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Review Article

Hormone Replacement Therapy for Menopausal Symptoms - A Summary of Current Scientific Evidence

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Abstract

Menopausal hormone replacement therapy (HRT) refers to replacement of one or more of the three key female sex hormones oestrogen, progesterone and testosterone for suppression of menopausal symptoms. It is vital that all women are granted easy access to health professionals for advice on how they can optimise their health during menopausal transition and the years beyond including discussion about lifestyle, HRT, and non-hormonal/complementary interventions.

Besides suppressing menopausal symptoms, HRT has some long-term health benefits such as protection against osteoporosis and heart disease especially if it is started early during the menopausal transition. The main risks associated with HRT such as venous thromboembolism and breast cancer can be minimised by choosing to take oestrogen through transdermal route rather than oral tablets and by using progestogens such as natural micronised progesterone or dydrogesterone. Overall, for most healthy women below the age of 60, benefits of HRT for menopausal symptoms outweigh any small increase in risks.

Keywords: *Hormone Replacement Therapy (HRT); Menopausal Symptoms*

Introduction and History

The global increase in life expectancy is 74 years for women, while the median age of the menopause remains at 51 years [1]. An increasing number of women will therefore live a significant portion of their adult lives in the menopause and many will seek help for debilitating menopausal symptoms that warrant interventions such as hormone replacement therapy (HRT). HRT refers to replacement of one or more of the three key female sex hormones - oestrogen, progesterone and testosterone. Very few medications have been a subject of as much controversy and intense debate over the years as HRT.

HRT was first used in the 1940s and its use increased in 1960s and 70s for treatment of menopause related problems. It was prescribed for suppression of menopausal symptoms and prevention of loss of bone mineral density. Two large clinical studies of HRT users were conducted in 1990s - The Women's Health Initiative (WHI) study was a randomised controlled trial (RCT) in the United States (US) and the other was the Million Women Study (MWS) [2,3] which was an observational study using questionnaires in the United Kingdom (UK). The results of these two studies published around 2003 raised safety concerns regarding long-term use of HRT due to findings suggesting increased risk of breast cancer and heart disease. The results were widely publicised and led to a profound drop in HRT prescribing and

reluctance amongst women to take up or continue HRT for their symptoms. Guidelines and recommendations that followed publication of these studies recommended that the healthcare professionals use the lowest effective dose of HRT for the shortest duration required for menopausal symptom relief and that it should not be used as a first line therapy for prevention of osteoporosis.

To date, the confusion and uncertainty that was created following these reports persists amongst healthcare professionals and HRT users despite the fact that there have been a number of new studies and reanalysis of results from the big studies which have led to changes in interpretation of the results and different conclusions about benefits and risks associated with long-term HRT use [4,5]. The participants in the WHI trial were women in their sixties and many had preexisting comorbidities including high body mass index (BMI) and were not representative of majority of healthy women who would wish to use HRT during peri-menopause or early menopause. Over the past decade, the balance of benefits versus risks appears to have shifted in favour of long-term HRT use for most women who wish to take it. This commentary describes the current scientific evidence regarding safety and efficacy of long-term use of HRT and the best practice clinical recommendations based on this evidence.

HRT for management of menopausal symptoms

About 75 - 80% of women will experience menopausal symptoms, and for a significant proportion, the symptoms may be severe (in about third) and persistent. Vasomotor symptoms (VMS) are the commonest including hot flushes and night sweats [4]. Other common reported symptoms include disturbed sleep, tiredness, depressed mood, brain fogging, low libido and heightened anxiety.

Oestrogen replacement as part of HRT remains the most effective treatment for VMS. The optimum dose and duration of HRT treatment should be decided based on the severity of symptoms and response to therapy. Arbitrary limits should not be placed on the dose or duration of HRT use. HRT use is also associated with improvement in mood and depressive symptoms which can be associated with menopause. Some women who have progesterone sensitivity may not tolerate progestogens in HRT and notice side effects such as low mood and bloating however, micronised progesterone is associated with fewer side-effects than the more androgenic synthetic progestogens. For women who remain sensitive to systemic progestogens, the levonorgestrel intrauterine system may minimise systemic progestogenic side-effects by direct release of progestogen into the endometrium. The levonorgestrel intrauterine system offers endometrial protection for up to five years from the time of its insertion as part of HRT and can be an especially useful option when other progestogens have failed to stop persistent irregular breakthrough bleeding. Other less commonly used alternatives to reduce exposure to systemic progestogen include cyclical use of oral progestogen every 2 - 3 months and vaginal administration of natural progesterone. Data regarding use of such off-license HRT regimen remain limited and patients should be counselled about the potential risks of endometrial pathology and the need for regular endometrial surveillance.

