Menopause and HRT: Doubts and Certainties

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18.1 Menopause, Aging, and the Role of HRT

A woman's life is characterized by physiological changes of sex steroid hormone concentrations, especially during menstrual cycle, pregnancy, and menopause.

Menopause is a consequence of loss of ovarian function. Deprivation of estrogen and progesterone levels causes menopausal symptoms. This hormonal change affects a large series of bodily targets, causing atrophy of tissues and metabolic modifications along with psychological and sexual changes that are variably experienced by women. Short-term consequences of estrogen deficiency include CNS-related symptoms and urogenital symptoms. Long-term consequences of estrogen deficiency include osteoporosis, cardiovascular disease, cognitive impairment, and dementia.

Good quality of life is an aspiration for all women. Menopause and aging both contribute to the decrease in quality of life experienced by most women at this stage in their life. In addition, according to the current literature, those women who particularly suffer from a reduced quality of life also tend to develop osteoporosis, diabetes, colorectal cancer, and cardiovascular diseases, thus suggesting that symptomatic individuals may be particularly vulnerable to menopausal changes.

There are two major categories of measures of quality of life: generic and specific tools. Among the most commonly used generic measures is the Short Form (SF)-36 Health Survey, which evaluates domains under the headings of physical functioning, role-physical, bodily pain, and general health with vitality, social functioning, role-emotional, and mental health under the mental health section. The Women's

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Health Questionnaire (WHQ) [1] provides instead a good example of a questionnaire investigating specific measures. Use of such tools can be useful in clinical trials as well as in busy practices to screen for those women who may specifically benefit from menopause-targeted interventions.

Use of hormone replacement therapy (HRT) in postmenopausal women has been popular for a long period but has now lost momentum due to emerging evidence that has highlighted the risks and advantages of this strategy. However, misperceptions on the real impact of hormone replacement have heavily impacted the dissemination of the use of these hormones, sometimes limiting the potential advantages for women who would have benefited from hormone use. This paper reviews the areas of certainty and those of doubt in this hot scientific field, with the aim to highlight the settings where use of HRT is beneficial and those where it may carry risks.

18.2 HRT: Types and Goals

HRT represents the most effective therapy for climacteric symptoms. It helps manage the short-term consequences of the fall of estrogens such as hot flushes, nocturnal sweats, anxiety, and mood swings. It also prevents long-term diseases such as bone mass loss, cardiovascular disease, and possibly degenerative neurological disorders. Efficacy on these targets of HRT depends on the administration of exogenous estrogens [2]. All women with an intact uterus who use systemic estrogen therapy (ET) should also be prescribed adequate progesterone support. Understanding the benefits and the risks of HRT is critical. Recent findings have opened a debate that has not yet settled, on the safety of these therapies, particularly in regard to breast cancer and to cardiovascular disease [3].

18.3 Short-Term Consequences

18.3.1 Vasomotor Symptoms

Sex steroids have a neuroprotective function and play region-specific roles in the central nervous system because of the presence of estrogen receptors throughout the brain, particularly in the basal forebrain and cortex. Consequently, gonadal steroid withdrawal during menopause heavily impacts brain function, negatively affecting mood, anxiety, and cognitive function. The most evident effect linked to estrogen deficiency in the brain is the development of hot flushes. Hot flushes represent thermoregulatory dysfunction due to inappropriate peripheral vasodilatation with increased cutaneous blood flow and perspiration, resulting in a rapid heat loss and a decrease in core body temperature below normal.

HRT is the most effective treatment for vasomotor symptoms and their potential consequences such as diminished sleep quality, difficulty in concentrating, irritability, and in general reduced quality of life [4, 5]. Low doses are efficient in resolving vasomotor symptoms in almost all symptomatic women; it is therefore appropriate

to begin hormonal therapy at low dosages and to increase them after some weeks if symptoms persist. Progesterone alone also reduces vasomotor symptoms but is not as effective as estrogen [6].

