NEW HORIZONS

Oestrogen replacement in postmenopausal women

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Abstract

Menopausal symptoms can disrupt a woman’s personal and social life. Vasomotor symptoms (hot flushes and night sweats) are the most common symptoms and can be treated very effectively with oestrogen-based hormone therapy. The decision to use oestrogen (often simply termed hormone therapy or hormone replacement therapy or HT) therapy involves balancing the potential benefits against the potential risks. Most agree that short-term oestrogen therapy, using the lowest effective dose, is a reasonable option for recently menopausal women with moderate-to-severe symptoms who are in good cardiovascular health (Martin and Manson. 2008. J. Clin. Endocrinol. Metab. 93, 4567–75). Whilst effective and safe in most instances, HT is not suitable for all women or for all menopause-related symptoms when alternatives are available. The role of HRT in chronic disease prevention is also discussed.

Keywords: menopause, oestrogen replacement therapy, older people

Introduction

Menopause is defined by the World Health Organisation (WHO) and Stages of Reproductive Ageing Workshop (STRAW) Working Groups as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy or radiation [1]. Usually, this equates to 12 months of amenorrhoea.

It is estimated that within the next 25 years, more than 1 billion women worldwide will be older than 50 years, and approximately 2 million will reach menopause annually. Natural menopause occurs on average between the ages of 50 and 51 (range 45–59) [2] and is an inevitable event for women in the process of normal ageing. It is a retrospective diagnosis and menopause is often preceded by months or years of irregular cycles, that is not associated with some other physiological or pathological causes. Menopausal symptoms may occur during this time.

A number of terms including ‘climacteric’, ‘perimenopause’, ‘menopausal transition’, ‘postmenopause’ and ‘menopause’ have been used to refer to the stages of reproductive ageing surrounding the final menstrual period [3]; however, WHO recommended the use of ‘perimenopause’ and ‘menopausal transition’ in place of ‘climacteric’ in 1996, and a model was developed in 2001 to describe the stages of the menopausal transition [4].

This model identifies seven stages of reproductive life and is primarily based on the characteristics of the menstrual cycle and secondarily on follicular phase follicle stimulating hormone (FSH) levels. FSH levels start to rise around the age of 38, but as women progress through the menopausal transition, the menstrual cycle length becomes irregular and FSH levels are raised in response to decreased ovarian hormone concentrations, although they fluctuate markedly. Menstrual cycles are then missed and ultimately stop, as does ovulation.

Up to 75% of women will experience adverse symptoms related to menopausal transition, of which, vasomotor symptoms (hot flushes and night sweats) are the most common in the Western world, causing significant morbidity in 25%. Other symptoms include vaginal symptoms and sexual dysfunction, urinary incontinence, trouble sleeping, depression, anxiety, labile mood, memory loss, fatigue, headache, joint pains and weight gain, which may be equally debilitating; causing significant disturbance to daily living, with an impact on the social and working lives of women in their perimenopausal years. There are of course some women who will experience none of these.
Within this article, we will briefly explore some of the most prevalent symptoms and consider the impact of hormone therapy (HT) on them and also on chronic disease.

**Vasomotor symptoms**

Hot flushes are characterised by a feeling of intense warmth, often accompanied by profuse sweating, anxiety, skin reddening and palpitations, and sometimes followed by chills. If left untreated, hot flushes resolve within 1 year, or less, in the majority of postmenopausal women [5], although a third will report symptoms that last up to 5 years after natural menopause, and in 20% hot flushes persist for up to 15 years [5] or longer.

Menopause induced by surgery is associated with about a 90% probability of hot flushes during the first year [6] and symptoms associated with surgical menopause are often more abrupt and severe and can last longer than those associated with a non-surgical menopause [7].

Hot flushes are the most common indication for the prescription of hormone therapy (HT) in the UK since it is effective in over 80% of cases [8]. There has, however, been confusion amongst both women and medical practitioners, following publication of the Women’s Health Initiative (WHI) [9] and Million Women Study (MWS) (2003) that the risks of HT may outweigh the benefits, and prescriptions of HT fell dramatically [10]. These studies aimed to assess the role of HRT in chronic disease prevention and WHI recruited largely asymptomatic, older women. MWS was a large observational study of women attending the breast screening service and aimed to assess the risk of cancer. Both demonstrated an increased risk of breast cancer and the WHI disputed any benefit for HRT in cardiovascular disease (CVD) and initially reported an increase in incidence although this was later modified by further analysis [11].

New analyses have led to a global consensus statement, endorsed by worldwide menopause societies, and published in 2013, which states that ‘MHT (menopausal hormone therapy) is the most effective treatment for vasomotor symptoms associated with menopause at any age, but treatment options are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause’ [12].

