INTRODUCTION

The rates of cardiovascular disease, osteoporosis, dementia and the decline of quality of life among elderly people in the next century will be greatly determined by the success of possible preventing measures. Postmenopausal estrogen deficiency is a causal or a contributing factor of different conditions and diseases that can induce a worsening of women health and quality of life. Menopause is not a disease, and the vast majority of women do not need therapies, but some of them need hormone replacement. However, randomized clinical trials have clearly indicated that postmenopausal hormone replacement therapy (HRT) is not a remedy that can be administered to everyone (1, 2). Some publication in the past few years have led to a change in the indication of an already established therapy such as the publication of the Women’s Health Initiative (WHI) results did for HRT. All the recent reports regarding HRT have caused great uncertainty and alarm among physicians, women, and media. Lately, the Chairman of the Committee on Safety of Medicines (CSM) in the UK issued further advice on the use of HRT. The new surprising conclusion is that the risk-benefit of HRT is unfavorable for the prevention of osteoporosis as first-line therapy in women who are over 50 years of age and at an increased risk of fractures, but no recommendations are made as to what agents should be used. Shortly after, the European Agency for the Evaluation of Medicinal Products (EMEA) advised all the Member States’ competent Agencies that HRT should not be the first choice of therapy for preventing osteoporosis.

WHI AND THE CLINICAL PRACTICE

Not one single study can be defined as definitive. The WHI study was a tremendous effort from the investigators, the NHI and the USA tax payers, but sometimes despite all best intentions the scientific results (i.e. population selection, drop-out rates, statistical power in subgroups, duration) were not at the level that such effort deserved. Notwithstanding, the WHI data have been over interpreted and misinterpreted. The results regarding the coronary heart disease have been over interpreted because the WHI study was conducted in a population of older (63 yrs of age, mean menopausal age 12 years) postmenopausal women, with a number of risks factors for cardiovascular disease (as obesity and hypertension) in an high percentage of the subjects. This fact renders the WHI a trial more similar to a secondary prevention study (women with already established coronary artery disease). Conversely, WHI results have been translated into primary prevention (women without cardiovascular disease) in young postmenopausal women. Besides, some post-hoc analyses, in sub-groups like the one on the supposed first year increase in cardiovascular events, have been used to guide clinical practice while others, like the fact that women taking HRT for 5 years are not at increased risk for breast cancer, or the 30% reduction in colorectal cancer incidence, have been disregarded. Some other findings of the WHI study were misinterpreted and several women had their therapy stopped because of WHI results. The scientific data are there, they are neutral. The disturbing part is the misinterpretation by some experts that led groups of scientists to redefine guidelines on the indication of HRT, and Regulatory Agencies to react in an inappropriate way. The statisticians and epidemiologists are indispensable scientists, and the good clinical practice cannot live without their precious work. As clinicians, we will always in debt with them for their important help. They are meant to give us all the valuable information they can give. However, the puzzle coming from their work will be a matter of clinicians’ knowledge and judgement. Unfortunately, this last EMEA measure will provoke further concerns, alarms and dismay on hormones. A growing proportion of perimenopausal women even suffering from serious climacteric symptoms will not be treated. The ultimate effect will be that untreated menopausal women will be transformed in an ever growing and now even enlarged population ready for a potential prescription of alternative expensive drugs. Research is still needed in the field of the climacteric medicine to improve our knowledge and skills in prescribing HRT when and if needed. Several points should be further evaluated.

THE MENOPAUSE CHARACTERIZATION

The understanding of menopause process should be studied in its characteristics including the different stage of ovarian senescence, leading from premenopause to the perimenopausal period to postmenopause. The menopausal transition should be better
defined, with large prospective trials, conducted either in normal women and in women before and after ovariectomy. These trials should identify the clinical, endocrinological and metabolic characteristics of different groups of women according to their personal and family history. This is relevant for common conditions such as osteoporosis, obesity and hypertension that often appear or worsen throughout the perimenopausal years. The study of human genoma will explain why women have different reactions to the same endocrinological modification. This information will guide the future interventions to improve postmenopausal healthcare.

