doses should be used and increased gradually until effective control of symptoms is achieved.

Unless contraindications develop, patients may elect to continue HT until the risks outweigh the benefits. Menopause occurs within a natural aging process; therefore, regular reassessment of the woman's health status is necessary. Women should be made aware that there is a slightly increased risk of stroke that tends to persist for the whole duration of treatment, and breast cancer risk with long-term estrogen-progestin use. However, healthy early initiators of HT will probably gain more profit than harm by improving bothersome symptoms, while obtaining offset benefits such as cardiovascular risk reduction, increase in BMD and a reduction in bone fracture risk, plus a decrease in colorectal cancer risk and overall mortality (Holm et al., 2019). Women with premature menopause and beginning HT before age 50 years seem to have the most significant advantage in terms of longevity, according to a very recent cohort study from the Netherlands (Brandts et al., 2019).

Tailoring treatment also means considering a women's needs such as her right to have a satisfying sex life or her obligation to preserve body image, her work, or her athletic performance. These are all critical factors to consider in choosing the right treatment option. Androgen replacement, in addition to HT, may, therefore, be taken into consideration in selected cases (Figs 2, 3, and 4). In this regard, HT may also help to maintain the ability to continue coping with her environment. In view of the role that women have in society, a new challenge of healthcare is that of guaranteeing a corresponding quality of life. Menopausal medicine is far from recommending HT to women for anything besides the treatment of bothersome menopausal symptoms, but it is very close to improving women's daily lives.

Data availability

No new data were generated or analyzed in support of this research.

Authors' roles

A.R.G. is the main author and responsible for manuscript drafting and critical discussion. P.M. is responsible for literature search, manuscript drafting, and critical discussion. A.G. is responsible for literature search, critical discussion, figures, and tables. T.S. is responsible for critical discussion.

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Conflict of interest

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