Replacement of systemic oestrogen can improve sexual function by its effect on desire and libido. Vaginal oestrogen replacement can improve dyspareunia which results from vulvovaginal atrophy. Use of systemic testosterone as part of HRT is associated with significant improvement in sexual function, including sexual desire and orgasm. Currently, it is recommended for the treatment of hypoactive sexual desire disorder (HSDD) in postmenopausal women. The NICE guidelines recommend considering testosterone treatment for menopausal women with low sexual desire if HRT with oestrogen and progestogen is not effective [5]. The aim of treatment is to maintain testosterone levels within female physiological range as this is not associated with any long-term serious adverse effects [4]. Yet another useful bleed-free oral HRT option is Tibolone - it has effects of oestrogen, progesterone and a weak androgen replacement which can be beneficial for improvement in libido levels and mood stability. Women who use systemic forms of HRT should have annual follow-ups with their healthcare professionals so that they have a regular appraisal of benefits versus risks in their unique circumstances. Arbitrary time limits should not be used to stop HRT treatment.

The genitourinary syndrome of the menopause (GSM - previously referred to as vulvovaginal atrophy) affects more than 50% of postmenopausal women. Topical vaginal oestrogen (in the form of pessaries, creams, or ring) is the treatment of choice for vaginal dryness

and dyspareunia due to oestrogen deficiency. Oestrogen receptors are also found in the bladder and oestrogen has a proliferative effect on epithelium of the bladder and urethra. Topical oestrogen can improve bladder symptoms such as frequency and urgency and reduce the incidence of recurrent urinary tract infections. It is not required to combine low-dose vaginal oestrogen preparations with systemic progestogen therapy for endometrial protection as these preparations do not cause endometrial stimulation. They can be continued as long as symptoms persist. Vaginal oestrogens may also be used in women with past history of breast cancer who suffer from severe GSM symptoms and do not respond to non-hormonal treatments [4,5]. Liaison with the woman's oncologist is important when advising such treatment and it may be worth considering switching women on aromatase inhibitors as adjuvant therapy to tamoxifen as the mechanism of action of these two agents is different.

Two new medications have been recently granted approval in the UK for treatment of GSM: 1. Intravaginal dehydroepiandrosterone (DHEA) has been found to be effective in treatment of symptoms of vulvovaginal atrophy. It improves vaginal epithelial mucin production, vaginal wall muscle thickness and affects composition of collagen. 2. Ospemifene is a selective oestrogen receptor modulator which is an oral agent effective for treatment of GSM. It provides an oral treatment option to women who do not wish to use vaginal oestrogen preparations. Neither of these two new medications have been adequately studied in women with history of breast cancer and hence not recommended for use in this group of women.

Oestrogen deficiency following menopausal transition has a detrimental impact on joints, connective tissue, bone mineral content and skin. Ageing and hormonal decline also appear to have an adverse effect on muscles with progressive loss of muscle mass. Healthy lifestyle which incorporates regular exercise is key to maintenance of muscle mass and bone health. HRT use is associated with improvement of joint pain and although conflicting data exist - oestrogen appears to benefit muscles as it is associated with greater muscle power and favourable muscle composition [4].

In women who have been diagnosed with premature ovarian insufficiency (POI), HRT is strongly recommended for suppression of menopausal symptoms, maintenance of sexual function and to minimise the risk of cardiovascular disease, osteoporosis, and cognitive decline until the age of natural menopause (51) [4]. The findings and concerns raised by the WHI study do not apply to this group of young women in whom there is no increased risk of breast cancer when HRT is only used for the purpose of physiological replacement of key sex hormones. Common side effects associated with the use of HRT include nausea, headaches, breast tenderness, bloating/fluid retention and irregular bleeding. Most side effects are temporary and dose-related, and respond to changes to type, route or dose of hormones. HRT should not be prescribed to women in following situations - current/past/suspected breast cancer, known/suspected oestrogen-dependent cancer, undiagnosed vaginal bleeding, untreated endometrial hyperplasia, active arterial or venous thromboembolic disease and active liver disease [5].