THE SIGNIFICANCE OF HORMONE REPLACEMENT THERAPY

Hormones are not drugs and are not meant to cure an illness. The administration of hormones after menopause is not a therapy of a disease. That is why the North American decision to change the wording of Hormone Replacement Therapy in Hormone Therapy is misleading (3). HRT, by definition, can only prevent and/or in some extent reverse the clinical and metabolic effects of estrogen deprivation in perimenopausal subjects who can develop atherosclerosis and osteoporosis. When a disease is already present, the role of hormones is secondary to that of other specific agents for the cardiovascular apparatus (statins, beta-blockers, etc) or for the bone (raloxifene, bisphosphonates) (3). Thus, focusing our attention on HRT, we need to improve our knowledge and skills in replacing the appropriate amount of hormones in the suitable women at the proper time, i.e. at the time or shortly after menopause.

PERSONALIZATION: TAILORING HRT DOSES AND COMBINATIONS

The main lesson from WHI is that one dosage of hormones does not and cannot suit all postmenopausal women. This is the basis upon which clinicians must decide the proper amount, type and route of administration of hormones for each patient. After menopause, women are not completely estrogen-depleted. Postmenopausal women are estrogen-deficient: the extent and the clinical relevance of this deprivation and its effects on different tissues, organs and apparatuses, depend on the time since menopause, type of menopause, and body weight. Different age-groups, at different times since menopause need progressively lower doses of hormones. In the clinical practice nobody prescribes a product specifically designed and studied for perimenopausal women to a population that is 30 years older (4-6). In this way investigations should focus on the use of different estrogen-progestogen doses and combinations in the age groups and conditions specific for women usually seeking medical assistance for menopause-related problems (4-6).

DECREASING THE CARDIOVASCULAR RISK

The choice of the correct HRT dose and the timing of treatment are relevant particularly for the effects on cardiovascular events. The early arm in the increased cardiovascular events described by the WHI and HERS trials, seems to be related to the delayed hormone treatment and to the specific characteristics of the populations in terms of age and CVD risk factors (1,2,5,6). A recent analysis of large, placebo controlled, randomized clinical trials conducted in over 7,000 postmenopausal women, aged 50-59 years, indicates that HRT is not associated with increased risk of coronary heart disease within the first year of treatment (7). The aim of these trials was to evaluate the vasomotor relief and endometrial safety associated with HRT in postmenopausal women aged 50 to 59 years. Cardiovascular events were noted for women using a variety of hormone therapies, including conjugated equine estrogens, conjugated equine estrogens plus medroxyprogesterone acetate, conjugated equine estrogens with trimestosterone, 17-beta estradiol with trimestosterone, or 17-beta estradiol with norethisterone acetate. During the first year of therapy in all cohorts, no cardiovascular-related deaths occurred. One subject in the active treatment groups had a myocardial infarction (equals an annual rate of 0.17 per 1000 patient years). Two women in the placebo group had myocardial infarctions (equals 3.7 events per 1000 patient years). The expected annualised rate of myocardial infarctions among the general population of women ages 50 to 59 years is 1.4 per 1000 women. The annualised rate in the study for stroke was 0.87 per 1000 patient years among women on active agents and 0 for placebo (expected rate for general population in this age-group is 0.8). Deep venous thrombosis occurred among the actively treated women at a rate of 1.04 per 1000 patient years, with an expected rate of 0.76 or greater. No deep venous thrombosis was reported among placebo subjects. The increase in deep venous thrombosis with hormone therapy is consistent with previous data (8). These findings suggest that the results of early coronary heart disease risk observed in the HERS and WHI studies are not applicable to healthy, younger postmenopausal women who seek treatment for menopausal symptoms. Thus, clinicians who use HRT to treat the symptoms of menopause in healthy, early postmenopausal women, should not be concerned about the risks of cardiovascular events.

It is relevant that the early arm for cardiovascular events evidenced in the HERS and WHI trials, was not evident in statins treated women. Thus, if women at high risk for cardiovascular events are properly treated they can receive an adequate HRT, when indicated. Future research on different schedules, route of administrations and combinations should take into account the possible concomitant use of specific cardiovascular drugs, particularly statins. The statin ability to stabilize the atherosclerotic plaques may be essential in reducing the potential harmful effect of prothrombotic action of estrogen in women with already atherosclerotic lesions. Further research in women treated with statins are needed to give more information on the optimal dose and combination for the replacement therapy of symptomatic postmenopausal women.

At this regard, any intervention alternative to HRT must be proven to be safe and effective for specific symptoms and/or risk profiles, avoiding inappropriate enthusiasms with products of unproven efficacy and safety (9).