18.3.2 Urogenital Symptoms

The epithelial linings of the vagina and urethra are very sensitive to estrogens. Atrophy of vaginal mucosal surfaces takes place quite consistently after the menopause. Vaginal atrophy causes vaginal dryness and itching. Vaginal pH, which is usually <4.5 in the reproductive years, increases to 6.0–7.5 in postmenopausal women. The increase in pH and the vaginal atrophy both decrease the protection against infections. HRT and vaginal estrogen therapy (ET) reduce symptoms related to urogenital atrophy such as vaginal dryness, vaginitis, and dyspareunia [7]. Local Et also benefits women with overactive bladder [8]. In contrast, systemic HT may worsen or provoke stress incontinence [9–11], although this is controversial. Some studies reported a decreased risk of recurrent urinary tract infections with vaginal estrogens [12, 13]. Low doses of vaginal estrogens improve sexual satisfaction by improving blood flow and lubrication.

18.4 Long-Term Consequences

18.4.1 Osteoporosis

Osteoporosis is characterized by low bone mass with microarchitectural disruption and skeletal fragility, resulting in an increased risk of fractures. Estrogen deficiency has been well established as a cause of bone loss. From 1.5 years before to 1.5 years after the menopause, spine bone mineral density has been shown to decrease by 2.5 % per year, compared with a premenopausal loss rate of 0.13 % per year. Sex hormones have a protective effect on the bones, reducing skeletal remodeling through many mechanisms: reduction in activation of bone metabolic units, enhanced survival of osteoclasts, improved efficiency of gastrointestinal calcium absorption, and renal calcium conservation [14]. HRT is effective to maintain or improve bone mineral density. It reduces postmenopausal osteoporotic fractures, even in women without osteoporosis [15, 16].

The results of the double-blind Postmenopausal Estrogen/Progestin Intervention (PEPI) trial and the Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial suggested that women treated with estrogen or estrogen/progesterone therapy have a significant increase in the body mass density (BMD) versus the placebo group, in which a loss of bone mass was observed [17]. In the Women's Health Initiative study (WHI), there was an evident reduction of all fractures among women receiving continuous combined conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) versus the placebo group. Total femoral bone mineral density increased by 3.7 % after 3 years of estro-progestin therapy versus 0.14 % recorded in the placebo group [18].

The WHI trial also confirmed the importance of an adequate concomitant calcium supplementation to prevent fractures.

The main role of HRT stays in the prevention of osteoporosis rather than in its treatment. However, HRT is an option to treat women with osteoporosis and a high risk of fractures when osteoporosis therapies are not appropriate or cause adverse effects or are incompletely effective. There is no evidence that HRT stops working with long-term treatments. The benefits of HRT decrease quickly after the discontinuation of treatment; in these cases, when needed to preserve bone mass, it is important to introduce a different treatment for osteoporosis [19, 20].

18.4.2 Cognitive Impairment and Dementia

Estrogens exert a number of protective effects on the brain, including inhibition of beta-amyloid formation, stimulation of cholinergic activity, reduction of oxidative stress, and protection against vascular risks [21].

Estradiol, in vitro, promotes breakdown of the β-amyloid precursor protein preventing the accumulation of β-amyloid. There is a clinical hypothesis that estrogens help to maintain cognition in women and prevent or delay the development of neurodegenerative disorders. In the long term, estrogen deficiency facilitates cognitive impairment and dementia.

Observational studies have reported association between HRT and reduced risk of developing Alzheimer disease [22]. Opposed to this rationale, the Nurses' Health Study (NHS) found no improvement on cognitive function from long-term use of HRT; in addition, there was evidence of a more rapid cognitive decline among those HRT users who started HRT long after their final menstrual period [23]. These results are probably associated with the detrimental effects on vascular events, even at the subclinical level, in this population of advanced age, that are nowadays established as a side effect of starting estrogen administration in elder women far from their menopause. The Women's Health Initiative Memory Study (WHIMS) has provided similar evidence, showing a worsening of verbal memory along with a positive effect on figural memory among elder women starting HRT [24]. However, in the Study of Women's Health Across the Nation (SWAN), a trial that looked at women at the time of their menopausal transition, women who initiated HRT before their final menstrual period had a beneficial cognitive effect. In line with the other studies, also in SWAN women who initiated HRT long after the final menstrual period had a worse effect on cognitive performance [25]. To date, it is not clear if HRT used soon after the menopause increases or decreases the rate of cognitive decline or later dementia risk.