HRT and long-term health

Bone health

About one in two women in the UK will suffer a fracture after the age of 50 and a 50-year-old woman has a 2.8% risk of death related to hip fracture during her lifetime [4]. All women should be offered healthy lifestyle advice including balanced diet, adequate calcium and vitamin D intake, regular exercise, quitting smoking and limiting alcohol intake. Individual risk assessment should be carried out regarding risk of developing osteoporosis and osteoporosis related fractures. Bone mineral density assessment should be offered on an individualised basis following risk assessment. HRT has a protective effect against osteoporosis and bone fragility fractures. It is now recommended that HRT should be considered the first-line therapeutic option for prevention and treatment of osteoporosis in women with POI or early menopause and menopausal women below the age of 60 years, particularly those with menopausal symptoms [4]. The

degree of bone protection offered by oestrogen depends on the dose and duration of treatment and will decrease after the treatment is discontinued.

Cardiovascular health

About 24,000 women die from coronary heart disease every year in the UK and cardiovascular disease is a leading cause for morbidity and mortality in women [4]. Oestrogen administration as part of HRT is associated with a significant reduction in the incidence of cardiovascular disease. Results from the WHI study which initially included women from all age groups (50 - 79 years) suggested an increase in the risk of cardiovascular disease in women using combined HRT. However, the long-term follow-up data showed no evidence for such a detrimental effect with combined HRT. In women below 60 years of age, who used oestrogen alone HRT, a significant decrease in coronary events was noted. Evidence from more recent studies and meta-analyses suggests that HRT started before the age of 60 or within 10 years of the menopause is associated with a reduction in atherosclerosis progression, coronary heart disease and death from cardiovascular causes as well as all-cause mortality. Long-term follow-up data from the WHI study showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who started HRT more than 10 years after the menopause [6].

Cognitive function

Brain function in women appears to be affected by the hormonal changes of menopausal transition. Symptoms such as forgetfulness, difficulty concentrating or multitasking, and brain fog are common during this phase. An improvement in symptoms related to cognition has been noted when HRT is started in early menopause as per observational study data. Based on current evidence (studies showing conflicting results), it appears that HRT is not likely to increase the risk of dementia or affect cognitive function adversely in women who start HRT before the age of 60 [4]. Currently, menopausal HRT is not recommended for the purpose of preventing dementia.

Risks associated with HRT

Venous thromboembolism (VTE) and stroke

Oral HRT increases the risk of VTE - risk is increased 2 - 4 fold and is highest in the first year after starting HRT. Increasing age, high BMI, impaired mobility, thrombophilia, or personal history of VTE are all additional risk factors. Transdermal HRT does not appear to increase the risk of VTE above that in non-users and is associated with a lower risk than oral oestrogens [4]. With oral HRT preparations, the risk depends on the type and dose of oestrogen. Conjugated equine oestrogens are associated with a higher risk of VTE than oestradiol. The type of progestogen also affects the VTE risk. Synthetic progestogens carry a higher risk than micronised progesterone and dydrogesterone. In women with risk factors for VTE, a combination of transdermal oestradiol and micronised progesterone or dydrogesterone appear to be the safest HRT options. Multidisciplinary management of such women with input from the haematology team should be considered in such situation. With regards to the risk of stroke, it is age related and overall, the risk is low in women under the age of 60. Oral oestradiol is associated with a small increase in the risk of stroke which is dose related. Transdermal oestradiol is not associated with an increase in the risk of stroke above the woman's own baseline risk. Transdermal oestradiol containing preparations should be the first line option when considering HRT in women with pre-existing risk factors for stroke or those above the age of 60. The type of progestogen in HRT impacts the risk of stroke and micronised progesterone or dydrogesterone remain the preferred progestogens in women who are at increased risk.

Breast cancer

Breast cancer is the commonest female cancer in the UK and about 11,400 women die from breast cancer in the UK each year. Based on observational studies in women taking HRT for five years the increased risk reported in absolute numbers is as follows [7]:

1. For women taking continuous combined HRT for five years from the age of 50, the risk of developing breast cancer between the age of 50 and 69 goes up by 1 extra case in 50 over 20 years from a background risk of 3 out of 50 women to 4 out of 50 women.

2. For women taking sequential combined HRT for five years from the age of 50, the risk of developing breast cancer between the age of 50 and 69 goes up by 1 extra case in 70 over 20 years from a background risk of 4 out of 70 women to 5 out of 70 women.

3. For women taking oestrogen only HRT for five years from the age of 50, the risk of developing breast cancer between the age of 50 and 69 goes up by 1 extra case in 200 over 20 years from a background risk of 13 out of 200 women to 14 out of 200 women.