DEVELOPING THE LOW DOSE AND EARLY INITIATION MODEL

Maintaining constant estrogen levels during menopausal transition, tapering the estrogen dose in the postmenopausal years and
using always the minimum effective dose are the markers of a management opposite to that used in the HERS and WHI trials where elderly postmenopausal women were treated with standard HRT dose even after a 10-15 year period of untreated hypostrogenism. And it is imperative to underline that we cannot treat with the same dosage and schedule women with an age varying from 50 to 79 years, with a drug that was studied and approved for the treatment of early postmenopausal women (10). If a given dose is suitable for a 50 years old lady, it is definitely an overdose at 70-79 years.

Primarily, women seek HRT treatment for symptomatic relief of hot flushes. The hot flushes themselves reveal the brain’s susceptibility to estrogen reduction and a myriad of additional negative effects (11). Estrogen has a positive effect on neurotransmission, improving neuroprotection, neuronite branching synaptogenesis, cerebral blood flow and trophic factor expression (11). Its depletion may impair memory, cognitive function and accelerate the onset of Alzheimer’s disease (11). According to the Cache County Study (12), early initiation and continuation of HRT after menopause may halt degeneration and provide some cognitive protection. Conversely, no neurocognitive protection was evident when HRT was started 10-15 years after menopause (12). This defensive brain effect depends on the duration of treatment and how early treatment is initiated. Accordingly, the need of long term treatment with safe HRT combination is not contradicted by the negative WHI results, where elderly women started the treatment many years after menopause (13). The same concept can be applied to the prevention of cardiovascular disease: beginning standard HRT 10-15 years after menopause in order to prevent the atherosclerotic process that is already present is a nonsense (6-8). An earlier initiation can reduce the progression of the atherogenesis, a later hormonal intervention can only be dangerous in terms of procoagulant effects in patients with atherosclerotic plaques (6-8).

Estrogen doses lower than the gold-standard 0.625 mg/day of oral conjugated estrogens or equivalent doses of other estrogens can relieve vasomotor symptoms and prevent bone loss (14-25). Future research should focus on the efficacy of early initiation and continuation of low-dose HRT on osteoporotic fractures and other health outcomes. However, the safety of the standard higher doses used in the past as well as in the HERS and WHI trials can not vaguely referre to newer HRT schedules with lower dosages. The choice of different estrogen doses may at least in part reduce the stimulation of breast tissue, since we know that breast cancer risk can be related to the endogenous estradiol levels. Thus, it is reasonable to speculate that using lower estrogen doses we can decrease also the breast stimulation while maintaining the clinical effect and the bone sparing action of HRT. However, data on this point are missing. Long term prospective trials will clarify the safety of lower dose HRT particularly in term of breast cancer risk.

THE PROTECTIVE EFFECTS OF HRT ON COLONRECTAL CANCER

Observational studies demonstrate that current use of HRT reduces the risk for colorectal adenoma and colon cancer by 30-40 %, and this protection is substantially reduced when HRT is stopped, while surgical menopause doubles the risk of colorectal adenoma (26). The protective effects of HRT on colon cancer has been confirmed by the WHI (1). Colon cancer protection by HRT is linked to the duration of use, with higher protection in women receiving HRT for more than 5 years (26). Thus, available data suggest a reduced risk of colorectal adenoma and colon cancer in HRT current users. The protective role of estrogens in colon carcinogenesis is still under study. ER-a and ER-b have been identified in normal colon in both sexes. ER-b is the predominant ER-subtype in the human colon and decreased levels of ER-b-1 and ER-b-2 mRNA are associated with colon tumourigenesis in the female. It has been demonstrated that the ER gene is methylated in 90% of colon cancer tissues. Methylation of DNA is equivalent to gene silencing, with inactivation of a number of genes downstream. Methylation-associated inactivation of the ER gene in ageing colon rectal mucosa could be one of the earliest events in colo-rectal carcinogenesis. In vitro, estrogens reduce the ER-gene methylation and inhibit cell proliferation. Estrogens may influence microsatellite instability which occurs in approximately 10–15% of colon tumours. Moreover, estrogens have been shown to increase the expression of vitamin D receptors (VD-R) in a variety of tissues: 1,25-dihydroxyvitamin D and several of its analogues are known to be potent antineoplastic and prodifferentiative agents in several cell types, including colon-derived cells. The protective effect of estrogens against dimethyldihydrazine-induced colon carcinogenesis in mice is associated with reduced methylation of the VD-R gene and with up-regulation of both VD-R gene transcription and protein expression. Therefore, increased VD-R activity may be one of the mechanisms by which estrogens protect against colon carcinogenesis. Moreover, exogenous estrogens and progestins decrease bile acid production, thus reducing its chronic irritative effect on the mucosa.