18.4.3 Cardiovascular Disease

Cardiovascular risk increases in postmenopausal women and the possible reasons are the accelerated rise in total cholesterol, changes of weight, blood glucose, and blood pressure with aging and menopausal status. Estrogen withdrawal also heavily

affects endothelial function. Decreasing of estrogens levels might independently contribute to all this conditions. Premature menopause and bilateral oophorectomy in young women are associated with an increased risk of cardiovascular disease, myocardial infarction and overall mortality. Observational studies suggest an interval of 5–10 years between loss of ovarian function and increased risk of cardiovascular disease.

Observational studies suggest that HRT prevents cardiovascular disease in postmenopausal women: HRT reduces the risk of coronary heart disease (CHD) of about 40 %. This has been largely confirmed by the Women's Health Initiative (WHI) trial, showing that women in whom HRT is initiated early around the time of menopausal transition have a significantly lower risk of cardiovascular disease such as myocardial infarction and heart failure. However, the vast majority of the women included in the WHI trial had a severely diseased vasculature due to the age and to the large prevalence of cardiovascular risk factors (obesity, high cholesterol, and hypertension), and this explains the failure of this trial in showing overall cardiovascular benefits with HRT in women over 60 years of age [18].

It is important to evaluate the levels of preexisting cardiovascular disease (CVD) at the time of therapy initiation because it influences the potential cardioprotective effects (and mostly the side effects) of HRT [26]. Consistent with the WHI findings, the Estrogen Replacement and Atherosclerosis (ERA) clinical trial reported that women with preexisting atherosclerosis receive no benefit on the progression of carotid atherosclerosis by HRT [27]. While estrogen levels may protect against the development of atherosclerosis, it does not appear to be protective against existing atherosclerosis. Trials are currently ongoing to assess whether use of HRT in younger postmenopausal women may slow down the progression of atherosclerosis.

18.4.4 Breast Cancer

Breast cancer is the most common cancer in women in Western countries. The pathogenesis is linked to estrogens that play an important role in the proliferation of breast cancer cells in vivo and in vitro [28].

Menopause is associated with important modifications in the breast. The fall of the cyclical exposure to estrogen and progesterone causes progressive atrophic changes in the glandular component and the breast becomes mostly constituted by adipose tissue. The climacteric is the time in a woman's life when breast diseases often became clinical evident and the risk in developing a breast carcinoma is stronger linked to aging rather than the fall of estrogens and progestins. Less is known on what particular hormone plays the major role in this phenomenon. Traditionally estrogen has been indicated as the main player, but recent evidence points out that progesterone and ovarian androgens might be more relevant.

Most evidence suggests that cancer transformation may not be related to estrogens exposure but that once this primal event takes place, then estrogens may

promote tumor growth and eventually spread. On the other side, progestins have traditionally been seen as protective against breast cancer development despite the absence of a strong biologic rationale for an antiestrogenic effect of progestins on the breast. This concept has been recently overturned by studies showing that HRT containing some specific types of progestin seem to be associated with higher risk of breast cancer.

Association between breast cancer risk and HRT has been studied in many epidemiological studies. A large meta-analysis published on the Lancet in 1997 indicated that the risk of breast cancer is increased in women using HRT and it is associated with the duration of use. This excess risk is reduced after HRT cessation and disappears within 5 years [29]. The WHI study reported a 26 % increase in the relative risk of breast cancer for combined estrogen–progestogen when compared with placebo. However, the parallel arm of the WHI study investigating the effect of the administration of estrogens alone, showed no increase of breast cancer, with a trend toward a reduction of the risk [18]. This study, along with the long-term analysis of the Nurse's Health Study, in general suggests that the impact on the incidence of breast cancer of hormone replacement therapy is limited and associated only with very long administrations, after 15–20 years of treatment [30]. The risk of breast cancer due to HRT is similar to that conferred by obesity and is not additive [31].