However, there remains a need for non-hormonal alternatives, as HT may not be suitable for women with a history of hormone-dependent cancer, for example breast cancer, and several treatment modalities may be considered, however none are as effective as HT (see Table 1).

**Urogenital symptoms**

The female urogenital tract arises embryonically from the urogenital sinus. High-affinity oestrogen and progesterone receptors have been found in the vagina, urethra, trigone of the bladder and pelvic floor musculature [38]. A loss of oestrogen results in urogenital ageing.

Reduced collagen, decreased elastin and thinning of the epithelium result in thinning of the tissues of the vaginal walls, which become pale and thin and lose their elasticity. A reduction in vaginal secretions and decreased tissue elasticity lead to a susceptibility to trauma and pain or irritation during or after intercourse. In a study of 94,000 postmenopausal women aged 50–79 years, 52% reported that they had been sexually active with their partner in the last year [39], and 22% of married women aged 70–70 years reported that they still have sexual intercourse [40].

In addition to vulvo-vaginal symptoms, the less acid pH of the oestrogen-deficient vagina increases the likelihood of urinary tract infections. There may also be urinary frequency and urgency, nocturia, and the urethral meatus may become more prominent and susceptible to trauma.

Genitourinary symptoms attributable to the menopause can affect up to 50% of women, however it is under diagnosed and under treated [41]. It may be chronic and without treatment is unlikely to improve over time. By increasing skin collagen content, and increasing acid mucopolysaccharides and hyaluronic acid, oestrogen therapy encourages the growth and development of vaginal epithelial cells which make up the thick layers of the vaginal wall, and condone a moist, supple and elastic environment [42].

**Vaginal symptoms and sexual dysfunction**

Vaginal symptoms become apparent 4–5 years after the menopause and objective changes as well as subjective complaints are present in 25–50% of all postmenopausal women [43]. Symptoms may include vaginal dryness (75%), dyspareunia (38%), vaginal itching, burning and pain (15%). Dyspareunia can adversely affect a postmenopausal woman’s sexual quality of life or intensity pre-existing sexual disorders [44].

Locally administered vaginal oestrogens are effective in the treatment of menopause-related vulval and vaginal symptoms and a Cochrane review reported equal efficacy across all products tested; creams, pessaries, tablets and vaginal rings [45]. Local oestrogen therapy will lower vaginal pH, thicken the epithelium, increase blood flow and improve vaginal lubrication [43].

A 2009 review [46] of topical oestrogen concluded that no studies show evidence of endometrial proliferation after 6–24 months of use, therefore it does not support the concomitant use of progestins (used to reverse the proliferating effect of oestrogen on the endometrium) with topical oestrogens and is endorsed by the International Menopause Society [47].

Vaginal oestrogen is controversial in women with a history of hormone-dependent cancer such as breast cancer, in whom vulval and vaginal symptoms are common, particularly those on endocrine therapy and although an increase in recurrence has not been reported, some oestrogen is absorbed into the systemic circulation [48, 49].

Non-hormonal treatment options include lubricants and moisturisers both of which can be effective although usually only in the short term [43, 50].
Ospemifene is a non-oestrogen, tissue-selective oestrogen receptor agonist/antagonist, or selective oestrogen receptor modulator (SERM, recently approved in the US for menopause-related vulvo-vaginal atrophy). Studies have shown improvements in vaginal pH and dryness [51, 52]; however, it should not be used in women with, or at high risk of, breast cancer.

Urinary symptoms

Overactive bladder (OAB) is a highly prevalent disorder, as much as 16.9%, with higher rates and symptom severity in postmenopausal women [53] and oestrogen deficiency has been implicated in the aetiology of urinary tract symptoms in up to 70% of women [54]. Oestrogen has been used for decades to treat this, yet a Cochrane review [55] concluded that there was insufficient evidence to support the use of local oestrogens and that systemic oestrogens may make incontinence worse. The Heart and Estrogen/Progestin Replacement Study (HERS) [56] and WHI studies showed no protective effect of HT against incontinence.

The Fourth International Consultation on Incontinence (ICI) concluded that there is no solid evidence to support the use of HT, oral or vaginal, for the treatment of urge urinary incontinence (UUI). Stronger recommendations include weight reduction, supervised pelvic floor muscle training and bladder training and antimuscarinics [57].

Osteoporosis

The onset of the menopause, with associated decline in oestrogen, results in a decrease in bone mineral density (BMD) and a subsequent significant increase in the prevalence of osteoporosis, which continues to increase through the postmenopausal period [58]. The number of hip fractures
worldwide due to osteoporosis is expected to rise 3-fold by 2050, from 1.7 million in 1990 to 6.3 million. The incidence increases with age partly due to bone fragility and partly because of the increased likelihood of falling that occurs due to deficiencies of both balance and vision.