The WHI long-term randomised clinical trials, published in 2020, reported on the association of HRT with breast cancer incidence and mortality and involved over 27,000 women, who were enrolled between 1993 and 1998 and followed-up through 2017 [8]. The report showed a significant decrease in the risk of breast cancer diagnosis (HR 0.78; 95% CI 0.65 - 0.93; p.0.005) and a significant reduction in breast cancer mortality (HR 0.60; 95% CI 0.37 - 0.97; p.0.04) when oestrogen-only HRT is taken. Women who took combined oestrogen and progestogen HRT had an increased risk of breast cancer compared to placebo (HR 1.28; 95% CI 1.13 - 1.45; $p < 0.001$) but had no significant difference in breast cancer mortality compared with placebo (HR 1.35; 95% CI 0.94 - 1.95; p.0.11). These important findings on breast cancer mortality contrast with the data from observational studies.

It is generally accepted that the best scientific clinical evidence comes from randomised clinical trials. The WHI study was a prospective, randomised, placebo-controlled trial with a 20-year follow-up. Based on the results of this study it appears that we are now compelled to consider a direct interpretation of its finding, namely that exposure to exogenous oestrogen only is not associated with an increased risk of breast cancer. The hormone problem in combined HRT therefor appears to be the progestogen, which is associated with the increased risk of breast cancer and causes most of the side effects that may induce women to withdraw from treatment. In practical terms, the risks associated with HRT such as breast cancer or thrombosis should be discussed in relation to the overall benefits and risks associated with HRT to help women make an informed choice. Women should be informed that the absolute risks of complications on HRT are low in healthy women under the age of 60, particularly compared to other modifiable risk factors such as excess alcohol intake, smoking and obesity.

Endometrial cancer

Unopposed oestrogen treatment increases the incidence of endometrial cancer and this risk can be mostly avoided by using combined oestrogen and progestogen therapy. Use of sequential combined HRT for more than five years may be associated with an increase in the risk of endometrial cancer. The risk increases with decreasing number of days progestogen is given as part of the monthly cycle (a minimum of 12 - 14 days of recommended daily progestogen dose is therefore advised as part of a monthly cycle). The WHI study reported a neutral effect on the risk of endometrial cancer with combined HRT compared to placebo after five years of use. However, a significant reduction was noted with combined HRT compared to placebo with long-term follow-up. In practical terms, after one year from the last menstrual period or one year of cyclical HRT use, women who wish to avoid a monthly withdrawal bleed should be offered a switch to a continuous combined bleed-free HRT regimen as this will minimise the risk of endometrial pathology.

Ovarian cancer

Observational study data have suggested an increased risk of ovarian cancer with HRT use. The WHI randomised placebo-controlled trial results following long-term follow-up found no evidence of increased risk of ovarian cancer with HRT use. It has been suggested that there may be a slight increase in the risk of developing serous and endometrioid ovarian cancer associated with HRT use, but the absolute risk remains small [4].

Other cancers

There is no association between cervical cancer and HRT, and a reduced risk of colorectal cancer with the use of oral combined HRT.

Bio-identical versus body-identical HRT

Conventionally used regulated menopausal HRT products such as 17-beta-oestradiol, micronised natural progesterone and testosterone are obtained from plant extracts and are similar to their biological equivalents in the body. These are referred to as 'body-identical' HRT and have become popular as natural progesterone has lower risk of VTE and breast cancer in comparison to synthetic progestogens [4].

Some clinics however offer compounded 'bio-identical' hormones for menopausal symptoms which are combinations of different plant oestrogens and progesterone. These products do not have the same level of regulation and individual preparations have not been evaluated with scientific rigour in randomised controlled clinical trials for their long-term effectiveness and safety. Bio-identical HRT preparations are therefore currently not recommended for use by the British Menopause Society in the UK.

Conclusion

Publication of The National Institute for Health and Care Excellence (NICE) guidelines on menopause in 2015 and recent press reports covering the long-term follow-up results from the WHI study as well as consensus statements from the British menopause Society have attracted the attention of healthcare professionals towards use of HRT for menopausal symptoms and the impact of hormone changes during menopausal transition on long-term health problems. It is vital that all women are granted easy access to healthcare professionals for advice on how they can optimise their menopausal transition and the years beyond. Advice should be individualised (based on risks versus benefits) and include lifestyle changes, HRT, and non-HRT as well as complementary therapies. For majority of women who use HRT for treatment of unpleasant menopausal symptoms, benefits of treatment outweigh the risks.

Conflicts of Interest

I declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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