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 [32].

It is not clear the role of HRT in survivors of breast cancer. Observational studies show that HRT may not increase the risk of recurrent breast cancer; these results have been questioned because of possible bias from the enrolment of women at lower risk [33–39]. The LIBERATE trial looked at the use of HRT with tibolone in women with a history of breast cancer and was terminated early, after 2 years of follow-up, when a significant number of new breast cancers were diagnosed. To date, HRT use in breast cancer survivors is considered by all guidelines contraindicated [40].

18.4.5 Endometrial Cancer

The risk of all endometrial malignancies occurs mostly in perimenopausal and early postmenopausal women. The possible biological explanation is in part linked to a prolonged and excessive exposure to endogenous or exogenous estrogens, not balanced by the cyclical production of progesterone. The risk of endometrial cancer is not clearly related with the dose but with the duration of unopposed estrogen exposure, as long-term administration correlates with fivefold higher risk. HRT with estrogen alone increases endometrial cancer risk, whatever the type and the dose of estrogen and the route of administration [41]. The addition of a progestin to ET is important to outset endometrial cancer risk, contrasting the stimulation of the endometrium by estrogens. With progestin the endometrial cancer risk is decreased either with cyclic or continuous HRT. Cyclic regimens including more

than 10 days of progesterone exposure per month appear to provide sufficient protection [42]. In general HRT is contraindicated in women with a history of endometrial cancer.

18.4.6 Colorectal Cancer

Colorectal carcinoma is the second most common cancer in women after breast cancer. Sex steroids play an important role on bile acid metabolism and directly affect the colonic epithelium [43]. Growing evidence shows that the incidence of colorectal carcinoma can be significantly reduced by HRT. A meta-analysis of 18 epidemiological studies of colorectal cancer and HRT showed a 20 % reduction of colorectal cancer risk in women who had ever taken HRT compared with those who had never used HRT [44]. The same results were showed by the WHI trial.

Conclusions

The clinical effect of HRT in postmenopausal women has been widely investigated. Although areas of uncertainty remain, there is also a lot of solid ground to provide counseling (Fig. 18.1). HRT is the best option to treat menopausal symptoms and should not be denied to women that have no contraindications. Use of HRT for longer periods of time has beneficial effects of the bones and on cardiovascular risk, particularly if initiated in early postmenopausal women. Thus, reassurance should be provided to these individuals. Breast cancer risk is mostly related to aging, and the possible additional risk imposed by HRT does not make a big difference and may largely depend on the formulation used. This is an area of current investigation and should not preclude use of HRT in women. Rather, women should be given correct information on the entity of the benefits and risks and followed up as clinically indicated. In this setting HRT is and will remain a precious clinical tool to manage menopausal women.

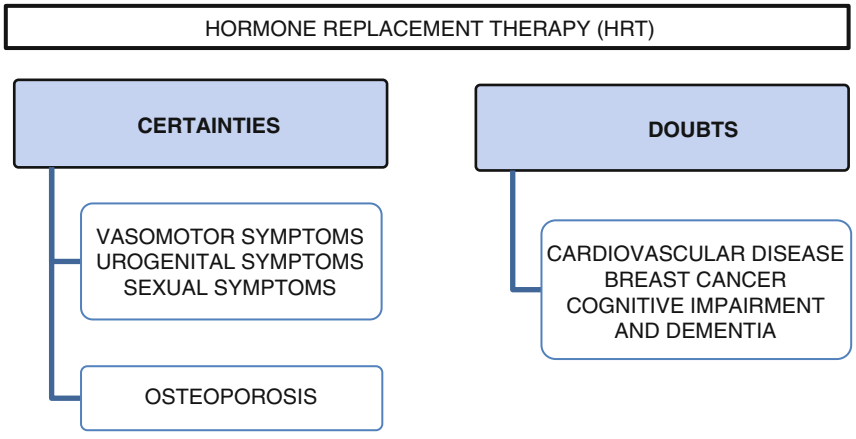

Fig. 18.1 Effects of *HRT* on menopausal disfunctions: doubts and certainties

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