THE EXCESS IN BREAST CANCER RISK

The real dilemma in the long-term use of HRT is the possible promotion of breast cancer. The most important data of the WHI and what prematurely terminated the study, was the effect of HRT on increased risk of invasive breast cancer. Although the risk exceeded the set limit, in reality it is not statistically significant with a lower boundary of 1.00 (27). This suggests that in this particular trial the small increase in risk with HRT use for five years could be simply due to chance. There was no increase until year 4, when there was a higher number of HRT women diagnosed with breast cancer compared with the numbers for the first 3 years. In year 5, there was a 2.6-fold increase in the number of breast cancers in the HRT group compared with the placebo group, largely because the number of breast cancers diagnosed in the placebo group was about two thirds than those diagnosed in the other years. At year 6, there was basically no difference between the two groups. This is an interesting (and surprising) finding that is also noted in the placebo arm for CHD and stroke. Is this a mere coincidence or is there a possible explanation? Moreover, the hazard ratio for previous non-users of HRT was only 1.06, thus the increase in risk was almost entirely in the previous user population, that was given HRT for a long-term period, over 10-15 years. Notwithstanding, the increase in breast cancer diagnosis in HRT
treated women is the major concern and ourselves as clinicians we must seek newer strategies to eliminate this trend. Besides the reduction of cumulative estrogen dose, the options can be different. The overall results reveal that the estrogen-progestogen combinations increased the rate of breast cancer after 5 years of use, while estrogen replacement alone had no remarkable effects. The combination of different progestogens as well as the use of different route of hormone administration may play a role in the ultimate breast effect (28). The flaws of the Million Women Study make this observational study unreliable to ascertain the real effect of different doses and combinations of HRT on breast cancer risk (29-30). We need more accurate data on the critical issue of the dose effect. All the literature preceding the WHI study was even more pessimistic in terms of breast cancer risk in HRT treated women (31-33).

THE ROLE OF PROGESTOGENS

The WHI data suggest that the critical issue in terms of HRT safety seems to be the progestogen, added to the estrogen therapy with the sole aim to protect the endometrium. Various progestogens have different risk/benefit profiles. We must underline that the WHI trial was conducted with the medroxyprogesterone acetate in a continuous combined regimen with oral estrogens. The impact of combined estrogen and progestin on risk of breast cancer has been controversial. Although protective effects analogous to those for endometrial cancer have been hypothesized for breast cancer, cyclical use of progestin to simulate normal menstrual cycles increases mitotic activity in the breast (34-35). However, data on the effects of the addition of progestins to estrogens on the risk of breast cancer are conflicting. In early reports, the estrogen progestin regimen was reported to reduce breast cancer risk (36-37). Conversely, the WHI confirms the small increased breast cancer risk with combined CEE/MPA therapy, as identified in previous observational studies (38). Therefore, it is clear that our efforts should be headed to protect not only the endometrium but also the breast from the unwanted proliferation with a compound definitely different from medroxyprogesterone acetate. According to the MWS, other progestogens may share the same dangerous effects on the breast, but the flaws of this observational study make unreliable the ultimate results. The Million Women Study do not give any information on the use of different progestogens such as dydrogesterone, trimegestone, cyproterone acetate, natural micronized progesterone, etc. Different progestogens could have different outcomes but data are missing.

