The climacteric syndrome is a complex condition characterised by a set of symptoms and degenerative changes that ensue due to the decline in production of sex steroids by the ovaries. Hence, there is a need for safe methods for the short- and long-term management of postmenopausal women. Hormone-replacement therapy (HRT) is widely used for the relief of menopausal symptoms and for the prevention of diseases linked to long-term hormonal deprivation. The use of HRT has increased rapidly in the past decade, but is currently a subject of debate because of the possible negative effects on the breast and on the cardiovascular system. Other molecules have been studied as alternatives to standard HRT to also relieve symptoms in women with contraindications to hormones or who refuse sex steroids for personal reasons. The aim of this article is to discuss the results of the principal studies performed in the past few years on the safety of HRT and of other climacteric therapies.

The Menopause

The climacteric is the consequence of the withdrawal of oestriol and progesterone due to the cessation of the cyclical ovarian function. This hormonal change affects a large series of bodily targets, causing atrophy of tissues and metabolic modifications along with psychological and sexual changes, which are experienced variably by women. The first signs include the typical vasomotor symptoms, nocturnal sweats and psychological instability. Soon after these first manifestations, atrophic changes and metabolic and body composition changes develop. Changes in the lipid profile and in body-fat distribution and quantity are associated with oestrogen deprivation and lead to a change in the metabolism of climacteric women towards ‘male’ status. The skeletal system is heavily affected in most individuals, with an accelerated bone loss that can lead to osteopenia or to overt osteoporosis. The function of the cardiovascular system is also affected by the changes in circulating sex steroids, with enhanced atherosclerotic degeneration. Circumstantial evidence indicates that the central nervous system may be affected in the long term, with an increased risk of neurodegenerative diseases such as dementia.

Hormone Replacement Therapy

Associations of oestrogens with or without a progestogen represent the most effective therapies for climacteric symptoms; but recent findings have opened an as-yet unresolved debate on the safety of these therapies, particularly in regard to breast cancer and to cardiovascular disease (CVD).

Cardiovascular System

Several long-term observational studies suggest that HRT prevents CVD in postmenopausal women. The conclusion of all of these trials is that HRT reduces the risk of coronary heart disease by about 40%. However, a large, randomised, placebo-controlled trial failed to confirm this benefit. The potential cardioprotective actions of oestrogen may depend on the levels of pre-existing CVD at the time of therapy initiation. For example, the Estrogen Replacement and Atherosclerosis clinical trial reported that women with pre-existing atherosclerosis receive no benefit on the progression of carotid atherosclerosis by oestrogen replacement. Thus, while oestrogen may protect against the development of atherosclerosis, it does not appear to be protective against existing atherosclerosis. Studies in women with low CVD risk concur with this. Indeed, in the Women’s Health Initiative (WHI) study, those women who started HRT early after the menopause, probably having less-developed CVD, showed better cardiovascular outcomes with a trend towards protection. However, the vast majority of women included in the WHI trial had a severely diseased vasculature due to age and to the significant prevalence of cardiovascular risk factors (obesity, high cholesterol and hypertension), and this might explain the failure of this trial in demonstrating overall cardiovascular benefits with HRT.

Bones

Osteoporosis is characterised by reduced bone mass that leads to...
reduced bone quality and resistance and, consequently, to an increased risk of fractures. Osteoporosis is a very common condition in postmenopausal women, causing significant morbidity and reduced quality of life.

Circulating oestriol has a protective effect on the bones, reducing skeletal remodelling through many mechanisms: reduction in activation of bone metabolic units; enhanced survival of osteoclasts; improved efficiency of gastrointestinal calcium absorption; and renal calcium conservation.3

By increasing bone-mineral density (BMD), HRT is the best (and more physiological) protective therapy against osteoporosis and fractures in postmenopausal women.

In the double-blind Postmenopausal Estrogen/Progestin Intervention trial and in the Women’s Health, Osteoporosis, Progestin, Estrogen trial, women treated with oestrogen or oestrogen/progesterone therapy had a significant increase in BMD versus the placebo group, in which a loss of bone mass was observed.5,6,8 Prospective randomised studies confirm these results. In the WHI study there was a clear reduction in the risk of fractures among women receiving continuous combined conjugated equine oestrogen plus medroxyprogesterone acetate or the oestrogen therapy alone.7,9,10

Cognitive Function
Due to the widespread presence of oestrogen receptors throughout the brain, oestrogen effects are also widespread and affect brain structure and function and provide neuroprotection against oxidative stress via antioxidant effects.11 Moreover, oestriol in vitro promotes the breakdown of the β-amyloid precursor protein, preventing the accumulation of β-amyloid. There exists, then, a biological plausibility for the clinical hypothesis that oestrogen helps to maintain cognition in women and prevents or delays the development of neurodegenerative disorders.

Observational studies in which the treatment is started in the early postmenopausal period show a decreased risk of Alzheimer’s disease with treatment.12 In contrast to these results, the WHI Memory Study (WHIMS) showed nearly a doubling of risk of all-cause dementia.13 One explanation for this discrepancy is that late initiation of hormone therapy (after 65 years), as in the WHIMS, may not be effective in preventing neurodegeneration and may instead precipitate vascular dementia, whereas early use confers benefit.2,14 While the prevention of Alzheimer’s disease with HRT is still to be established, it seems that the initiation of HRT in patients aged 65 or more may increase the risk of impaired cognitive function.