There is currently no universally accepted policy for population screening in the United Kingdom to identify those individuals with osteoporosis or those at high risk of fracture. The National Osteoporosis Guideline Group (NOGG) advise that fracture probability should be assessed in postmenopausal women, using FRAX, a tool developed by WHO integrating clinical risk factors and bone mineral density to determine fracture risk, where assessment would influence management [59].

Optimal management of osteoporosis is aimed at primary prevention in those at risk, whilst general management includes assessment of the risk of falls and their prevention, maintenance of mobility and correction of nutritional deficiencies, particularly of calcium, vitamin D and protein [59].

Pharmacological interventions include bisphosphonates, denosumab, parathyroid hormone peptides, raloxifene and strontium ranelate. All have been shown to reduce the risk of vertebral fracture and some have been shown to reduce the risk of non-vertebral fractures [39]. However, all are associated with side effects and many women will fail to comply.

There is evidence from randomised controlled trials, including WHI, that HT reduces the risk of spine and hip, as well as other osteoporotic fractures even in women at low risk. It would appear that half of the traditional bone conserving doses (oestradiol 2 mg, conjugated equine oestrogen [CEE] 0.625 mg and transdermal 50 mcg patch) are effective in conserving bone mass and are successful means of fracture prevention.

Regulators do not recommend HT as first-line treatment in the prevention of osteoporosis, because risks, in terms of increased breast cancer risk, outweigh benefits since long-term use is necessary as efficacy decreases when treatment is stopped. However, some support its use in osteoporosis prevention [60], a concept supported in the most recent SIGN Guideline on Management of Osteoporosis (http://www.sign.ac.uk/guidelines/fulltext/71/section6.html#). Oestrogen remains the treatment of choice in women with premature ovarian failure and may be the best option in women under the age of 60, however, 'the initiation of standard dose HT is not recommended solely for fracture prevention in women over 60′ [60].

### Cardiovascular risk

The incidence of CVD increases with age and menopause may have an adverse effect. Many risk factors e.g. lipids and lipoproteins, insulin resistance and fat distribution are adversely affected, although a clear rise in risk at the time of the menopause itself is not apparent. Observational studies including several large cohort studies, principally undertaken in the USA (Framingham and the Nurse’s Health Study) and carried out during the 1970s and 1980s, suggested that HRT had a significant protective effect on CVD risk and thus, prior to the publication of the WHI [9], hormone therapy was thought to confer CVD risk reduction, particularly coronary events [61, 62]. This leads to the inclusion of HRT arms in the WHI study. Oestrogen alone was administered to hysterectomised women and oestrogen with progestogen in those with a uterus. The principal results of the WHI trial, the largest randomised controlled primary prevention trial of the most commonly prescribed HRT in the USA, demonstrated an increased number of coronary heart disease events and strokes and concluded that the risks outweighed the benefits [9].

However, the average age of participants in WHI was 63 years old (range 50–69), 12 years older than the average age of menopause in the United Kingdom. It is likely, therefore, that many of the older participants already had subclinical atherosclerosis. This is probably why these data support the findings of the HERS which was a study aimed at investigating the use of HRT in secondary prevention of heart disease [63], which also failed to demonstrate any benefit in those women with established CVD.

Analysis of data, stratified by age and time since menopause, synthesised from the two WHI trials, has demonstrated more favourable results for all-cause mortality and myocardial infarction in women aged 50–59, and those close to menopause [64]. A non-significant protective effect is demonstrated by combined oestrogen and progestogen and a significant effect with oestrogen alone. This is supported by the Danish Osteoporosis (DOPS) trial which has also demonstrated a significant reduction in risk of mortality, heart failure or myocardial infarction, after 10 years of hormone replacement therapy, started soon after menopause [65]. This apparent benefit in young women starting HT close to the time of menopause has been dubbed the 'critical period hypothesis' or the 'window of opportunity'.

It has been suggested that these differences seen in age-stratified effects of HT on CVD result from the differential effects of sex steroid hormones on early and later stages of atherosclerotic disease [66], with unstable plaques at risk of rupture predominating at later stages.

### Stroke

Sex hormones are known to be thrombogenic and an increase in deep vein thrombosis risk is seen with oral HRT. It appears that the same is true for stroke where a statistically significant increase was noted in all age groups [11]. Obviously, the baseline risk in women around the age of 60 is low but the incidence increases sharply with age. It was this adverse effect that led to the premature closure of the oestro- gen only arm of WHI [67]. All women must be warned of this risk particularly those electing to take HRT into older age although it is probable that the risk is diminished by administration of HRT via the transdermal route which avoid live first pass metabolism.