SMOKING-ASSOCIATED CANCERS AND HRT

Exogenous estrogens and progestins can protect the chronic irritative effect on the mucousae. This mechanism has been proposed for the protective effect that HRT seems to exert on smoking-associated cancers. In a population-based cohort of 29,508 Swedish women aged 25-65 years (oral cavity, pharynx, hypopharynx, esophagus, larynx, lung, bladder, and uterine cervix) the use of HRT was associated with a significantly reduced risk of smoking-associated cancers. The effect seems to be related to the time of HRT use, and it is specific for smokers. In fact in non smokers the rate of these tumors was not affected by the use of HRT (39). The Authors refer this promising protective effect of hormones to the possible action on degenerating mucosae for the chronic smoking-induced inflammatory processes (39). Due to the number of women that are currently smoking, this possibility should be explored in larger prospective trials. Even more recently, a case control analysis has been published (40) reporting a protective effect of HRT on lung cancer. HRT use was also associated with a lower risk of death and improved survival compared with the women not taking HRT, particularly in current smokers. The risk estimates were not statistically significant in never or former smokers. The joint effects of HRT use and mutagen sensitivity suggest that HRT use modifies lung cancer risk for genetically susceptible women. The possible biological role of HRT in lung cancer remains understudied, and only extensive research can explain the mechanisms of this protective effect of HRT for lung cancer.

NEW COMBINATIONS: THE ROLE OF SERMS

Furthermore, different molecules should be studied in depth as for the actions on the breast and cardiovascular system, and their specific mechanisms of actions should be elucidated. Selective estrogen receptor modulators (SERM) are a promising family of molecules and some of these compounds have positive effects on breast cancer prevention as well as on cardiovascular risk parameters. Tamoxifene administration in the NSABP P1 trial was not associated with increased incidence of adverse events, including endometrial cancer and venous thromboembolic events in women aged 50 or younger (41). This observation suggests that in the presence of adequate circulating estradiol levels, tamoxifen does not act as an estrogen agonist at these target tissues. In addition, the combination of HRT and tamoxifen does not adversely influence their biological effects on cardiovascular risk factors, bone density and clotting factors (43-44). Altogether, these considerations provide a strong rationale for further investigations of the combination of tamoxifen and HRT in an attempt to reduce the risk, maintaining the benefits of both therapies. A large multicenter placebo-controlled phase III trial in postmenopausal healthy women on HRT, called the HOT Study, is currently ongoing to test whether the combination of HRT and low dose tamoxifen (5 mg/day) retains the benefits while reducing the risks of either agent maintaining a high compliance rate. The addition of a SERM, such as tamoxifen, capable of reducing this growth promoting effect on the breast could therefore be useful for women’s health maintenance. However, one of the major concerns about tamoxifen is the increased risk of endometrial cancer, and thus the simultaneous progestogen administration in the HRT combination is mandatory to neutralize agonistic activity on the endometrium of both tamoxifen and estrogen. A step forward could be the use of a more “selective” second or third generation SERM that is able to act as an antiestrogen on both the endometrium and breast tissue, avoiding the use of progestogens. A randomized, double-blind, placebo-controlled, parallel treatment trial of raloxifene and placebo were tested in a group of 91 postmenopausal women with at least two signs of vaginal atrophy. Patients were treated with a 17beta-estradiol ring and randomized to receive concomitant raloxifene 60 mg/day or placebo for 6 months (44). The result of this trial demonstrates that the
concomitant administration of raloxifene does not alter the effects of the 17beta-estradiol ring on alleviating signs and symptoms of genitourinary atrophy in postmenopausal women. However, at endometrial and breast safety data are missing. Appropriate clinical trials should be performed before prescribing systemic estrogen administration in association with raloxifene. A novel SERM (EM-652) has been reported to block the effects of estrogen administration on breast tissue, uterine weight as well as the endometrium stimuli in castrated estrogen repleted animals (45). Conversely, this novel SERM did not alter the cholesterol-lowering action and the bone sparing effects of estradiol (45). The possible use of estrogen alone in conjunction to SERMs in order to protect both the endometrium and the breast is currently investigated in randomized clinical trials. These large ongoing trials in the near future should provide us with answers on the possible use of SERM as possible and safer alternatives to progestogens for the long-term estrogen treatment of postmenopausal women.

CONCLUSIONS
Menopause is not a disease, but a generic clinical sign, that is not associated to a precise clinical condition. Each single woman has her own menopause. It is important to treat each woman as a biologically unique patient. Thus, we have to emphasise the need for individualised treatment programs, according to personalised patient profiles. Different doses and combinations on different women's populations must be fully explored taking into account not only efficacy but also safety. Early intervention with personalized low dose HRT should be considered as the first line intervention. Combination with specific cardiovascular drug may offer a safe and effective strategy for the reduction of cardiovascular risk in women with cardiovascular risk factors. Estrogen administration in association with raloxifene warrants further studies. Long term estrogen replacement must be explored and original combinations with new progestogens and innovative SERMs will offer novel opportunities.

References


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