Breast Cancer
Breast cancer is the most common cancer in women in developed countries. Oestrogens have clear proliferative activity on breast-cancer cells in vivo and in vitro,25 so it may be biologically sound that prolonged exposure to oestrogens increases the risk of breast cancer. However, it is not clear if exposure to oestrogens has any effect on cancer development per se. Most of the currently available evidence suggests that cancer transformation may not be related to oestrogen exposure but that, once this primal event takes place, oestrogens may promote tumour growth and eventually spread. On the other hand, progestins have traditionally been seen as protective against breast-cancer development despite the absence of a strong biological rationale for an anti-oestrogenic effect of progestins on the breast.

Correlation between HRT use and breast-cancer risk has been studied in many epidemiological studies. A large meta-analysis published in 1997 indicated that the risk of breast cancer is raised in women using HRT and increases with increasing duration of use.14 This excess risk is reduced after HRT cessation and disappears within five years.11 Recently, the WHI study reported a 26% increase in the relative risk of breast cancer for combined oestrogen–progestogen compared with a placebo. However, the parallel arm of the WHI study investigating the effect of the administration of oestrogens alone showed no increase of breast cancer, with a trend towards a reduction of risk.12 This study, along with the long-term analysis of the Nurse’s Health Study, in general indicates that the impact of HRT on the incidence of breast cancer is limited and associated only with very long administrations.15 In addition, recent trials call for new research to better understand the role of progestins, showing that – based on the compound – the risk of breast cancer changes.16

Endometrial Cancer
The majority of all endometrial malignancies occurs mostly in peri-menopausal and early post-menopausal women. The pathogenesis is, in part, linked to prolonged and excessive exposure to endogenous or exogenous oestrogens, not balanced by the cyclical production of progesterone. The risk of endometrial cancer is not clearly related to the dose but rather to the duration of unopposed oestrogen exposure, as long-term administration correlates with a five-fold higher risk.17 HRT with oestrogen alone increases endometrial cancer risk, whatever the type and dose of oestrogen and the route of administration.18 Progesterone has a well-known anti-oestrogenic effect on the endometrium.21 The addition of a progestogen to the oestrogen-replacement therapy is then mandatory to avoid the risk of endometrial cancer, contrasting the stimulation of the endometrium by oestrogens. To this extent, in the presence of a progestin, endometrial-cancer risk is decreased either with cyclical or continuous HRT. Cyclical regimens that include more than 10 days of progestogen exposure per month appear to provide maximum protection.22

Colorectal Cancer
Colorectal carcinoma is a leading cause of illness and death in developed countries, being the second most common cancer in women after breast cancer.21 There is strong evidence to show that the incidence of colorectal carcinoma can be significantly reduced by HRT. A meta-analysis of 18 epidemiological studies of HRT and colorectal cancer showed a 20% reduction of colon- and rectal-cancer risk in women who had ever taken HRT compared with those who had never taken HRT.23 In addition, the WHI trial showed a significant reduction in colon cancer risk in HRT users. The possible biological explanation of this reduction of risk includes the effect of sex steroids on bile-acid metabolism and direct effects on the colonic epithelium.24

Other Therapies
Other molecules have been studied as alternatives to standard replacement therapy with sex-steroid hormones.

Tibolone
Tibolone is a synthetic steroid that is rapidly converted to two metabolites with oestrogenic activity and to a third metabolite characterised by a mixed progestogenic/androgenic activity.25 Tibolone controls hot flushes,
The effects of phyto-oestrogens on the central nervous system in humans are poorly understood. Scattered reports suggest a beneficial effect of phyto-oestrogens on memory, but the evidence on this issue is insufficient.

Breast Cancer
To date, 13 studies have been performed to assess the direct relationship between the individual dietary intake of soy products and the risk of breast cancer; however, none have reported statistically significant breast-cancer reductions. Recent data indicate that surrogate markers of breast cancer risk – such as mammographic breast density – are not altered by phyto-oestrogens, supporting the view that this class of compounds may act differently from standard hormonal therapies on the breast.

Endometrial Cancer
Reports on the effect of phyto-oestrogens on endometrial cancer are limited. In Hawaii’s multi-ethnic population, soy intake has been related to reduced endometrial-cancer risk. Similar data have been found in non-Asian women in San Francisco.

Raloxifene
Raloxifene is a non-steroidal selective oestrogen receptor modulator (SORM). This compound induces oestrogenic or anti-oestrogenic actions depending on the tissue. Raloxifene is not effective on vasomotor symptoms, which can even be worsened during raloxifene administration, therefore making it an unsuitable agent for the treatment of symptomatic menopausal women.

Cardiovascular System
While previous trials suggested potential reduction of cardiovascular events in post-menopausal women receiving raloxifene, the recent publication of the Raloxifene Use for The Heart trial has instead shown no reduction of cardiovascular events. However, this compound is active in vascular cells where, in general, it behaves like an oestrogen, possibly inducing protective effects.

Bones
Raloxifene acts as a powerful oestrogen on the bone, where it prevents bone loss and provides an effective treatment for osteoporosis.

Breast Cancer
Recent evidence from the large Study of Tamoxifen and Raloxifene trial indicates that raloxifene administration to postmenopausal women results in a clinically relevant reduction of breast-cancer risk that is comparable to that achieved with tamoxifen. Newer SORMs with partially different characteristics are currently under
development by the pharmaceutical industry and many of these compounds are in advanced clinical development.

Conclusions

While all the available therapies for early post-menopausal symptoms or for the prevention of the consequences of long-term oestrogen deprivation have specific risk/benefit ratios, clinical selection is the key to maximising the advantage for each patient. Overall, the safety profile of hormonal preparations is extremely reassuring, and the big claims of carcinogenic actions of these drugs are not justified.

References