Assessment of CVD risk should be undertaken as part of standard care for women of menopausal age. HRT does not
increase blood pressure and also has no adverse impact on the risk of developing diabetes or diabetes control [68, 69], thus it can be used in some women with increased risk although care should be exercised in those who have had previous cardiovascular events.

**Mood and memory disorders**

Oestrogen facilitates synaptogenesis, induces growth factor production, protects against oxidative stress and regulates neurotransmission (e.g. serotonin, norepinephrine and acetylcholine) in brain systems associated with cognition and mood [70, 71].

Although oestrogens affect brain tissues and brain processes in ways expected to reduce dementia risk and improve the course of cognitive ageing, this is not supported by clinical findings. Many observational studies imply that oestrogens reduce the rate of AD, however it now seems that there is no benefit to be had by starting hormones, and there may even be an increased risk when started in women over the age of 65 [72].

Data from the HERS trial suggested that for symptomatic postmenopausal women, HT was associated with lower depressive symptoms. Two small RCTs demonstrated that transdermal oestradiol had antidepressant efficacy [73], however, compelling evidence is lacking regarding the antidepressant efficacy of HT alone.

Isolating the effects of ageing from the effects of the menopause is difficult, but there is currently no evidence to support the use of HT for improvement or prevention of cognitive decline. Any beneficial effects of HT in mood disorders may be more likely to occur in women with concomitant vasomotor symptoms [74].

**Obesity**

Both animal and human studies have suggested that oestrogen deprivation may lead to an accumulation of intra-abdominal fat stores and predispose to central obesity. It has also been shown that not only do postmenopausal women have much lower levels of physical activity when compared with their pre-menopausal counterparts, but there is also a change to the metabolism of adipose tissue which contributes to the accumulation of body fat [75] with the associated increase in cardiovascular risk associated with central adiposity. Overweight women have 1.5 to 2.0 times increased odds of reporting hot flushes and this risk increases with severity of obesity [76].

Central obesity is an important risk factor for progression of all types of pelvic organ prolapse (POP), due to chronically increased abdominal pressure and neurogenic disease. Obese postmenopausal women suffer more commonly from prolapse (cystocele 48 versus 32%, rectocele 58 versus 37% and uterine descent 69 versus 43%) than non-obese postmenopausal women. In the WHI study, the majority of women gained weight and the overall rate of prolapse increased from 40.9% at baseline to 43.8% at year 5 of evaluation. Being overweight or obese at baseline was associated with progression in cystocele, rectocele and uterine prolapse compared with women with healthy BMI. Weight loss does not appear to be significantly correlated with regression of POP, suggesting that damage to the pelvic floor related to weight gain is probably irreversible [77].

In the Study of Women’s Health Across the Nation (SWAN), women who had high levels of physical activity over the menopausal transition maintained their weight most effectively, providing a clue to a successful weight maintenance strategy during midlife [78].

**Conclusion**

Forty percentage of women will seek medical advice for the management of menopausal symptoms. Vasomotor symptoms are the most commonly reported and hormone therapy is a reasonable option for some. However, although other commonly associated symptoms of the menopause may occur as a result of oestrogen deficiency; replacing it is not always the treatment of choice.

The use of HT should be made on an individual basis, after careful consideration of quality of life and personal risk factors. In addition to any pharmacological treatments considered, lifestyle modifications are essential.

**Key points**

- Vasomotor symptoms (hot flushes and night sweats) are the most common menopausal symptoms and can be treated very effectively with oestrogen-based hormone therapy. The decision to use oestrogen (hormone replacement) involves balancing the potential benefits against the potential risks. Most agree that short-term oestrogen therapy, using the lowest effective dose, is a reasonable option for recently menopausal women with moderate to severe symptoms who are in good cardiovascular health.
- Locally administered vaginal oestrogens are effective in the treatment of menopause-related vulval and vaginal symptoms such as dryness, dyspareunia and pain.
- There is no solid evidence to support the use of hormone therapy, oral or vaginal, for the treatment of urge urinary incontinence.
- Hormone therapy decreases osteoporotic fractures and women taking HRT for symptoms may decide to continue for this reason even though regulators do not recommend hormone therapy as first-line treatment in the prevention of osteoporosis. Each must weigh up the risk (in terms of increased incidence of breast cancer and stroke) against this benefit.
- There is currently no evidence to support the use of hormone therapy for improvement or prevention of cognitive decline.
Conflicts of interest

None declared.

References

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